

Understanding Lymphoma and Chronic Lymphocytic Leukemia/ Small Lymphocytic Lymphoma (CLL/SLL)



A Guide for Patients,
Survivors, and
Loved Ones

LYMPHOMA

RESEARCH • FOUNDATION

**Lymphoma Research Foundation
(LRF) Helpline and Clinical Trials
Information Service**

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Understanding Lymphoma and CLL/SLL

A Guide for Patients, Survivors, and Loved Ones

2023

This guide is an educational resource compiled by the Lymphoma Research Foundation (LRF) to provide general information on lymphoma and chronic lymphocytic leukemia (CLL). This booklet is not intended to replace individualized medical care or the advice of a patient's doctor.

Patients are strongly encouraged to talk to their doctors for complete information on how their disease should be diagnosed, treated, and followed. Before starting treatment, patients should discuss the potential benefits and side effects of cancer therapies with their physician.

Contact the Lymphoma Research Foundation

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ABBREVIATIONS

3D-CRT	Three-Dimensional Conformal Radiation Therapy
ABMS	American Board of Medical Specialties
ABVD	Doxorubicin/hydroxydaunorubicin, Bleomycin, Vinblastine, Dacarbazine
ABVE-PC	Doxorubicin, Bleomycin, Vinblastine, Etoposide, Prednisone, Cyclophosphamide, Dacarbazine
ACIP	Advisory Committee on Immunization Practices
ADC	Antibody-Drug Conjugate
AIDS	Acquired Immunodeficiency Syndrome
AIHA	Autoimmune Hemolytic Anemia
AITL	Angioimmunoblastic T-Cell Lymphoma
ALCL	Anaplastic Large Cell Lymphoma
ALK	Anaplastic Lymphoma Kinase
ALL	Acute Lymphoblastic Leukemia
ANC	Absolute Neutrophil Count
APLES	Age, Performance Status, Lactate Dehydrogenase Level, Number of Extranodal Sites and Stage
app	Application
ASCO	American Society of Clinical Oncology
ASH	American Society of Hematology
AVD	Doxorubicin, Vinblastine, Dacarbazine
AYA	Adolescents and Young Adults
<i>Bcl2</i>	B-Cell Lymphoma 2
BCMA	B-cell maturation antigen
BEACOPP	Bleomycin, Etoposide/VP16, Doxorubicin, Cyclophosphamide, Vincristine, Procarbazine, Prednisone
BEGEV	Gemcitabine, Vinorelbine
BTK	Bruton Tyrosine Kinase
BV	Brentuximab Vedotin
BV-AVD	Brentuximab Vedotin, Doxorubicin, Vinblastine, Dacarbazine
BVB	Brentuximab Vedotin, Bendamustine
CAR	Chimeric Antigen Receptor

CBC	Complete Blood Count
CCR4	C-C Chemokine Receptor Type 4
CDC	Centers for Disease Control and Prevention
CDOP	Cyclophosphamide, Liposomal Doxorubicin, Vincristine, Prednisone
CELMoDS	Cereblon E3 Ligase Modulatory Drugs
CEOP	Cyclophosphamide, Etoposide/VP16, Prednisone, Procarbazine
CEPP	Cyclophosphamide, Etoposide, Prednisone, Procarbazine
ChIVPP	Chlorambucil, Vinblastine, Procarbazine, Prednisolone
CHOEP	Cyclophosphamide, Doxorubicin, Vincristine, Etoposide, Prednisone
CHOP	Cyclophosphamide, Doxorubicin, Vincristine, Prednisone
CHP	Cyclophosphamide, Doxorubicin, Prednisone
CLL	Chronic Lymphocytic Leukemia
CME	Continuing Medical Education
CMP	Comprehensive Metabolic Panel
CODOXM-IVAC	Cyclophosphamide, Vincristine, Liposomal doxorubicin, Cytarabine/high-dose Ara-C, Methotrexate, Ifosfamide, Etoposide
COVID-19	Coronavirus Disease 2019
CPR	Cardiopulmonary Resuscitation
CR	Complete Remission
CSF	Cerebrospinal Fluid
CSF-1R	Colony Stimulating Factor-1 Receptor
CT	Computed Tomography
CTCL	Cutaneous T-Cell Lymphoma
CTLA-4	Cytotoxic T-Lymphocyte Associated Protein 4
CVP	Cyclophosphamide, Vincristine, Prednisone
del	Deletion
DHAP	Dexamethasone, Cytarabine/high-dose Ara-C Cisplatin
DHAX	Dexamethasone, Cytarabine, Oxaliplatin
DICE	Dexamethasone, Ifosfamide, Cisplatin, Etoposide/VP16

DLBCL	Diffuse Large B-Cell Lymphoma
DNA	Deoxyribonucleic Acid; Genetic Material
DNR	Do Not Resuscitate
EBV	Epstein-Barr Virus
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
ENMZL	Extranodal Marginal Zone Lymphoma
EPOCH	Etoposide/VP16, Prednisone, Vincristine, Cyclophosphamide, Doxorubicin/hydroxy daunorubicin
ESHAP	Etoposide/VP16, Methylprednisolone, Cytarabine/high-dose Ara-C, Cisplatin
ESR	Erythrocyte Sedimentation Rate
EZH2	Enhancer of Zeste Homolog 2
F	Fludarabine
FC	Fludarabine, Cyclophosphamide
FDA	U.S. Food and Drug Administration
FISH	Fluorescence In Situ Hybridization
FL	Follicular Lymphoma
FLIPI	Follicular Lymphoma International Prognostic Index
FMLA	Family and Medical Leave Act
FNA	Fine Needle Aspiration
FND	Fludarabine, Mitoxantrone, Dexamethasone
G	Gemcitabine
GCD	Gemcitabine, Carboplatin, Dexamethasone
GCVP	Gemcitabine, Cyclophosphamide, Vincristine, Prednisolone
GDP	Gemcitabine, Dexamethasone, Cisplatin
GemOX	Gemcitabine, Oxaliplatin
GVD	Gemcitabine, Vinorelbine, Liposomal Doxorubicin
GVHD	Graft-Versus-Host Disease
GVL	Graft-Versus-Lymphoma Effect
GVT	Graft-Versus-Tumor Effect
HBV	Hepatitis B Virus

HCV	Hepatitis C Virus
HD Ara-C	Cytarabine/High-Dose Ara-C
HD MTX	High-Dose Methotrexate
HDAC	Histone Deacetylase Inhibitors
HDMP	High-Dose Methylprednisolone
HGBCL	High-Grade B-Cell Lymphoma
HIV	Human Immunodeficiency Virus
HL	Hodgkin Lymphoma
HTLV	Human T-Cell Lymphotropic Virus
HyperCVAD/ MTX-Ara-C	Cyclophosphamide, Vincristine, Doxorubicin/ hydroxydaunorubicin, Dexamethasone, Methotrexate, Cytarabine/high-dose Ara-C
ICE	Ifosfamide, Carboplatin, Etoposide/VP16
IFRT	Involved-field Radiation Therapy
IGEV	Ifosfamide, Gemcitabine, Prednisolone, Vinorelbine
IgG	Immunoglobulin G
IGHV	Immunoglobulin Heavy Chain Variable Region Gene
IGRT	Image-Guided Radiation Therapy
IHC	Immunohistochemistry
IM	Intramuscular
IMiD	Immunomodulatory Drug
IPI	International Prognostic Index
IRB	Institutional Review Board
ISRT	Involved-Site Radiation Therapy
ITP	Immune Thrombocytopenia
IV	Intravenous
JAK	Janus Kinase
LAG-3	Lymphocyte Activation Gene-3
LDH	Lactate Dehydrogenase
LP	Lymphocyte-Predominant
LRF	Lymphoma Research Foundation
LSRMP	Lymphoma Scientific Research Mentoring Program

MALT	Mucosa-Associated Lymphoid Tissue
MBL	Monoclonal B-Cell Lymphocytosis
MCL	Mantle Cell Lymphoma
MF	Mycosis Fungoides
MMAE	Monomethyl Auristatin E
MOPP	Mechlorethamine, Vincristine, Procarbazine, Prednisone
MR	Minor Response
MRD	Minimal Residual Disease
MRI	Magnetic Resonance Imaging
mRNA	Messenger Ribonucleic Acid
mTOR	Mammalian Target Of Rapamycin
MUGA	Multigated Acquisition Scan
MZL	Marginal Zone Lymphoma
NCCN-IPI	National Comprehensive Cancer Network- International Prognostic Index
NCI	National Cancer Institute
NGS	Next Generation Sequencing
NHL	Non-Hodgkin Lymphoma
NIH	National Institutes Of Health
NK	Natural Killer Cell
NLPHL	Nodular Lymphocyte-Predominant HL
NSAID	Nonsteroidal Anti-Inflammatory Drug
O	Obinutuzumab
OEPA/COPD	Doxorubicin, Vincristine, Etoposide, Prednisone, Doxorubicin, Cyclophosphamide, Dacarbazine
P	Pralatrexate
PA	Physician Assistant
PCR	Polymerase Chain Reaction
PD-1	Programmed Death-1
PD-L1	Programmed Death-1 Ligand
PET	Positron Emission Tomography
PI3K	Phosphoinositide3-Kinase

PICC	Peripherally Inserted Central Catheter
PMBL	Primary Mediastinal Large B-Cell Lymphoma
PML	Progressive Multifocal Leukoencephalopathy
Pola-R-CHP	Polatuzumab vedotin-piiq, Rituximab, Cyclophosphamide, Doxorubicin, Prednisone
PR	Partial Remission
PrEP	Pre-Exposure Prophylaxis
PS	Performance Status
PTCL-NOS	Peripheral T-cell Lymphoma-Not Otherwise Specified
R	Rituximab
R-IPi	Revised- International Prognostic Index
RIT	Radioimmunotherapy
RNA	Ribonucleic Acid
ROR1	Tyrosine-Protein Kinase Transmembrane Receptor
RS	Reed-Sternberg
RXR	Retinoid X Receptor Activator
SAB	Scientific Advisory Board
SEER	Surveillance, Epidemiology, and End Results
slg	Surface Immunoglobulin
SLL	Small Lymphocytic Lymphoma
SMILE	Methotrexate, Leucovorin/Levoleucovorin, Ifosfamide, Mesna, Dexamethasone, Etoposide/VP16, Pegaspargase
SMZL	Splenic Marginal Zone Lymphoma
SNP	Single Nucleotide Polymorphism
TK	Tyrosine Kinase
TLS	Tumor Lysis Syndrome
TNF	Tumor Necrosis Factor
TSBT	Total Skin Electron Beam Therapy
WBC	White Blood Count
WHO	World Health Organization
WM	Waldenström Macroglobulinemia
XPO	Nuclear Export Receptor Exportin 1 Inhibitor

INTRODUCTION

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

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

Chapter 1: Understanding the Disease

Lymphoma is a type of blood cancer that can affect white blood cells called *lymphocytes*, in the *lymphatic system* (tissues and organs that produce, store and carry white blood cells), the blood, and the *bone marrow* (the spongy tissue inside large bones such as the pelvis, vertebrae and ribs). Normally, lymphocytes work together with other cells of the immune system to defend the body against bacteria, viruses, parasites, and other foreign substances. They can also fight cancer cells. Lymphocytes travel in the bloodstream and in the lymphatic system to accumulate in specialized structures called lymph nodes (bean-shaped structures that help the body fight infection), in the bone marrow, and in the spleen. Lymph nodes are part of the lymphatic system and typically are the sites in which the body develops an immune response (the immune system recognizes and attacks harmful or foreign substances) to viruses and bacterial infections.

This chapter explains these and other terms that will help people understand lymphoma and how it affects a person's health so patients can better participate in their care.

What is Cancer?

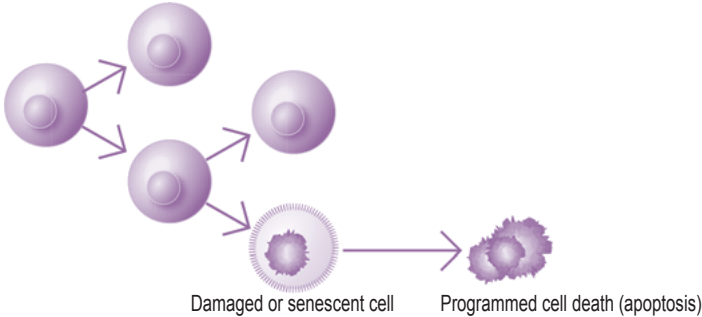
The body is made up of many different types of specialized cells organized into tissues and organs, which perform the tasks needed to sustain life. To keep the body running smoothly, cells in the body grow, work, and multiply in a very controlled fashion.

Most normal cells have a limited lifespan after which a self-destruct mechanism (process) is triggered for cells that are *senescent* (too old) or get damaged; this process is called *apoptosis* or programmed cell death. However, sometimes *mutations* (permanent changes) in the genetic material (DNA) of a cell overcome this self-destruct mechanism and allow the cell to continue to live and grow indefinitely, preventing the damaged cell from ever dying. Usually, the body's immune system identifies and gets rid of these cancerous cells, but sometimes these can escape the immune

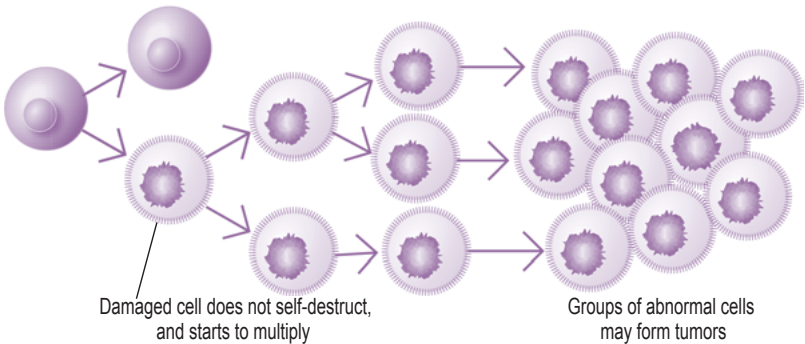
system, multiply uncontrollably, and pile up forming a mass called a tumor that can grow to interfere with normal organ function.

HOW CANCER FORMS INSIDE THE BODY

Normal cell division



Cancer cell division



Most cancers are named after the organ or cell where the cancer originated. For example:

- A cancer that started in the pancreas is called pancreatic cancer.
- A cancer of the lymphocytes is called a *lymphoma* or *lymphocytic leukemia* depending on whether the cancerous lymphocytes are located primarily in the lymph nodes and other lymphatic tissues (lymphoma) or primarily in the bone marrow and the blood (lymphocytic leukemia).

What Are the Different Types of Blood Cells?

There are three main classes of blood cells:

- Red blood cells (or *erythrocytes*) — Red blood cells carry oxygen from the lungs to all the tissues in the body. Red blood cells also remove the carbon dioxide waste produced by cells and bring it to the lungs to be exhaled. A low number of red blood cells is called *anemia*. A person with anemia may feel tired, weak, and short of breath.
- Platelets (or *thrombocytes*) — Platelets are cell fragments produced by cells in the bone marrow. They clump together in a blood clot to stop bleeding from broken blood vessels. A low number of platelets is called *thrombocytopenia*. People with thrombocytopenia are more likely to bruise and bleed with minor trauma. They are also more likely to have severe and recurring nosebleeds and bleeding gums.
- White blood cells (or *leukocytes*) — White blood cells work as part of the immune system to help the body fight infections. The main types of white blood cells are:
 - *Granulocytes* — There are three types of granulocytes: neutrophils, basophils, and eosinophils. Neutrophils help fight bacterial infections. A low number of neutrophils in the blood is called *neutropenia*. People with neutropenia are more likely to get infections (mostly bacterial infections). Basophils are cells that take part in inflammatory reactions (i.e., an immune response against injury or infection that can cause symptoms such as fever, redness, swelling, and pain). Eosinophils also help fight infections, particularly those caused by parasites, and they become plentiful during allergic reactions.
 - *Monocytes* — These also play an important role in immunity by attacking cells infected with viruses or bacteria. They also get rid of senescent (too old) cells.
 - *Lymphocytes* — These are discussed below.

Blood cells have a varied lifespan from a few hours (e.g., neutrophils) to more than 3 months (e.g., red blood cells). Therefore, the body needs to constantly maintain its supply of these cells. New blood cells are made by *hematopoietic* (blood-forming) *stem cells* found in the bone marrow, which are immature (nonspecialized) cells that can develop into any kind of blood cell as needed.

What Are Lymphocytes?

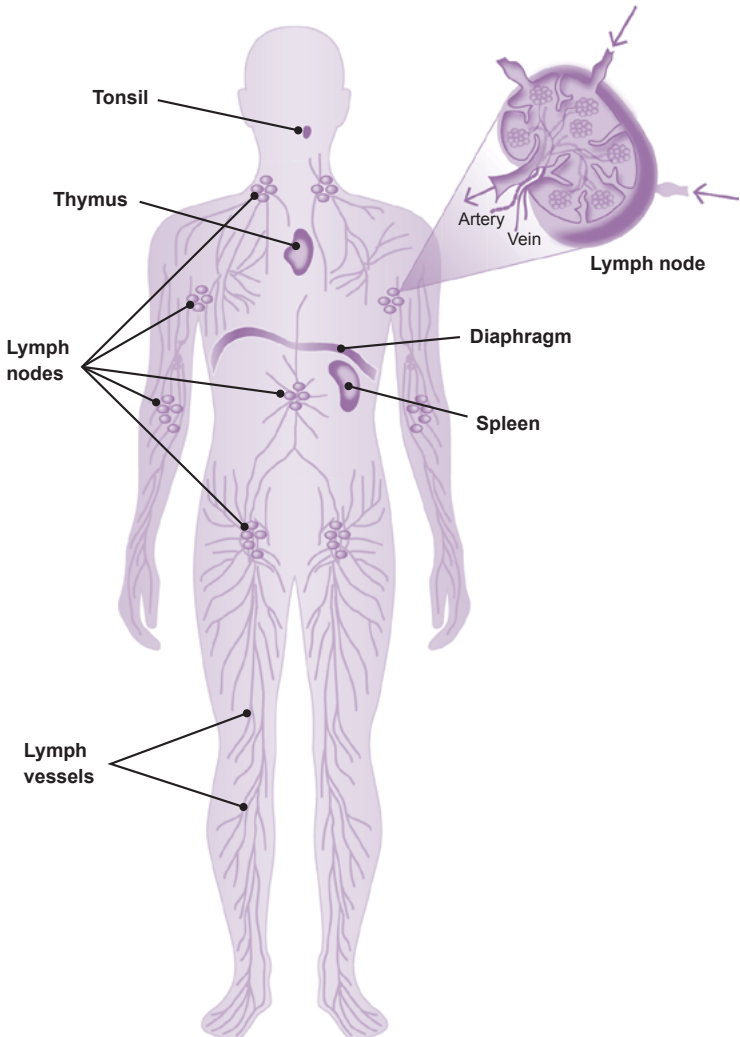
Lymphocytes are a type of white blood cell. There are three main types of lymphocytes:

- B lymphocytes (B-cells) — B-cells make antibodies to fight infections. They are called “B” cells because they were first discovered in the “Bursa of Fabricius” in birds (similar to the appendix in humans). Later, similar cells were found in humans.
- T lymphocytes (T-cells) — These cells can be considered the “coordinators” of the immune system. Some help B-cells make antibodies, some attack and kill infected cells, and others help control or regulate the way other parts of the immune system fight infections. They are called “T” cells because they develop in the thymus gland, a small organ in the front of the chest.
- Natural killer (NK) cells — NK cells attack and kill cancer cells and virus-infected cells. They also make proteins called cytokines that help the body get rid of viruses and tumor cells.

What is the Lymphatic System?

As shown in the following image, the lymphatic system is a spidery network of thin tubes called lymphatic vessels, somewhat similar to the blood vessels that make up the circulatory system (the system that moves blood across the body). Like blood vessels, lymphatic vessels branch out into all tissues of the body. Lymphatic vessels carry *lymph*, a liquid that contains lymphocytes to help fight infection. Thanks to the lymphatic and circulatory system, immune cells are free to move around and reach areas of the body where an infection or an injury occurred.

THE LYMPHATIC SYSTEM



Within this huge network of vessels are groups of lymph nodes, which are also commonly known as “glands.” Lymph nodes filter the lymph fluid, removing bacteria, viruses, and other foreign substances from the body. Hundreds of lymph nodes are normally found at locations throughout the body, including the neck, underarms, chest, abdomen, and groin.

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

If large numbers of foreign substances are filtered through a lymph node or series of lymph nodes, swelling may occur, and the nodes may become tender to the touch. Most swollen lymph nodes are a reaction to infection and are not cancerous. Lymph nodes can also become enlarged in states of inflammation, such as in autoimmune diseases (the body's immune system mistakes its own healthy cells for abnormal cells and attacks them) like rheumatoid arthritis.

How Does the Immune System Work?

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

The immune system provides two different types of immunity:

- *Innate* (meaning “inborn” or “natural”) immunity — This type of immunity is provided by natural barriers in the body, substances in the blood, and specific cells that attack and kill foreign cells. Examples of natural barriers include skin, mucous membranes, stomach acid, and the cough reflex. These barriers keep germs and other harmful substances from entering the body. *Inflammation* (redness and swelling) is also a type of innate immunity. Blood cells that are part of the innate immune system include neutrophils, macrophages, eosinophils, basophils and NK cells.
- *Adaptive* (meaning adapting to external forces or threats) immunity — This type of immunity is provided by the thymus gland, spleen, tonsils, bone marrow, circulatory system, and lymphatic system. B-cells and T-cells, the two main types of lymphocytes, carry out the adaptive immune response by recognizing and inactivating (disable) or killing invading organisms, either directly or by activating cells of the innate immune system. The adaptive immune system develops a memory of the invader, so that the next time the body is infected by the same invader, the immune response will develop more quickly and strongly.

What is Lymphoma?

Lymphoma is a type of cancer that originates from lymphocytes in the lymph nodes and other tissues in the lymphatic system. There are two major categories of lymphomas: Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). Each category is further subdivided into numerous types that differ in the type of cell they originated from (B, T, or NK cells), the way they develop and spread, and the way they are treated. Unlike other cancers, lymphoma therapy and prognosis (how well the patient will do) are determined by the lymphoma type, the presence of certain markers in lymphoma cells, and other factors like age and other medical issues, more than by the stage of the disease (how advanced the disease is).

Part 1 — Learning the Basics in Lymphoma

Chapter 2: Seeking Medical Attention

This chapter explains the signs and symptoms of lymphoma and discusses how a doctor determines whether a person has the disease.

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

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

What Are the Signs and Symptoms of Lymphoma?

Some patients with lymphoma do not have any obvious signs or symptoms of the disease at the time of diagnosis. Their doctors might detect the lymphoma during routine blood tests and/or a physical examination. For others, lymphoma is discovered when symptoms occur and patients go to the doctor because they are worried, uncomfortable, or not feeling well.

As shown in Table 2.1, lymphoma may cause different signs and symptoms depending on where it is located in the body. Keep in mind that these are only the most common signs and symptoms and many are not specific to lymphoma and may be due to other conditions.

Table 2.1. Signs and Symptoms Commonly Found in Patients

Sign or Symptom	Possible Reasons
<ul style="list-style-type: none">■ Lumps under the skin on the sides of the neck, above the collarbone, or in the underarms, elbows, or groin	<ul style="list-style-type: none">■ Lymph nodes, or “glands,” that swell when the lymphocytes respond to an infection or because of an increased number of abnormal lymphocytes.
<ul style="list-style-type: none">■ Swollen, tender abdomen	<ul style="list-style-type: none">■ Enlarged lymph nodes in the abdomen.■ Accumulation (buildup) of fluid in the abdomen.■ Enlarged liver or spleen.

Sign or Symptom	Possible Reasons
<ul style="list-style-type: none"> ■ Abdominal pain, nausea, vomiting, decreased appetite, or feeling full more easily 	<ul style="list-style-type: none"> ■ Enlarged lymph nodes or an enlarged spleen pressing on nearby normal structures (for example, the diaphragm, nerves, or spine). ■ Enlarged spleen pressing on the stomach, which can make a person feel full after eating only a small amount of food. ■ Pain in the spleen. ■ Lymphoma in the intestine (or causing swelling near the intestine) possibly blocking bowel movements. ■ Lymphoma of the stomach or abdominal lymph nodes.
<ul style="list-style-type: none"> ■ Constitutional symptoms (common symptoms in all NHL patients), including fevers for no known reason, unexplained drastic weight loss, and drenching night sweats that soak clothing and sheets (also called B symptoms) 	<ul style="list-style-type: none"> ■ Increased levels of inflammatory chemicals (substances that cause inflammation in the body) in the blood that are released by lymphoma cells or by the immune system.
<ul style="list-style-type: none"> ■ Coughing, trouble breathing, or chest pain or pressure 	<ul style="list-style-type: none"> ■ Lymphoma in the chest, which may press on the windpipe or bronchi (tubes leading to the lungs). ■ Pleural effusion (fluid surrounding the lungs).
<ul style="list-style-type: none"> ■ Headache, trouble thinking or finding words, weakness in extremities (legs or arms), loss of balance, personality changes, double or blurred vision, facial numbness, trouble speaking, or seizures 	<ul style="list-style-type: none"> ■ Lymphoma of the brain or spinal cord, or lymphoma originating in other parts of the body that has spread to or near the brain or spinal cord.
<ul style="list-style-type: none"> ■ Shortness of breath, fatigue (extreme tiredness), pale skin, and easy bruising 	<ul style="list-style-type: none"> ■ A shortage of oxygen-carrying red blood cells (anemia) and thrombocytopenia.
<ul style="list-style-type: none"> ■ Severe or frequent infections 	<ul style="list-style-type: none"> ■ Reduced ability to fight infection because of decreased numbers of certain types of white blood cells or low levels of gamma globulins.

When Should a Patient Seek Medical Attention?

Anyone who has an enlarged lymph node that does not return to normal size or continues to grow within one month, especially for lymph nodes outside the inguinal region (groin area) and/or persistent symptoms should see a doctor to make sure that lymphoma or another serious condition is not present. A good guideline is to seek medical attention if any of the signs or symptoms listed in Table 2.1 last longer than two weeks, or sooner if the symptoms are severe enough to impact a person's daily life. It is important to note that most patients with these symptoms do not have lymphoma, as diseases or conditions not related to lymphoma may cause many of these symptoms.

What Does The Doctor Look For?

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

- Ask details about symptoms including duration (how long), frequency (how often), intensity (how severe), and pain; these can be tracked in Lymphoma Research Foundation's mobile device app. (LRF's mobile app *Focus on Lymphoma* can keep track of symptoms and make communications with the doctor and healthcare team easier and more accurate. To learn more about this resource, visit our website at lymphoma.org/mobileapp, or contact the LRF Helpline at 800-500-9976 or helpline@lymphoma.org.)
- Measure blood pressure, pulse and other vital signs.
- Listen to the heart and lungs.
- Check the throat for enlarged tonsils.
- Look for any physical signs of infection or any other cancers, especially on the skin.
- Check for swollen lymph nodes under the chin, in the neck and tonsil area, above the shoulders, on the elbows, in the underarms, and in the groin.
- Examine other parts of the body to look for swelling or fluid that may be caused by swollen lymph nodes.

- Examine the abdomen to see whether the liver and/or spleen are enlarged and to feel for masses (lumps).
- Look for any weakness or *paralysis* (inability to make voluntary movements) that may be caused by an enlarged lymph node pressing against nerves or the spinal cord.

If the doctor suspects lymphoma after reviewing the symptoms reported and the signs discovered during the examination, additional tests will be requested to confirm the diagnosis.

Part 1 — Learning the Basics in Lymphoma

Chapter 3: Diagnostic Procedures

Doctors need the results of various diagnostic tests (clinical tests used to identify a disease) to determine accurately whether a patient has lymphoma. This chapter explains the purpose of each test and describes what to expect during and after the test procedures. Before agreeing to any procedure, patients should make sure they understand the reasons for the procedure and what will be involved. Here is a list of questions patients may want to ask their doctor:

PATIENT TIP

Questions to Ask Before Having a Diagnostic Procedure

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

How Is Lymphoma Diagnosed?

A tissue *biopsy* (see below) is the test required to establish an initial diagnosis of lymphoma. After that, one or more of the following tests may also be used to help with the diagnosis:

- *Immunophenotyping* of the cells collected from the biopsy (to describe the cells according to markers present on their surface).
- Genetic testing (to confirm the cytogenetic [the study of chromosomes and their abnormalities] results or to find out detailed information on genetic abnormalities in lymphoma cells). A chromosome is a thread-like molecule that contains the DNA (genetic material).
- Complete blood count (CBC) with *differential* (a blood test that counts the number of each type of blood cell and the amount of hemoglobin [the protein that carries oxygen in the blood]).
- Erythrocyte sedimentation rate (ESR) test. ESR measures how quickly red blood cells separate from the blood sample. Elevated ESR can be a signal of inflammation in the body.
- Comprehensive metabolic panel to check liver and kidney function.
- Testing for infection with the human immunodeficiency virus (HIV) and hepatitis B and C viruses.
- Imaging scans, like positron emission tomography (PET), computed tomography (CT) scans, or magnetic resonance imaging (MRI).

What Is a Biopsy?

A biopsy is a procedure in which a piece of the abnormal tissue is removed from the body and examined under a microscope. The information provided by this tissue sample is crucial to correctly diagnose the disease and to decide on the best course of treatment. A biopsy is the only way to confirm a lymphoma diagnosis.

Table 3.1 shows the three main types of biopsies used in patients with suspected lymphoma.

Table 3.1. The Three Main Types of Biopsies

Excisional or Incisional Biopsy	<ul style="list-style-type: none">■ This type of biopsy is often considered the standard (method that is accepted and used by most doctors, and considered appropriate by experts) to establish an initial diagnosis of lymphoma because it allows the removal of bigger samples. The larger the sample, the more tissue can be examined, which improves the accuracy of the diagnosis. The additional tissue removed can also be used to perform other tests that may impact treatment.■ A surgeon cuts through the skin to remove an entire lymph node (<i>excisional biopsy</i>) or a large portion of a lymph node or other tissue (<i>incisional biopsy</i>).■ If the lymph node is close to the skin surface, the procedure can be done under local anesthesia (a local injection that numbs only the affected area). If the lymph node is in the chest or abdomen, the patient is sedated (the patient relaxes to the point of sleep but can wake up if needed to communicate) and the surgeon removes the tissue either <i>laparoscopically</i> (through a tube inserted in the body) or by performing more extensive (in a large physical area) surgery.
Core Needle Biopsy	<ul style="list-style-type: none">■ This procedure is used when the lymph nodes being examined are deep in the chest or abdomen or in other locations that are difficult to reach with excisional biopsy, or when there are medical reasons for avoiding an excisional or incisional biopsy.■ A large needle is inserted into the lymph node or other organ, and one or more small tissue samples are withdrawn using a syringe attached to the needle. This can generally be done under local anesthesia, and stitches are usually not required.■ Rarely, the material collected may not be adequate (enough) for diagnosis, so a subsequent excisional or incisional biopsy may be necessary.■ Often the core needle biopsy is guided by an imaging test, such as an ultrasound, CT scan, or PET scan.■ It can also be used to check for lymphoma remaining, spreading or returning after treatment.
Fine Needle Aspirate (FNA) Biopsy	<ul style="list-style-type: none">■ This procedure is performed with a very thin needle that is smaller than the kind used for a core needle biopsy.■ Because of the small needle size, the sample only contains scattered cells, without preserving how the cells are arranged in the lymph node. Therefore, this test cannot provide enough information for a definitive initial diagnosis of lymphoma in the vast majority of cases.■ An FNA biopsy may be used if another, more accurate biopsy is not possible. It can also be used to check for cancer spreading and <i>relapse</i> (return of the disease) after treatment.

After a tissue sample has been removed, it is examined by a *pathologist* (doctor who specializes in the diagnosis of diseases by studying the cells from a patient's body fluids and tissue samples) under a microscope. A *hematopathologist* (pathologist who has undergone additional training in the diagnosis of blood diseases, including lymphoma) may also examine the sample. These specialists identify and classify the lymphoma cells by looking at their shape and size and how they are grouped in the sample using methods such as immunophenotyping (detailed below).

An *oncologist* (doctor who specializes in treating patients with cancer) or *hematologist* (doctor who specializes in treating patients with blood cancers and other blood disorders) uses the pathologist's report, along with results of other diagnostic tests, to confirm a diagnosis. If the pathologist's interpretation of the biopsy is uncertain, the biopsy should be reviewed by an expert hematopathologist.

Biopsies that are interpreted as "normal" may still contain lymphoma cells. This may occur when the sample is small and therefore it is not an accurate example of the rest of the lymph node. Sometimes a repeat biopsy is needed to establish the diagnosis. It takes an experienced hematopathologist working with the hematologist or oncologist to determine the need for more tissue sampling.

What is a CBC with a Differential Test?

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

- The number of red blood cells.
- The amount of hemoglobin (the protein that carries oxygen) inside the red blood cells.
- The number of total white blood cells and the numbers of each type of white blood cell (neutrophils, eosinophils, basophils, lymphocytes, and monocytes).
- The number of platelets.

The results of the CBC with differential assist in the diagnosis of lymphoma by ruling out (excluding) other types of blood cancer. The CBC with differential test is often repeated during the course of treatment to help

determine how much the treatment has affected the different blood counts and, in some cases, to help evaluate how well the treatment is working against the lymphoma.

What is Immunophenotyping?

Immunophenotyping is a process that can be used to distinguish (tell apart) among different types of cells (for example, normal lymphocytes vs lymphoma cells) based on the presence of antigens (proteins on the surface of certain cells). Antigens are specific to different cell types, just as landmarks are specific to different cities. Every antigen can be recognized by a specific type of antibody (protein produced by B-cells that binds to antigens and helps the immune system fight disease) that locks onto that particular antigen. Table 3.2 describes the immunophenotyping testing methods of flow cytometry and immunohistochemistry used in the diagnosis of lymphoma.

Table 3.2. Immunohistochemistry and Flow Cytometry Tests

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

What are Chromosome Abnormalities?

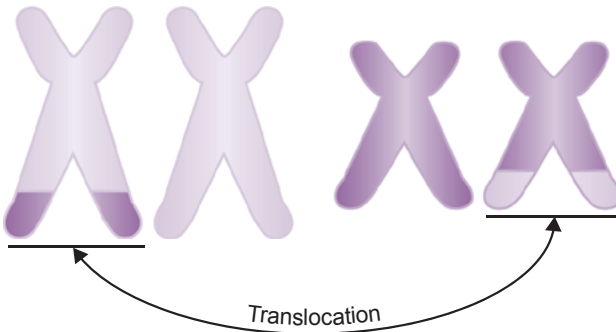
In every cell, DNA (genetic material) is wound up tightly into chromosomes. Normal human cells have 23 pairs of chromosomes. Some lymphoma cells have a different number of chromosomes (more or less than 23 pairs), or they may have abnormal chromosomes that have undergone a mutation (permanent change in the DNA). These changes can cause lymphoma cells to multiply uncontrollably. Some of the most common types of chromosome abnormalities that occur in lymphoma are described below.

Translocation

One type of chromosomal abnormality found in some types of non-Hodgkin lymphoma (NHL) is called a *translocation*, which occurs when parts of two different chromosomes break off and switch places with each other, as shown in the figure below. Some subtypes of NHL such as follicular lymphoma often or always carry a particular translocation.

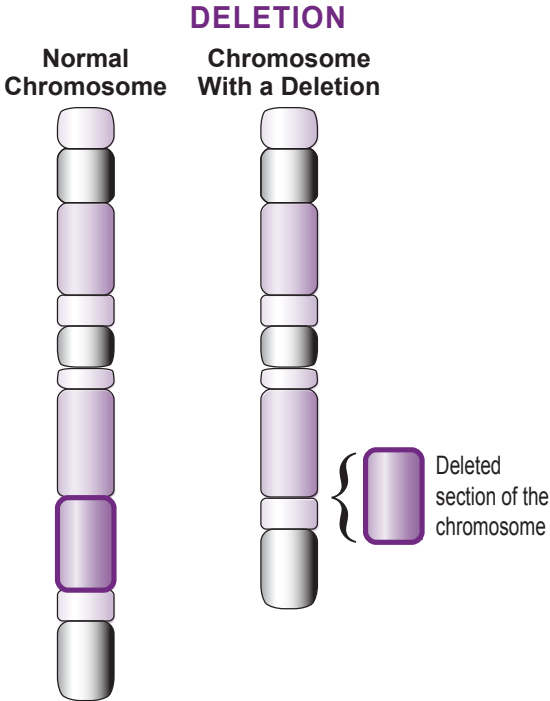
TRANSLOCATION

Two different chromosomes exchange portions of their genetic material



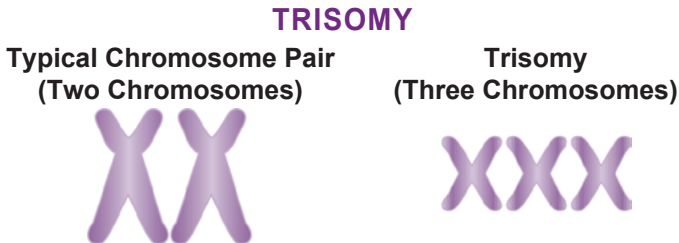
Deletion

Another type of chromosomal abnormality is called deletion, which happens when part of a chromosome is missing. Deletions are annotated (marked) using the abbreviation “del”, followed by the chromosome number and the location on the chromosome (“q” for the long arm, or “p” for the short arm) where the deletion has occurred. For example, deletions in chromosomes 11 [del(11q)], 13 [del(13q)], and 17 [del(17p)] are common in patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL).



Trisomy

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



Types of Tests and Analyses for Detecting Chromosome and Genetic Abnormalities

Genetic tests examine specific sections of the DNA called genes to identify abnormalities present in lymphoma cells that may cause uncontrollable lymphocyte growth. A variety of tests are available to provide genetic information to better understand chromosome and genetic abnormalities in a patient or the subtype of disease present. Note that these tests aim to reflect the genetics of the cancer cells themselves, and not the genetics of normal cells, or the genetic material that is passed down from generation to generation. Examples of tests that are used to detect chromosome and genetic abnormalities are described in Table 3.3. These tests are important for learning more about a patient's particular disease and what treatments may be most effective for that patient.

Table 3.3. Types of Tests Used in Clinical Practice for Detecting Chromosome and Genetic Abnormalities

<p>Fluorescence In Situ Hybridization (FISH)</p>	<ul style="list-style-type: none"> ■ FISH uses fluorescent chemicals that attach to certain parts of chromosomes to show the presence of translocations and other abnormalities. ■ FISH can be performed on samples of blood, lymph node tissue, bone marrow or other specimens. ■ The test results from FISH are usually available within a few days, which is quicker than the time required for cytogenetic testing.
<p>Single-Nucleotide Polymorphism (SNP)</p>	<ul style="list-style-type: none"> ■ SNP uses fluorescent chemicals that attach to certain parts of DNA pieces to detect small abnormalities, and other mutations. ■ This method allows for the testing of a wide range of mutations called polymorphisms and is often used together with FISH.
<p>Polymerase Chain Reaction (PCR)</p>	<ul style="list-style-type: none"> ■ A method to amplify (create several copies) DNA pieces to detect genetic abnormalities. ■ It may aid in doctors distinguishing between subtypes of CLL. It may also help establish diagnosis of various types of NHL when other test results are uncertain
<p>Copy Number Variation Analysis</p>	<ul style="list-style-type: none"> ■ Detects whether there are extra or fewer copies of a given gene
<p>Multiplex Next Generation Sequencing (NGS)</p>	<ul style="list-style-type: none"> ■ Collects the genetic sequence (the order of the units that form the DNA) for all DNA. It allows for several DNA sequences to be tested together to identify genetic changes that may contribute to disease. ■ Large sample numbers can be tested during one single experiment.

Doctors may use some or all of these tests to learn more about the genetics of a patient’s lymphoma.

Other existing genetic tests that might be experimental and not currently used in clinical practice are described in Table 3.4.

Table 3.4. Other Types of Tests for Detecting Chromosome and Genetic Abnormalities

Genome Wide Association Study	<ul style="list-style-type: none"> ■ DNA changes associated with a disease are identified and can be used to predict the presence of the disease
Whole Exome Sequencing	<ul style="list-style-type: none"> ■ Collects the genetic sequence for all DNA that codes for proteins to identify genetic changes that may contribute to disease.
DNA Sequencing	<ul style="list-style-type: none"> ■ Identifies variations (genetic changes such as mutations) in the DNA that could contribute to disease
RNA Sequencing	<ul style="list-style-type: none"> ■ Identifies expression (the process that controls when and where proteins are made) levels of genes that can help identify abnormal patterns of expression that may contribute to disease.
Machine-Based Learning	<ul style="list-style-type: none"> ■ A computer-based approach to analyze a large amount of genetic information and answer a variety of questions related to genes or genetic abnormalities

In recent years, genomics (the study of the entire set of genes and chromosomes in an individual) has helped doctors define subsets of patients within lymphoma subtypes based on their genetic profiles, which sometimes helps to make decisions about treatments. It is important for patients to discuss the interpretation of diagnostic tests with their doctor.

Part 1 — Learning the Basics in Lymphoma

Chapter 4: Receiving a Diagnosis of Lymphoma

Receiving a cancer diagnosis can be overwhelming. It is perfectly normal to be shocked by the diagnosis, anxious about the future, and confused about the decisions that need to be made. This chapter will help patients and caregivers prepare for the start of treatment by explaining the next steps and providing tips for talking with doctors about any questions or concerns. Patients can also call the LRF's Helpline at (800) 500-9976 or email.

PATIENT TIP

First Steps to Take After Receiving a Diagnosis

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

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

Questions to Ask to Select the Best Medical Team

- What are the credentials (proof of their qualifications) of the doctor, the other members of the medical team, and the hospital or cancer center?
- In the case of adolescent or young adults, does the treatment center have a designated adolescent or young adult program or at least appropriate support services and experience with this age group?
- Is the doctor board certified as a medical oncologist or hematologist? Has he or she passed qualifying examinations by the American Board of Internal Medicine (organization driven by doctors) to approve their competency (skills) in these specialties?
- Is the oncologist a lymphoma specialist or a general oncologist?
- How much experience do the doctor and treatment center have in treating patients with lymphoma in particular?
- How many patients with this type of lymphoma are being treated at this center now?
- Does the doctor and/or center participate in clinical trials?
- Does the clinic or center have modern surgical facilities (operation rooms and tools) and diagnostic equipment (machines and tools for testing patients for their disease)?
- Is the doctor or clinic associated with any major medical center or medical school?
- In case of an emergency, what arrangements are made for medical assistance after hours and on weekends?
- Is my health insurance accepted at this center? Will the treatment center file claims for reimbursement and process the paperwork?
- What kind of patient resources (such as disease education materials) does the clinic or cancer center have for patients with lymphoma?
- If I see other specialists (cardiologist, endocrinologist, etc.), will the doctor coordinate my cancer care with my other doctors?

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

Mental Health Resources

While each experience is different, a lymphoma diagnosis often comes with mixed emotions. You may have a hard time trying to return to your routine as it was before you were diagnosed with lymphoma. For instance, some things you once did easily may now be challenging, or you may not have the same energy.

It is also very common for patients to feel anxious about the future and find it particularly hard not knowing what will happen next. While feelings of sadness and worry are normal and may even decrease over time, this can have a negative impact on your daily life. This can manifest in different ways, like trouble sleeping, changes in appetite, lack of interest in activities you previously enjoyed and inability to handle daily chores.

You may want to seek help from a trained counselor or a mental health professional if these symptoms last longer than two to three weeks. Mental health professionals can help you develop skills to reduce stress levels and cope with anxiety and depression. Complementary therapies such as acupuncture, meditation, and massage can also be beneficial in the management of the emotional effects of treatment.

Options for support networks to help navigate through this new stage are described on the next page.

Where Can I find Support?

Identify at least one person with whom you feel you can be honest about your feelings. You can open up to friends and family or join a support group for cancer survivors.

The LRF's one-to-one peer support program - Lymphoma Support Network - connects patients and caregivers with volunteers who have experience with lymphomas, similar treatments, or challenges, for mutual emotional support and encouragement. For more information about this program, please contact the LRF Helpline at (800) 500-9976 or helpline@lymphoma.org, or visit lymphoma.org/resources/supportservices/lrn.

Maybe you can find assistance with patient organizations offering support such as Cancer Care (call 800-813-4673) or visit cancercare.org/support_groups) and the Cancer Support Community (call (888) 793-9355 or visit cancersupportcommunity.org). For some individuals, faith and spirituality is the best route to find comfort. Some members of your place of worship may help you cope with your concerns, such as feeling alone, fear of death, searching for meaning, and doubts about faith. As mentioned earlier, speaking with a mental health professional can also be very helpful.

There are many options available, and it is important that you choose the one that is right for you. Having a reliable support network can provide a means to work through your negative emotions and help you cope with physical effects of treatment or deal with aspects of daily life (like family, school or work responsibilities). Follow-up care can also include home care, occupational or vocational therapy (therapy that helps patients returning to work following an injury or disease), pain management or physical therapy.

Part 1 — Learning the Basics in Lymphoma

Chapter 5: Work-Up Before Treatment Can Begin

After the initial diagnosis of lymphoma, the doctor may order other tests such as blood tests, genetic tests, imaging studies, heart and lung function tests, a bone marrow biopsy, and, less frequently, additional biopsies. This process is often called the *work-up* or *staging* studies. Some of these tests are needed to determine a person's disease stage - a measure of whether and how much the disease has spread to other parts of the body. Other tests check how the disease has affected a person's overall health and major organ functions. Together, these test results provide the information needed to help patients and their doctors decide on the best course of treatment. This chapter explains the reasons for the various tests, how these tests work, what to expect, and how lymphoma is staged.

What Evaluations Are Used in the Work-Up for Lymphoma?

Patients with lymphoma may undergo some or all of the following work-up tests before starting treatment. Many of these tests may be repeated during treatment.

- Physical examination with special attention to the size of the lymph nodes, liver, and spleen.
- Determination of general health status (also called *performance status* or *functional status*) to see how well a patient feels and how well they can carry out normal daily activities, such as getting washed and dressed, going to work, and doing chores.
- Identification of any *comorbidities* (other health problems besides lymphoma that patients may already have), such as diabetes, heart disease, or chronic lung disease, that could affect the choice of lymphoma treatment and the response to treatment.
- Questioning about the presence of fever, night sweats, weight loss, chills and itching (also called “B symptoms”).
- Complete blood count with differential.
- Blood tests to measure levels of beta-2 microglobulin (a prognostic marker [helps predicting the likely course of a disease]),

lactatedehydrogenase (LDH) (which is found in high levels in the blood of many patients with fast-growing tumors), and uric acid (which builds up in the blood due to the death of cancer cells and causes damage to the kidneys and other organs).

- Measurement of ESR.
- Testing for infection with HIV, hepatitis viruses, and other viruses.
- Measurement of levels of an antibody called immunoglobulin G (IgG) that helps fight infections.
- Reticulocyte count (to determine how fast the bone marrow is making red blood cells), and haptoglobin (to determine if red blood cells are being destroyed in the vascular system [network of arteries, veins, and capillaries that supplies blood to the tissues of the body]).
- Comprehensive metabolic panel which tests kidney and liver function.
- Pulmonary studies to evaluate lung function.
- CT and/or positron emission tomography-CT (PET-CT) scans of the neck, chest, abdomen, and pelvis. In general, the results of these imaging tests are the most important when determining the stage of lymphoma.
- Echocardiogram (ECHO) or multigated acquisition (MUGA) scan to evaluate heart function.
- Magnetic resonance imaging (MRI) is often used for suspected bone or nervous system (including brain) involvement.
- Excisional, incisional, or core needle biopsy (see Table 3.1 in Chapter 3 for more information about biopsies).
- Bone marrow aspiration and/or biopsy.
- Advanced diagnostic testing for chromosomal or genetic changes.
- Lumbar puncture (detailed in Table 5.2. below).

What Types of Imaging Tests May Be Used?

A doctor will order imaging tests to help identify areas of the body where the lymphoma has spread, and, later on, to determine how well treatment is working. Most of these tests are painless and require no anesthetic. Several types of imaging procedures (described in Table 5.1) may be needed to thoroughly evaluate the extent of disease.

Table 5.1. Types of Imaging Tests

Computed Tomography (CT) Scan	<ul style="list-style-type: none">■ A CT scan takes X-rays from many different angles around the body. A computer combines the pictures obtained from these different angles to give a detailed image of organs inside the body.■ Patients with lymphoma often have CT scans of the neck, chest, abdomen, and pelvis to find out how many lymph nodes are involved and how enlarged they are, as well as whether any internal organs are affected by the disease.■ Before a CT scan, the patient may be asked to drink a contrast liquid and/or receive an intravenous (IV; liquid that is infused directly into a vein) injection of a contrast dye that will more clearly outline any abnormal areas in the body.
Magnetic Resonance Imaging (MRI)	<ul style="list-style-type: none">■ An MRI uses magnets and radiofrequency waves to acquire images from different angles throughout the body. MRIs do not involve the use of radiation.■ An MRI can provide important information about tissues and organs, particularly the bones and nervous system that is not available from other imaging techniques, but it is also less helpful in other areas such as the lungs.■ Patients may receive IV contrast for MRIs, similar to CTs, but this contrast is made of a different substance. Patients who have an allergy to CT contrast, shellfish, or iodine can take MRI contrast.■ MRI scans cannot replace CT scans, because they do not provide clear images of lymph nodes as well as CT scans do.
Positron Emission Tomography (PET)	<ul style="list-style-type: none">■ A PET scan evaluates lymphoma activity in all parts of the body.■ Radioactive fluorodeoxyglucose (a type of sugar) is injected into the body. A positron camera is then used to detect radioactivity and produce cross-sectional (information collected from many different sections of the body) images of the body. This test relies on the fact that cancer cells metabolize (consume) sugar faster than normal cells, so that more consumption on a PET scan indicates more metabolic activity, suggesting the presence of the malignant (cancer) cells.■ While CT scans provide information about the size of a lymph node, PET scans can better indicate whether the lymph node contains active lymphoma cells.■ PET scans help distinguish growing tumors from an old injury or scar tissue (a mark left on the skin or body tissue while healing from an injury) and may be used to assess a patient's response to treatment.■ PET and CT scans are often combined into a single test (PET-CT), in which the CT procedure is slightly modified (changed) from that described above.

Why Might Another Type of Biopsy Be Needed?

Once the lymphoma diagnosis is made, the doctor may order other types of biopsies for additional pathology studies to see whether the disease has spread to other parts of the body (see Table 5.2).

Table 5.2. Other Types of Biopsies

Bone Marrow Aspiration and/or Biopsy	<ul style="list-style-type: none"> ■ Bone marrow is the soft, spongy material found inside bones. ■ Lymphoma can spread to the bone marrow or start in the bone marrow. ■ A bone marrow aspiration and biopsy may be done to determine the amount of disease in the bone marrow. ■ For the aspiration part of this procedure, the doctor cleans and numbs the skin over the hip, inserts a thin, hollow needle into the hip bone, and removes a small amount of liquid from the bone marrow using a syringe. ■ A bone marrow biopsy is often performed immediately after the aspiration and removes a piece of bone. ■ Although these procedures may be done without anesthesia some centers offer light sedation based on patient and doctor preference.
Lumbar Puncture (Spinal Tap)	<ul style="list-style-type: none"> ■ This procedure is used to determine whether the lymphoma has spread to the cerebrospinal fluid (CSF), the liquid that surrounds the brain and spinal cord. ■ This test is only used for patients with certain types of lymphoma or for those who have symptoms suggesting that the disease has reached the brain. ■ After numbing a small area of the lower back with a local anesthetic, the doctor uses a thin needle to remove a sample of fluid, which is sent to a laboratory for analysis.
Pleural, Pericardial, or Peritoneal Fluid Sampling	<ul style="list-style-type: none"> ■ This procedure is used to determine whether the lymphoma has spread to the lining of the chest or abdomen, where it can cause fluid to accumulate. ■ The doctor numbs the skin with a local anesthetic, inserts a small needle, and uses a syringe to remove a sample of the fluid for laboratory analysis. ■ The fluid is called pleural fluid when found inside the chest, <i>pericardial</i> fluid when found surrounding the heart, and <i>peritoneal</i> fluid when found inside the abdomen.

What Is Performance Status?

Performance status (PS) is a numerical rating of patients' general health and their ability to carry out normal daily activities (such as getting washed and dressed, going to work, and doing chores). Measurement of PS helps doctors determine which treatments a patient should get and how well the treatment is working; it also affects the eligibility for clinical trials. As shown in Table 5.3, PS can be graded using the Eastern Cooperative Oncology Group (ECOG; scientific organization that conducts cancer research) PS on a scale of 0–4, with the lower numbers indicating better health. Some institutions may prefer the Karnofsky PS, which uses a scale of 0-100, with higher numbers indicating better performance. Note that in younger patients, other PS scales may be used.

Table 5.3. The Eastern Cooperative Oncology Group (ECOG) Performance Status Scale

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

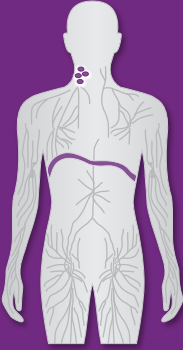
How is Lymphoma Staged?

Staging is used to describe how widely the lymphoma has spread. Doctors use the stage of disease, along with test results and other factors, to decide the best time to begin treatment and what treatments are likely to be the most effective for each patient.

Patients with Non-Hodgkin Lymphoma (NHL; except Chronic Lymphocytic Leukemia [CLL] and Small Lymphocytic Lymphoma [SLL]) and Hodgkin Lymphoma (HL) are staged using the Ann Arbor and Lugano systems. For adults, there are two main divisions of lymphoma (limited and advanced disease) and four stages designated by Roman numerals I through IV. Stages I and II are considered limited disease, although Stage II may be considered advanced in patients with bulky disease (tumors greater than 10 centimeters [~4 inches] wide). The presence of bulky disease is usually noted by adding the letter X to the stage. Stages III and IV are considered advanced disease. Although some patients have advanced lymphoma at the time they are diagnosed, their disease can often be successfully treated.

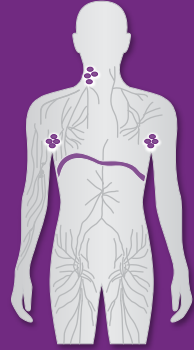
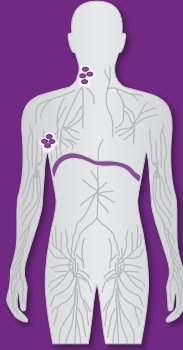
The Ann Arbor staging system has traditionally been used for staging lymphoma. Although this older staging system is still in use, a modification of the Ann Arbor staging system called the Lugano Classification was proposed in 2014. This system is shown in the figure on the next page.

STAGING OF LYMPHOMA (LUGANO CLASSIFICATION)



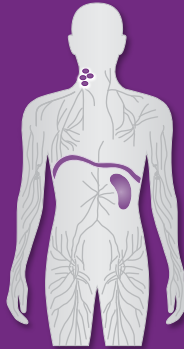
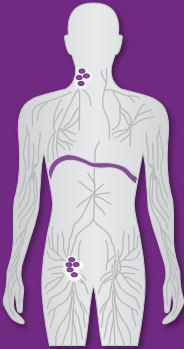
Stage I:

- Involvement of a single lymph node or group of adjacent nodes



Stage II:

- Involvement of two or more groups of lymph nodes on the same side of the *diaphragm* (muscle that separates the chest from the abdomen)



Stage III:

- Involvement of lymph nodes on both sides of the diaphragm, or
- Involvement of lymph nodes above the diaphragm plus spleen involvement



Stage IV:

- Widespread disease in lymph nodes, bone marrow, and organ involvement, such as liver or lungs

Stage I–IV lymphoma can be further classified based on whether “B symptoms” (fever, unexplained weight loss of greater than 10 percent

of body weight, and drenching night sweats) are present. An “A” designation means that the patient does not have “B symptoms,” while the “B” designation means that the patient does have “B symptoms” (see Table 2.1 in Chapter 2 for additional discussion of “B symptoms”).

In children, lymphoma is staged using a different system in which the lymphoma is classified as low-, intermediate-, or high-risk.

How is CLL/SLL Staged?

Because CLL/SLL is almost always widely spread through the body, a different staging system is used. Patients with CLL are staged using either the Rai staging system or the Binet classification system. Doctors in the United States tend to use the Rai system (Table 5.4), while the Binet system (Table 5.5) is more popular in Europe. Rai staging establishes risk groups (low, intermediate and high) that indicate the likelihood that the disease may worsen or require treatment. Both staging systems are designed to assess the quantity of the disease present and whether the disease is considered active or progressing (when the tumor is growing and/or spreading). It is important to note that patients with CLL/SLL do not necessarily progress through stages in order.

Table 5.4. The Rai Staging System for CLL/SLL

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

Table 5.5. The Binet Staging System for CLL/SLL

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

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

How is Treatment Determined?

The doctor will discuss the risks, benefits, and side effects associated with the different treatment choices applicable to the patient's particular situation. Patients and caregivers should share questions and concerns with the doctor so that together they can decide which option is best. It is always helpful for patients to write down their questions and go over them with their treating physician and/or healthcare team. The following questions can be used to guide the conversation and help patients make an informed decision.

PATIENT TIP

Questions to Ask Before Treatment Begins

- What is my exact diagnosis? What subtype of lymphoma do I have? May I have a copy of the report from the pathologist?
- What is the stage of my disease? In what area of the body is it specifically located?
- What are my prognostic factors, and what does that mean?
- What are my treatment choices? Which do you recommend for me and why? Would choosing one treatment prevent me from getting a different kind of treatment later on? How are the different treatments administered?

Questions to Ask Before Treatment Begins *(continued)*

- What is a clinical trial? Are clinical trials available that are studying new treatments for my type of lymphoma? Would a clinical trial be appropriate for me? How would I benefit? Are there any drawbacks of participating in a clinical trial?
- Do I need more than one type of treatment?
- What is the goal of treatment? What are the expected benefits of each type of treatment?
- How will we know if the treatment is working? What tests will I need to determine if treatment is working, and how often will I need to be tested?
- What are the risks and possible side effects of each treatment? Can these side effects be prevented or controlled?
- What should I do to take care of myself during treatment?
- Are there any late (appear only months, years or decades after treatment has ended) or long-term (occur during treatment and continue for months or years) side effects I should be aware of?
- Will treatment impact my fertility or ability to have children in the future? Is there time for sperm banking/egg harvesting before starting treatment?
- How long will the treatment last?
- What are the chances the treatment will be successful?
- How will the treatment affect my normal activities (for example, work, school, childcare, driving, sexual activity, and exercise)?
- Is there anything my caregiver needs to do to prepare to care for me while I undergo treatment?
- Will I be able to work during treatment? Will I be able to drive or take public transportation during my treatment?
- Should I take care of other medical or dental issues before I start treatment?
- How much will the treatment cost? Will my insurance cover some or all of it? What will my out-of-pocket costs be?

When to Get a Second Opinion?

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

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

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

Getting a Second Opinion

- Most hematologists/oncologists/lymphoma specialists associated with medical schools or cancer centers may be willing to provide a consultation and work together with a local oncologist to provide treatment and follow-up care.
- As part of the second opinion, another pathologist must review the tissue and blood samples to confirm the diagnosis. The pathology of lymphoma is often complex, and some pathologists may have limited experience analyzing lymphoma cells, so it is valuable to have the pathology results reviewed by an expert hematopathologist with extensive experience in lymphoma. In addition, it is essential to review radiology studies including CT scans and PET scans.

PATIENT TIP

Getting a Second Opinion *(continued)*

- To get a second opinion, you will need to provide the consulting doctor with a complete copy of all medical records, pathology samples, images and scans, and reports. When you set up the appointment, ask the office for a list of the materials you need to bring. It will be useful to keep your own copy of all these records in case you have questions or concerns later on.

To identify lymphoma specialists to contact for a second opinion:

- Ask your current doctors, family members, other patients, friends, and coworkers.
- Contact the patient referral service at your local hospital and at the nearest hospital associated with a medical school; many hospitals have online directories that can be searched to find a specialist in your area.
- Visit LRF's website at www.lymphoma.org or contact the LRF Helpline by phone (800-500-9976) or email (helpline@lymphoma.org). However, note that LRF does not provide a physician referral service.
- Visit the American Society of Clinical Oncology (ASCO) website at www.cancer.net to search their oncologist database.
- Visit the American Society of Hematology (ASH) web page at www.hematology.org/patients to search for hematologists with expertise in lymphoma.
- Visit the American Board of Medical Specialties (ABMS) Certification Matters website at www.certificationmatters.org to find out if doctors are board certified in a particular specialty.

How to Communicate with the Healthcare Team?

Patients and caregivers can ease some of their anxieties by establishing open, honest communication with their healthcare team regarding their diagnosis and treatment. This can help patients and caregivers better

understand the treatment regimen, including how it works, what tests are involved, and what side effects and complications may be associated with it.

A good first step is to write down all questions that come to mind. Before meeting with a doctor, nurse, or physician assistant, patients should consider organizing their questions into a list to bring to the visit. Since time with doctors, nurses, and physician assistants may be limited, patients should put the two or three most important questions at the top of their list. However, it is also important that a member of the patient's medical team reads through all the questions, because some may be more important than the patient realizes. LRF's mobile app, *Focus On Lymphoma*, can save and organize your list of questions to review with your healthcare team. For assistance with preparing questions to ask your healthcare team, contact the LRF Helpline at (800) 500-9976 or email helpline@lymphoma.org.

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

Oncology nurses are often well informed about cancer treatments and are an excellent source of information on a wide range of topics. Additionally, oncology social workers are available to assist with practical, emotional, and other support needs throughout the diagnosis and treatment process.

Although family members are often very concerned about their loved ones and want information concerning their care, confidentiality (privacy) rules prohibit doctors from giving out information to anyone without the patient's permission. **For efficiency, one family member should be chosen as the family contact, and the healthcare team should know that person's identity and contact information.** Most importantly, it is essential for patients and their caregivers or family contact person to have the names, addresses, office numbers, and emergency contact information

of the physicians involved in their care, so that they can communicate with the oncologist or hematologist regularly or in the event of an emergency. Adding these phone numbers directly to a cell phone may be helpful so patients or caregivers have the numbers directly on hand, if needed.

Open communication between patients and doctors is essential. The tips below can be used to help patients better communicate with their healthcare team. For assistance with communicating with your doctor, contact the LRF Helpline at (800) 500-9976 or email helpline@lymphoma.org.

PATIENT TIP

Communicating With Your Doctors

At home:

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

Communicating With Your Doctors *(continued)*

At your next doctor's visit:

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

How to Be a Self-Advocate?

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

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

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

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

Self-Advocacy

- Do not be afraid to ask your doctors or nurses questions about your care. An educated patient asking questions is not 'being a challenge to your physician' (or 'being a difficult patient').
- Learn more about lymphoma by asking your doctor for information and visiting reliable websites, such as LRF at www.lymphoma.org.
- Take advantage of counseling, support groups, nutritional counseling, fitness classes, expressive arts, and other services offered at your doctor's office, cancer center, or hospital.
- Consider joining LRF's Lymphoma Support Network, a nationwide peer support program that matches patients and caregivers with people who have had similar experiences. For information about the program, call (800) 500-9976 or email helpline@lymphoma.org.

PATIENT TIP

Adolescents and Young Adults

Adolescents and young adults (AYAs) ages 15 to 39 years are more likely to be diagnosed with lymphoma than younger children. The young age and maturity level of AYAs has a significant effect on their ability to manage their diagnosis and treatment. Factors such as the belief that “it cannot happen to me,” overall healthcare-related knowledge, unique concerns regarding body image and fertility issues, and relationship matters must all be considered when building a treatment plan for AYAs. Additional issues such as health insurance questions, potential financial hardships, and peer concerns must all be managed carefully.

There are many programs offered at cancer centers throughout the United States to help AYAs receive expert care for their disease and offer support for psychosocial and fertility/sexual health concerns. AYAs and their caregivers might want to consider the tips given below.

PATIENT TIP

Special Considerations for Adolescents and Young Adults

- It is critical to seek appropriate medical care instead of depending on internet platforms or social media as a primary source of information about their symptoms.
- It is important to try to overcome feelings of discomfort when discussing questions and concerns about a diagnosis, treatment, side effects, or even topics like sexuality with the doctor or healthcare team. Communication between patients and their doctors is extremely important and is always kept confidential.
- Some AYAs may feel more comfortable having their parents present during appointments, while others may prefer to speak with their doctors alone. It is also okay to ask their doctor about seeking a second opinion about their disease and/or treatment.
- It is a good idea for AYAs to speak with their doctors and healthcare team before treatment about what kinds of physical changes to expect so they are fully prepared if these changes arise.

Special Considerations for Adolescents and Young Adults *(continued)*

- AYAs and their caregivers are strongly encouraged to keep copies of all medical records by using the Lymphoma Care Plan document available on the Lymphoma Research Foundation's (LRF's) website at www.lymphoma.org/publications.
- It is important for AYAs to keep an open line of communication with their parents. However, many AYAs find people their age with cancer may be able to provide unique insights (understanding) and support. Many people also benefit from speaking with a therapist or counselor trained in cancer.
- Issues with fertility (ability to have children) should be discussed with the healthcare team at the time of diagnosis, because AYAs can take steps to preserve (keep) their fertility before their lymphoma treatment begins.
- Meeting with academic advisors or school administrators can help clarify the best course choices to complete educational goals. Federal laws allow students with disabilities (mental or physical condition that limits physical or sensation activities) to receive special accommodations (e.g., extended time to complete tests, audio textbooks, free tutoring, or modified housing).
- AYAs should consider arranging a meeting with their workplace's human resources representative to discuss possible and appropriate accommodations before and after treatment.
- Young adults in general are at risk of being uninsured. A provision of the Patient Protection and Affordable Care Act allows young adults to remain on their parent's health plans until the age of 26 years. Visit www.healthcare.gov/young-adults/ for more information. The Samfund provides support through direct financial assistance and free online support and education (www.thesamfund.org/).

Part 1 — Learning the Basics in Lymphoma

Chapter 6: What to Know Before Starting Treatment

What Are Prognostic Factors?

The characteristics that help predict a patient's prognosis (prediction of the likely course of a disease) are called *prognostic factors*. Favorable or good prognostic factors tend to be associated with better outcomes (overall longevity or good response to treatment), while unfavorable prognostic factors tend to be associated with worse outcomes.

To help doctors determine the best course of treatment, patients with lymphoma are grouped in prognostic categories reflective of their risk factors. Some of the adverse prognostic risk factors are listed in Table 6.1 and are derived from the International Prognostic Score, a model commonly used for HL and some forms of NHL. Note that the risk factors are somewhat different in pediatric patients. Keep in mind that no two patients are alike and that statistics can only predict how a large group of patients will do (not what will happen to an individual patient). The doctor most familiar with the patient's situation is in the best position to interpret the increased risk, understand how it applies to a patient's particular situation, and respond to any questions you might have.

Table 6.1. Adverse Prognostic Risk Factors

Stage	Adverse Prognostic Risk Factors
Limited Disease	<ul style="list-style-type: none"> ■ 60 years or younger. ■ <i>Bulky disease</i> (a tumor in the chest larger than one-third of the width of the chest, or a tumor at least 10 centimeters or 4 inches wide). ■ Cancer that has spread directly outside the lymph nodes to an adjacent site. ■ ECOG score ≤ 1 (patient able to function normally). ■ A high ESR: over 30 in someone with B symptoms, or over 50 for someone without B symptoms. ■ Abnormal levels of LDH. ■ Cancer in three or more nodal areas. ■ The presence of “B symptoms” (fever, weight loss, and night sweats).
Advanced Disease	<ul style="list-style-type: none"> ■ Male. ■ 45 years or older for HL, and older than 60 years for NHL. ■ Stage IV disease (lymphoma is in two or more organs outside of the lymph nodes). ■ Low blood albumin (a type of protein) level (less than 4 grams per deciliter). ■ Low hemoglobin level (less than 10.5 grams per deciliter) ■ High white blood cell count (15,000 cells per microliter or greater). ■ LDH above the upper limit of normal. ■ Low lymphocyte count (fewer than 600 cells per liter, or fewer than 8 percent of the total white blood cell count).

What is Decreased Blood Cell Production?

The bone marrow constantly produces red blood cells, white blood cells, and platelets. Several types of therapies for lymphoma temporarily interfere with the ability of the bone marrow to produce enough of one or more of these different types of blood cells. This is called *myelosuppression*. For this reason, chemotherapy is given in treatment cycles every 2 to 4 weeks (usually every 3 weeks), so that the body can recover from myelosuppression and other side effects.

To prevent and monitor myelosuppression, samples of a patient’s blood are tested with a CBC with differential, which measures the numbers of red blood cells and platelets, as well as all the different subtypes of white blood cells. These tests are usually done before and sometimes during the treatment process. Table 6.2 describes five of the most common conditions involving a decrease in blood cell production.

Table 6.2. Five Common Conditions Caused by Decreased Blood Cell Production

<p>Anemia</p>	<ul style="list-style-type: none"> ■ <i>Anemia</i> is a decrease in the number of red blood cells. ■ The most common marker of anemia is a low level of hemoglobin (protein present in red blood cells that is responsible for transporting oxygen). ■ Many chemotherapy drugs cause mild or moderate anemia. ■ Anemia can make people feel tired and short of breath, especially when it is severe. ■ Although seldom needed, drugs or red blood cell transfusions (a procedure in which donated blood is given intravenously to a patient can be used to treat severe anemia.
<p>Leukopenia</p>	<ul style="list-style-type: none"> ■ <i>Leukopenia</i> refers to a decrease in the number of leukocytes, or white blood cells. Leukocytes include lymphocytes (B-cells and T-cells), neutrophils, basophils, eosinophils, and monocytes. ■ Patients with low levels of neutrophils and lymphocytes are at increased risk of infections.
<p>Lymphopenia</p>	<ul style="list-style-type: none"> ■ <i>Lymphopenia</i>, also called lymphocytopenia, refers to a decrease in the number of lymphocytes. Lymphocytes produce antibodies that fight bacterial and viral infections. About 20 to 40 percent of white blood cells are lymphocytes. ■ Patients with low levels of lymphocytes (notably neutrophils [see below]) are at increased risk for infections.

Neutropenia

- *Neutropenia* refers to a decrease in neutrophils, the primary type of white blood cells that fight bacteria or other infections.
- Patients with low neutrophil counts are at higher risk for serious and even life-threatening infections. Symptoms of infection include fever and chills.
- During chemotherapy, doctors regularly monitor the patient's *absolute neutrophil count (ANC)*, the number of neutrophils in the peripheral blood. Because patients with an ANC below 500 cells per microliter are at particularly high risk for infections, doctors may decrease the chemotherapy dosage or delay the next treatment until the ANC returns to 500 or greater.
- Some patients require treatment with antibiotics and hospitalization to prevent or treat infections.
- To avoid a patient missing a dose of chemotherapy, doctors sometimes prescribe drugs like filgrastim (Neupogen, Granix, Zarxio) and pegfilgrastim (Neulasta) to reduce the time and intensity of neutropenia. These drugs can sometimes cause bone pain, which is usually temporary. Bone pain in the chest can simulate (imitate) heart disease; patients experiencing unexplained chest pain should seek medical attention immediately.
- Unless contraindicated (not recommended), bone pain can be managed with nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen (Advil and others) or naproxen (Aleve, Naprosyn), the antihistamine loratadine (Claritin, Alavert) or the analgesic acetaminophen (Tylenol).

Thrombocytopenia

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

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

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

Table 6.3. Terms Used to Describe Treatment and Its Outcomes

Cure	This word is used cautiously by doctors for subtypes of lymphoma that are potentially curable when there are no signs of the lymphoma reappearing after many years of continuous complete remission.
Complete Remission (CR)	This term is used when all signs of lymphoma have disappeared after treatment. It does not mean that the lymphoma is completely cured; rather, it indicates that the symptoms have disappeared, and the lymphoma cannot be detected using current tests (such as CBC or imaging methods). Relapses can occur in patients who experience CR. If complete remission is maintained for a long period, it is called a <i>durable remission</i> . A complete remission is a necessary first step for cure.
Partial Remission (PR)	This term is used if a lymphoma tumor has responded to treatment and shrunk to less than one-half of its original size.
Minor Response (MR) or Minor Improvement	This term is used if a lymphoma tumor has shrunk following therapy but is still more than one half of its original size.
Minimal Residual Disease (MRD)	This refers to the small number of cells that remain in the blood or bone marrow after the completion of treatment.
Stable Disease	This term means the disease has not gotten worse or better following therapy.
Disease Progression	This term means the disease has worsened or the lymphoma has grown or spread during therapy or observation. Other terms used to describe disease progression are relapse, treatment resistance, or resistant disease.
Primary or Frontline Therapy	This term is used to describe the first therapy that a patient receives. The choice of primary therapy depends on the type of lymphoma and the characteristics of the disease.
Refractory Disease	This term is used to describe lymphoma that does not respond to treatment or in which the response to treatment does not last very long.
Relapse	This term refers to disease that reappears or grows again after a period of remission.

Chapter 7: Treatment of Patients with Lymphoma

This chapter overviews the most common therapies currently used in the treatment of lymphoma. It is important to note that each type of lymphoma is different, and a treatment that works for one type may not necessarily be the best treatment choice for another type. For detailed descriptions of the treatments approved for each type of lymphoma, see Chapters 11 and 14.

Keep in mind that new therapies may have been approved by the U.S. Food and Drug Administration (FDA) since this guide was published. Read Chapters 12 and 15 to learn more about emerging treatments under investigation.

How are Drugs Given?

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

Most chemotherapy and monoclonal antibody drugs used to treat lymphoma are given by IV infusion. One main reason for this is that IVs provide flexibility in dosing, allowing the medication to be given all at once or slowly over many hours or days. Many chemotherapy drugs also cannot be given orally because they are not stable when turned into oral pills, they are not easily absorbed from the stomach and intestines into the bloodstream, or because they are too harsh for the stomach lining to tolerate. For some drugs, subcutaneous administration is possible, takes less time than IV methods, and avoids the need for a catheter (discussed below).

To administer IV drug therapy, a doctor, nurse, or physician assistant first inserts an IV catheter, which is a small flexible tube used to deliver medications into a vein. While some catheters are designed for short-term use, others can stay in the patient’s body for weeks or months, making it easier to administer multiple cycles of drug therapy over time. Several

commonly used types of catheters are described in Table 7.1. Patients and caregivers should discuss with their doctor which catheter, if any, would be best for their particular situation.

Table 7.1. Catheters Used to Administer Drug Therapy

Type of Catheter	Description	Advantages	Disadvantages
Peripheral Venous Catheter	A needle is used to insert a small, flexible tube into a small vein in the hand or arm.	Can be inserted quickly and easily by a nurse; no need for surgical insertion (the catheter is inserted into the body through a surgical opening). Good for a single infusion or other temporary use.	Cannot be left in place for more than three days at a time due to infection risk. Sterile dressing (clean pads or gauzes free of bacteria used to treat wound sites) needs to be kept clean and dry and replaced daily; the line needs to be injected periodically with a blood thinner (heparin) to prevent blockage. Cannot be used to draw blood for blood tests.
Peripherally Inserted Central Catheter (PICC line)	A long, thin plastic tube is inserted into a large vein in the arm, and the tip is guided up through the body into the large vein that enters the heart.	Can be kept in place longer than a peripheral venous catheter. Can be used to draw blood sample as well as to give drugs. Good for patients who need to have many short infusions or continuous infusions in a hospital or at home.	Not intended to remain in place as long as some surgically placed catheter types. Patients must learn to clean and take care of the external tubes to prevent infection and blockage. The tubes on the outside of the body make it more obvious that a catheter is in place.

Type of Catheter	Description	Advantages	Disadvantages
Tunneled Catheter (e.g. Hickman, Broviac)	One to three tubes are surgically inserted into the subclavian vein (underneath the collarbone). Six to 12 inches of tubing remain outside the skin in the upper chest wall.	Can be left in place for months or years with low infection risk. Easy to draw blood and give drugs using standard needles without having to pierce the skin each time.	Requires a small surgery to be inserted. Patients must learn to clean and take care of the external tubes to prevent infection and blockage. The tubes on the outside of the body make it more obvious that a catheter is in place.
Infusaport or Portacath	A catheter is surgically inserted through the subclavian vein (deep vein that moves blood back to the heart) and attached to a small reservoir (port) that lies under the skin. Nothing is visible on the outside except for a bump on the chest.	Patients do not have to do anything to care for it; a nurse keeps the line open by “flushing” it once a month with a small amount of injected liquid.	Requires surgery to be inserted. Patients must be injected through the skin covering the port with a special needle each time it is used. Can be hard to use to draw blood samples because blood clots often cause clogging. Requires another minor surgical procedure to be removed.

What Types of Treatments Can Be Used in Patients with Lymphoma?

There are four general types of approaches and treatments for patients with lymphoma:

- **Active surveillance**, also known as *watchful waiting* (observation with no treatment given), in which the patient is closely monitored to see if/when treatment should be started.

- Drug Therapy, including one or more of the following types of drugs:
 - Chemotherapy, which affects general cell growth and *proliferation* (the ability of cells to multiply).
 - Immunotherapy, which helps the body's immune system attach to the lymphoma cells (monoclonal antibodies, bispecific antibodies, antibody-drug conjugates, immune checkpoint inhibitors, radioimmunotherapy, and immunomodulators).
 - Targeted therapies, which affect specific molecules lymphoma cells use to grow and spread.
- Cellular therapy, which uses healthy human cells to replace or repair damaged tissues and/or cells:
 - Stem cell transplantation, which adds new stem cells back into the body after chemotherapy with or without radiation, replacing the cells that were destroyed and restoring the bone marrow's ability to make new blood cells.
 - Chimeric antigen receptor (CAR) T-cell therapy, which uses the patient's own T-cells to treat cancer.
- Radiation therapy, which uses high-energy radiation to kill lymphoma cells.

Each of these types of therapies is described below.

What is Active Surveillance?

With the active surveillance approach, patients' health and disease are monitored through regular checkups and periodic evaluation procedures, such as laboratory and imaging tests, but they do not receive any anti-lymphoma treatments. This approach is used in patients with *indolent* (slow growing) lymphomas who have no significant symptoms and would not yet benefit from treatment. Patients with non-aggressive disease continue to remain untreated if they do not show any signs or symptoms and there is no evidence that the lymphoma is growing or of significant concern. This approach may be used after the initial diagnosis of lymphoma, after *relapse* (disease returns after treatment), or for advanced lymphoma without indication for treatment, depending on the

situation. Patients are moved from active surveillance to treatment if they begin to develop lymphoma-related symptoms or if there are signs that the disease is clearly progressing. Before initiating treatment, a biopsy is always performed to confirm that the lymphoma is not transforming into an aggressive type of NHL.

As there are a number of reasons that your team may recommend initiation of treatment, it is important to report any new or ongoing symptoms or other medical concerns during follow-up visits with your oncology team. Throughout the observation period, biopsies could be performed when there are worrisome symptoms.

Although active surveillance may not be what a patient is expecting after the diagnosis of a lymphoma, many patients can safely delay initiation of treatment for 10 years or longer (some will never need treatment). As a result, it is important to discuss with your physicians what concerns you may have related to active surveillance so that these can be addressed.

Active surveillance most often is not a treatment option for patients with *aggressive* (fast-growing) NHL or HL. Usually, treatment for these patients should start as soon as possible after diagnosis. Active surveillance is common for patients with FL, MZL, and CLL/SLL or other indolent lymphomas, who do not show signs of active disease.

PATIENT TIP

Questions to Ask Before Starting Active Surveillance

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

What is Chemotherapy?

Chemotherapy drugs work by attacking lymphoma cells that may grow and multiply very quickly, which is a common characteristic of cancer cells. During chemotherapy, patients receive the treatment at certain intervals (periods), such as once every two, three, or four weeks, followed by a rest period. This regular treatment schedule is called a *cycle*. The length of the rest period and the number of cycles vary depending on the patient's disease and the types of drugs used.

Most patients with lymphoma who are treated with chemotherapy receive combination chemotherapy, meaning two or more drugs, instead of a single drug. The purpose of combining drugs is to increase how effectively they damage or kill cancer cells, to diminish the chances of the cancer cells becoming resistant to treatment, and to allow lower doses of each drug to be used to minimize side effects. The chemotherapy drugs are combined to create a *treatment regimen*—a specific schedule that determines which drugs are given on which days of each treatment cycle.

Oncology nurses are usually responsible for administering (giving) the chemotherapy prescribed. Most patients receive their chemotherapy treatments in an infusion center located in an outpatient (a patient who attends treatment at the clinic but does not stay overnight) clinic, hospital outpatient department, or doctor's office, but sometimes patients have to stay overnight in the hospital for their treatment.

Common chemotherapy regimens used for HL, NHL, are described in Chapters 14 (Table 14.1), and 11 (Table 11.1). While chemotherapy plays a very limited role in the treatment of CLL/SLL, it may be used in combination with other types of drugs (see Chapter 11, page 105).

What is Immunotherapy?

The term *immunotherapy* refers to treatments that help boost the body's own immune response. The immune system normally patrols the body for cancer cells, and when a cancer cell is detected, the immune system launches an attack to eliminate it. However, some cancer cells can "hide" from the immune system and can continue to grow in an uncontrolled manner until they form tumors or spread through the body.

Immunotherapies help the immune system recognize lymphoma cells and eliminate them from the body.

For more information, read the sections below about types of immunotherapy and see the *Immunotherapy and other Targeted Therapies* fact sheet on LRF's website at lymphoma.org/publications.

What are Monoclonal Antibodies?

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

Monoclonal antibodies are molecules that have been engineered (modified) in a laboratory to attach to one specific target (antigen) on the surface of cancer cells and they are effective for patients with cancer cells expressing that specific antigen. These antibodies are all made from one “mother” B lymphocyte, which is why they are called *monoclonal* (one clone). Once administered to the patient, the monoclonal antibodies travel through the blood and attach themselves to the cells that have antigens they recognize. This can either stop or slow down the growth of cancer cells that have that specific target, or it can trigger an “alarm” that makes it easier for other cells in the immune system to recognize and destroy the cancer cell. Before beginning monoclonal antibody therapy, patients are tested for a hepatitis infection (inflammation of the liver due to infection with hepatitis virus) which could become activated.

The monoclonal antibody therapies used in lymphoma treatment are given to patients as IV infusions or subcutaneously at a doctor's office or clinic. To prevent serious allergic reactions (life-threatening immune responses to a substance that is harmless in most people) to the infusion/injection, patients are given an antihistamine such as diphenhydramine (Benadryl), acetaminophen (Tylenol), and sometimes steroids before the antibody infusion/injection. Occasionally patients will experience an allergic reaction despite the pre-medications. Your treatment team will be prepared for this and will be able to control the allergic reaction in most cases and then continue the antibody therapy.

What are Bispecific Antibodies?

A bispecific antibody is an antibody that recognizes two different antigens, which can be on the same cell (a cancer cell) or two different cells (a cancer cell and a healthy immune cell). Bispecific antibodies used to treat lymphoma are called T-cell engagers and work by linking cancer cells to healthy immune cells. Like monoclonal antibodies, bispecific antibodies can be administered through an IV or subcutaneously.

What are Antibody-Drug Conjugates?

An antibody-drug conjugate (ADC) is a chemotherapy drug attached to a monoclonal antibody. The monoclonal antibody in the ADC recognizes and binds to a protein on the cancer cell surface. Once the ADC is inside the cell, the chemotherapy drug separates from the ADC and kills the cancer cell by damaging its DNA and/or blocking its ability to multiply. Similar to monoclonal antibodies, antibody-drug conjugates are given intravenously.

What are Immune Checkpoint Inhibitors?

Immune checkpoint inhibitors are monoclonal antibodies that recognize immune checkpoint proteins. Checkpoint proteins (such as CTLA-4/B7-1/B7-2 and PD-1/PD-L1) regulate (activate or slow down) the immune responses against the body's own cells. Some cancers can activate checkpoint proteins and thus escape being found and killed by the immune system. Checkpoint inhibitors block this mechanism, thereby restoring the immune system's ability to attack the cancer cells and rid them from the body. These drugs are given intravenously.

What is Radioimmunotherapy?

Radioimmunotherapy consists of a targeted antibody attached to a radioisotope (a particle that emits radiation). These drugs act as a "guided missile" to destroy lymphoma cells by attaching to them and delivering small doses of radiation.

What are Immunomodulators?

Immunomodulatory drugs have many ways of working against cancer cells. They cause tumor cells to die, help keep tumors from getting nutrients from the blood, and stimulate (activate) the immune system to help destroy cancer cells.

What are Targeted Therapies?

Targeted therapies are drugs that block molecules that cancer cells use to survive, grow and spread. By doing that, these drugs may kill the cancer cells, slow down or stop their growth, or stimulate the immune system to attack and kill cancer cells. Targeted therapies attack lymphoma cells in a more specific way than chemotherapy drugs. Common targeted therapies include:

- Kinase inhibitors, like tyrosin kinase (TK), Bruton's tyrosine kinase (BTK) and phosphatidylinositol-3 kinase (PI3K) inhibitors.
- Histone deacetylase (HDAC) inhibitors.
- Proteasome inhibitors.
- B-cell lymphoma-2 (BCL2) inhibitors.
- Enhancer of zeste homolog 2 (EZH2) inhibitors.
- Nuclear export receptor exportin 1 (XPO) inhibitors.
- Retinoid X receptor (RXR) activators.

What is Cellular Therapy?

Cellular therapy is the introduction of *autologous* (patient's own cells) or *allogeneic* (cells from a related or unrelated donor) healthy human cells into the patient's body for medical purposes. Both stem cell transplantation and chimeric antigen receptor (CAR) T are forms of cellular therapy, and many of the steps in the procedures are similar. Stem cell transplants use unmodified (original and unchanged) autologous or allogeneic stem cells. The cells used in CAR T-cell therapy are genetically reprogrammed (the DNA of the cells is modified) in the laboratory so they can recognize and fight cancer once they have been infused back into the patient. Currently approved CAR T-cell therapies are exclusively autologous, but approaches using allogeneic cells are under investigation.

What is CAR T Therapy?

CAR T-cell therapy is a type of personalized cellular immunotherapy in which a patient's T-cells are enhanced by the addition of an engineered gene. First, the patient's blood is collected, the T-cells are separated out, and the rest of the blood is returned to the patient. The T-cells are genetically modified to produce special receptors (proteins located

inside or outside the cell that receive signals from other cells or their environment) on their surface called *chimeric antigen receptors* (CARs), which allow them to recognize and kill malignant cells. Once the CARs are genetically engineered into the patient's T-cells and grown in the lab, the patient receives chemotherapy to reduce the number of immune cells in the body and allow the CARs to work. Finally, the patient receives the CAR T-cell therapy via IV infusion typically in an inpatient hospital admission. This process can take up to 2 to 4 weeks or longer from collection to cell infusion depending on the treatment and the insurance coverage. During this period, bridging therapies (such as chemotherapy or targeted therapies) can be used to control disease while waiting for CAR-T cell therapy and reduce the risk of CAR T-cell associated toxicities.

Once in the body, the genetically modified cells can grow to large numbers and increase the immune response by directly attacking the cancer cells. The CAR T-cells can survive for long periods of time and can multiply rapidly and increase in number if they detect cancer cells. This provides ongoing tumor control and protection against recurrence. Some patients have had very good responses to CAR T-cell therapy, with no tumor cells detected after treatment.

For additional information about the process of CAR T-cell therapy, please view the *Cellular Therapy* guide on LRF's website at lymphoma.org/publications.

PATIENT TIP

Questions to Ask Before Deciding to Undergo CAR T-Cell Therapy

- Would CAR T-cell therapy be a good treatment option for me?
- Are there any medical conditions that would exclude me from getting CAR T-cell therapy?
- What are the benefits and risks associated with this procedure?
- What complications may arise as a result of receiving CAR T-cell therapy?
- What are the short- and long-term side effects I might experience?

Questions to Ask Before Deciding to Undergo CAR T-Cell Therapy *(continued)*

- What can be done to lessen side effects?
- Would choosing this treatment prevent me from getting a different kind of treatment at a later point?
- How do I identify a certified treatment center?
- How long will I need to be in the treatment center?
- How long will I need someone to care for me after treatment?
- What are the responsibilities of a caregiver?
- Will my insurance cover this procedure?
- How sick will this treatment make me?
- How will we know if the treatment is working?
- How and for how long will the treatment affect my normal activities (e.g. work, school, childcare, driving, sexual activity and exercise?)
- What is my chance of full recovery?

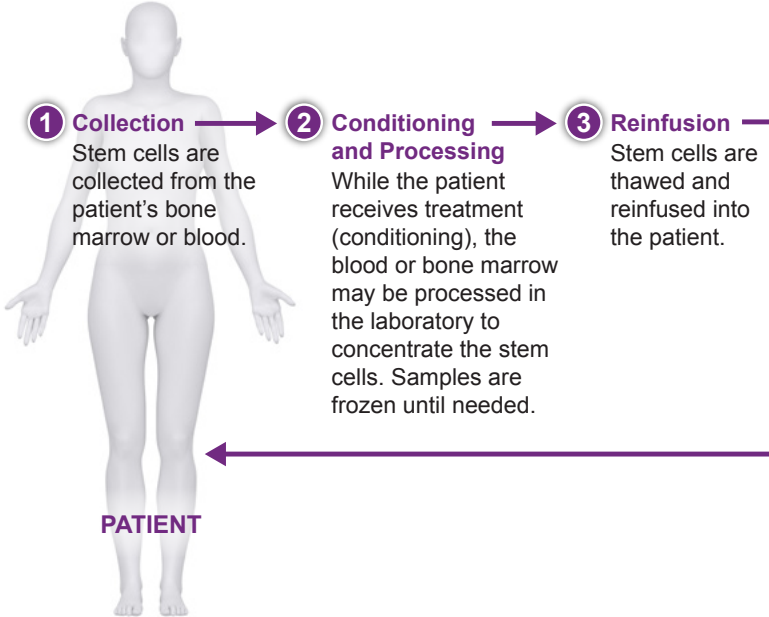
What is Stem Cell Transplantation?

A stem cell transplant adds stem cells (blood-forming cells) back into the body after chemotherapy with or without radiation, replacing the cells that were destroyed and restoring the bone marrow's ability to make new blood cells.

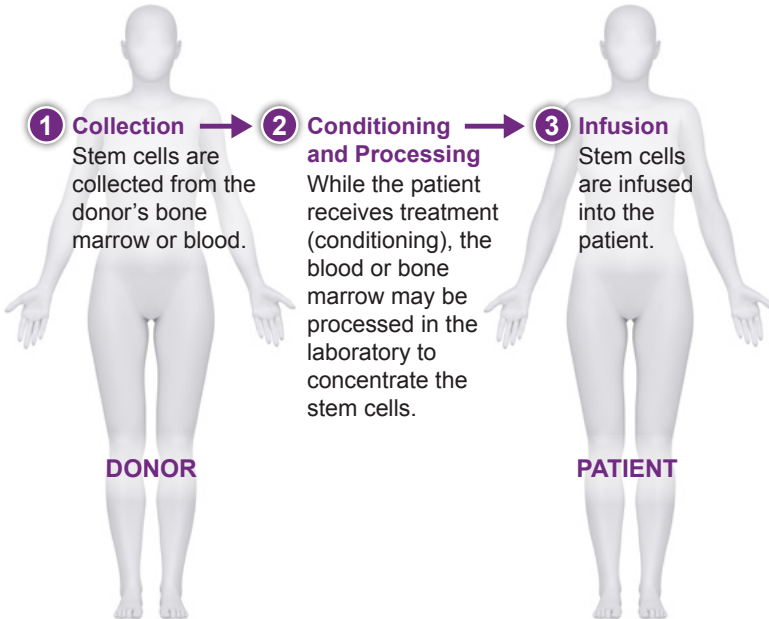
There are three types of stem cell transplantation that differ based on the source of the stem cells: *autologous*, *allogeneic* and *syngeneic*.

In an autologous stem cell transplant, patients are their own donor. Autologous stem cell transplantation is used in patients with cancers that are responding to chemotherapy. In an allogeneic stem cell transplant, the donor is another person who is genetically similar to the patient; this person is often a brother or sister. Donor stem cells may also come from the patient's child, the patient's parent, an unrelated person, or donated umbilical cord blood. In a syngeneic stem cell transplant, the donor is the patient's identical twin.

AUTOLOGOUS STEM CELL COLLECTION



ALLOGENEIC STEM CELL COLLECTION



The ability to transplant the patient's own stem cells (autologous stem cell transplant) allows doctors to use higher doses of chemotherapy than the body would normally tolerate, increasing the probability of treatment success.

Allogeneic transplants require immunosuppressant therapy to reduce the risk of rejection of the transplanted cells (also called 'graft') and graft-vs-host disease (GVHD, where the graft attacks the patient's healthy cells). In allogeneic, the donated cells recognize the patient's lymphoma cells as foreign and attack them, resulting in an immunologic response called the graft- versus-lymphoma (GVL) effect. For this reason, allogeneic transplantation generally controls lymphoma better than autologous transplantation. However, the toxicity and risk of complications is also higher in an allogeneic transplant, because the donor cells can recognize the normal organs of the patient as foreign and attack them, resulting in a serious complication known as GVHD. The decision about which treatment to use is a complex one and should involve a detailed discussion with the patient's doctor and a referral to a major cancer center with expertise in transplantation.

Because high-dose chemotherapy and stem cell transplantation place great strain on a patient's body, these types of therapies are not options for everyone. For patients who are not candidates for traditional stem cell transplantation, reduced-intensity transplantation (also called nonmyeloablative or mini-allogeneic stem cell transplantation) may be an option. This approach uses lower doses of chemotherapy and/or radiation prior to allogeneic transplantation. This option is available only for allogeneic transplantation, because it takes advantage of the GVL effect, in which the transplanted cells recognize the cancerous cells in the patient's body as foreign and destroy them. Patients receiving reduced-intensity transplants may avoid some of the side effects that occur with higher-dose chemotherapy. However, they are still at risk for serious side effects including GVHD, in which the donor immune cells attack the normal organs of the patient.

In deciding if transplantation is a good option, doctors consider the patient's subtype of lymphoma, health status, age, medical history, cancer stage, and response to previous therapy. For more information on stem cell transplants, view the Understanding Cellular Therapy guide on LRF's website at www.lymphoma.org/publications.

Suggested questions for patients to ask their healthcare team before deciding to undergo stem cell transplantation are listed below.

PATIENT TIP

Questions to Ask Before Deciding to Undergo Stem Cell Transplant

- What type of transplant is most appropriate for me (autologous or allogeneic) and why?
- If an allogeneic transplant is being considered, how will a donor be found? What are the risks associated with this procedure?
- What are the benefits associated with this procedure?
- What are the short-term and long-term side effects I might experience after my transplant?
- What can be done to lessen the side effects?
- Will getting a transplant make me ineligible for other lymphoma treatments or clinical trials?
- How long will I need to be in the hospital?
- Will I need someone to care for me after the transplant? For how long?
- Will my insurance cover this procedure?
- How will we know if the treatment is working?
- How and for how long will the treatment affect my normal activities (e.g., work, school, childcare, driving, sexual activity, and exercise)?
- What is my chance of making a full recovery?
- Is the transplant and related treatment part of a clinical trial? (see Chapter 8 for additional details on clinical trials).

What is Radiation Therapy?

Radiation therapy (also called *radiotherapy*) uses high-energy X-rays or other types of radiation to kill cancer cells and shrink tumors. The term is generally used to describe *external-beam radiotherapy*, in which a radiation beam is delivered from a machine to the tumor site. Radiation enters the cancer cells and damages its DNA which causes cell death.

Certain drugs can also deliver particles with radiation directly to tumor cells with little effect on the rest of the body (see the section “What is Radioimmunotherapy?” on page 56).

A radiation oncologist directs the radiation therapy. The part of the body selected to receive the radiation is called the *radiation field*. Doctors usually limit the radiation field to the affected lymph nodes, the areas immediately surrounding lymph nodes, or other areas where lymphoma is present. Doctors determine the type of radiation used and the size of the radiation field depending on the type of lymphoma and how much it has spread.

To prepare for radiation therapy, the healthcare team marks the patient's body with tiny ink dots to make sure that only the targeted areas receive radiation. On the day of treatment, lead shields (lead barriers that protect from radiation) are used to protect the normal tissues around the radiation field. The radiation team also uses plastic forms, pillows, and rolled blankets to make patients comfortable and keep them in the proper position.

Patients lie still on a table beneath a large machine that delivers the radiation painlessly. Once the preparations have been made, it takes only a few minutes to deliver the prescribed dose. The total dose of radiation is usually divided and given over one to six weeks. During and after radiation treatment, patients need to carefully protect the radiation site from exposure to sunlight. It is most important to not become sunburned.

Some of the more common types of radiation therapy and delivery methods used for lymphoma are shown in Table 7.2.

Table 7.2. Methods for Delivering Radiation Therapy

Image-Guided Radiation Therapy (IGRT)/ Tomotherapy	<ul style="list-style-type: none">■ Repeated imaging scans (CT, MRI, or PET) are used to track changes in tumor size and location throughout the course of treatment.■ Adjustments in dose and position can be made to accommodate changes in the tumor, which can increase the accuracy of treatment and reduce the area that is exposed to radiation, saving more normal, healthy tissue.
Three-Dimensional Conformal Radiation Therapy (3D-CRT)	<ul style="list-style-type: none">■ Very sophisticated computer software and advanced machines deliver radiation to a precisely shaped area of the body.
Electron Beam Radiation	<ul style="list-style-type: none">■ A machine sends <i>electrons</i> (negatively-charged particles) directly to the area where the lymphoma was found and sometimes to nearby lymph nodes.
Proton Therapy	<ul style="list-style-type: none">■ A charged particle called a proton is delivered in an external beam.■ Radiation exposure to normal surrounding tissues can be reduced, which allows higher doses to be delivered to the tumor.■ Useful therapy for patients with tumors near the heart, lungs, or esophagus that are difficult to treat with other radiotherapy methods.
Total Skin Electron Beam Therapy (TSBT)	<ul style="list-style-type: none">■ A weak radiation beam that only penetrates the outer layers of the skin is directed to the entire surface of the body.
Photopheresis or Extracorporeal Photochemotherapy	<ul style="list-style-type: none">■ A fraction of the patient's blood is removed from the body, treated with a chemical that makes lymphocytes more likely to die when exposed to ultraviolet radiation, and infused back into the patient.

Questions to Ask Before Starting Radiation Therapy

- What is the goal of my radiation therapy?
- How will the radiation be given?
- How long will the treatment last, and how often will it be given?
- How will I feel during the therapy?
- What are the side effects of radiation therapy? Is there anything that can be done to prevent them?
- Are there any lasting side effects?
- What can I do to take care of myself during and after the therapy?
- How will we know if the radiation therapy is working?
- How will the radiation treatment affect my normal activities (work, school, childcare, driving, sexual activity, and exercise)?

What is Palliative Radiation?

Radiation may be given to help ease symptoms caused by the spread of tumors in the body. This type of therapy is called *palliative radiation*. Growing tumors can press on organs and nerves, causing pain and inhibiting function. In this case, the goal of radiation treatment is to ease pain and improve the quality of life of the patient, not to cure the lymphoma or increase survival time. Palliative radiation is frequently combined with anti-inflammatory (agents that treat inflammation) and pain medications to maximize relief.

What is Maintenance Therapy?

Maintenance therapy refers to the ongoing treatment of patients whose disease has responded well to treatment. The purpose of maintenance therapy is to enhance (improve) response to prior therapy and to improve the duration (period) of remission.

Maintenance therapy in most situations consists of drugs given at the same doses during longer intervals than those used during initial therapy. Depending on the type of lymphoma and the drugs used, maintenance therapy may last for weeks, months, or even years.

For more information on maintenance therapy, see the Maintenance Therapy fact sheet on the Lymphoma Research Foundation's (LRF's) website at lymphoma.org/publications.

PATIENT TIP

Questions to Ask About Maintenance Therapy

- Is maintenance therapy an option for me?
- Why are you recommending maintenance therapy?
- Why are you NOT recommending maintenance for me?
- What are the benefits and risks?
- What are the long-term side effects of maintenance therapy?
- Am I at a higher risk for infections by being on maintenance therapy?
- How often and for how long will I receive this treatment?
- Does my insurance cover this treatment?
- Is this better for me than active surveillance?

What are Complementary and Alternative Therapies?

Complementary therapy can be used in addition to standard therapy to help improve a patient's quality of life and to relieve the effects of drug therapy, radiation, and surgery. Motivations for using complementary therapy include improved physical and emotional well-being. **Patients and caregivers should talk to their doctor and healthcare team before starting any form of complementary therapy, because a few of these approaches may interfere with their lymphoma treatment and make it less effective.** A healthy lifestyle that includes regular exercise may improve overall quality of life. Herbal therapies (the use of plants to treat disease), supplements, vitamins, and other oral agents (agents taken

by mouth), however, may cause side effects, have drug interactions (a reaction between the supplement and the treatment drug), or make their lymphoma treatment less effective. Marketing may suggest that a product is “natural” or that it is an “anti-cancer therapy” however, it is important to discuss this with the healthcare team to ensure the product is safe and compatible with the prescribed treatment plan. Open communication is essential to ensure safe, effective, and comprehensive care throughout treatment and following treatment as a cancer survivor. Table 7.3 outlines some forms of complementary therapy for cancer, also known as integrative medicine or integrative oncology.

Table 7.3. Forms of Complementary Therapy

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

Alternative therapy refers to any treatment used instead of standard therapy (accepted by medical experts as the proper treatment for a specific disease and used widely by healthcare professionals). Alternative therapies are not recognized as effective by the medical profession.

Currently, there are no proven alternative therapies to conventional cancer care for patients with lymphoma. Patients should not use alternative remedies to replace the care suggested by their doctors.

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

Chapter 8: Clinical Trials

What Is a Clinical Trial?

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

In the United States, a new drug must pass through a strict approval process governed by the U.S. Food and Drug Administration (FDA; organization responsible for the approval of drugs and making sure that drugs are safe and efficacious) before it can become a standard therapy for use in humans. The FDA-regulated approval process for drugs includes preclinical studies (done in laboratories) and clinical trials (done in hospitals and clinics). In addition to the FDA, all trials must be approved by an Institutional Review Board (IRB) consisting of experts (such as doctors and investigators) and lay persons (someone who is not an expert or does not have knowledge in a certain area) to ensure that the study is conducted in an appropriate and ethical (being right in the moral sense) manner that does not endanger patients in any way.

As shown in Table 8.1, there are four main types or phases of clinical trials. The first three (Phase I, Phase II, and Phase III) are usually required before a drug is considered for approval by the FDA. Certain drugs can receive a temporary approval through the FDA accelerated approval process until a phase III trial is completed. Phase IV trials, sometimes called postmarketing studies, are conducted after a drug has received FDA

approval. Each phase is designed to find out certain information, building upon the information learned from the previous phase. Patients may be eligible to participate in different types of clinical trials depending on their health status, type and stage of lymphoma, and the types of treatments, if any, they have previously received.

Table 8.1. The Four Main Phases of Clinical Trials

Phase	Purpose	Typical Number of Volunteer Patients
Phase I	<ul style="list-style-type: none"> ■ To identify a safe dose (the quantity and strength of a drug) of a new drug or combination of drugs (which may or may not be approved). ■ To decide on a dosing schedule for the drug. ■ To see which side effects are related to therapy. 	<ul style="list-style-type: none"> ■ 6-30 patients with 1 or more types of cancer.
Phase II	<ul style="list-style-type: none"> ■ To see if a new treatment is effective against a certain type of cancer at the dose determined in Phase I. ■ To confirm and learn more about the side effects identified in Phase I. 	<ul style="list-style-type: none"> ■ ~100 patients with the same type of cancer. ■ More than 100 patients in 2 study arms for randomized Phase II studies.
Phase III	<ul style="list-style-type: none"> ■ To compare the new treatment or new use of an existing treatment with the current standard treatments. ■ To obtain detailed information about how well the treatment works and the types and intensity of side effects it causes. 	<ul style="list-style-type: none"> ■ From 100 to several thousand patients with the same type of cancer. ■ Patients are randomly assigned to a treatment group (standard therapy or experimental treatment).
Phase IV	<ul style="list-style-type: none"> ■ To find out more information about the long-term safety and efficacy of a new treatment after it has already been approved by the FDA and is being used by patients outside of a clinical trial. 	<ul style="list-style-type: none"> ■ Several hundreds to several thousand patients with the same type of cancer.

Why Is a Placebo Sometimes Used in Phase III Trials?

A *placebo*, or sugar pill, is an inactive ingredient that is used as a comparator (to be used for comparison with trial drug) in some randomized (random selection of patients or samples) clinical trials. We know from past studies that sometimes patients in a clinical trial treated with placebo experience benefits from participation. This may happen because patients enrolled in clinical trials have extra people involved in their care, may have more frequent visits, or other reasons. For these reasons and others, having a group who receives the placebo for comparison can help researchers to better understand the additional benefits of the new treatment being tested. The placebo is made to have the same appearance as the experimental pill, or to have the same appearance as the experimental IV agent, so that patients cannot tell whether they have been randomized to the control group receiving the placebo or the experimental group receiving the new treatment. In some trials known as double-blind studies, the doctors and nurses also do not know who is receiving which type of treatment.

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

When Should a Clinical Trial Be Considered?

While clinical trials can be a good option for patients lacking treatment options at all stages of disease, they are often useful for patients with relapsed (disease came back after treatment) or refractory (disease does not respond to treatment) lymphoma.

Clinical trials offer both benefits (advantages) and risks (the possibility of having a negative effect). Patients in clinical trials who are randomized to the experimental group may be able to benefit from a new treatment that is not otherwise available to all patients. However, this new treatment may or may not be more effective than the standard therapy. At the very least, patients who are randomized to the control group receive the standard therapy that they would have received if they had not enrolled in the trial.

Another advantage of clinical trials is that the health of enrolled patients is monitored very closely. The healthcare team studying the new treatment can explain all the possible benefits and risks of a specific clinical trial.

Every clinical trial is led by a principal investigator who is a medical doctor. Clinical trials also have a research team that may include doctors, nurses, physician assistants, social workers, and other healthcare professionals. Patients usually continue regular visits with their current healthcare provider, who may work with the research team to ensure that any investigational treatment does not interfere with their current medications or treatments for other medical conditions. There are several entities and processes in place that supervise clinical trials to ensure the patients' safety. These include safety monitoring boards (a team of people responsible to monitor safety), monitoring processes and audits (inspections).

Lymphoma research continually evolves as doctors and scientists discover new therapies and more effective ways of giving existing treatments. Chapters 12 and 15 further describe clinical trials and some of the options currently under investigation.

What is Informed Consent in a Clinical Trial?

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

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

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

It is important for patients to remember that even after signing the consent form, they can leave the study at any time. If a patient leaves the study or decides not to take part in the study, the doctor can discuss other treatment options available. A list of questions patients might ask their doctor about clinical trials is provided on the following page.

What is the Cost of Participating in a Clinical Trial

Clinical trials are very expensive for the study sponsor (entity that pays for or contributes to the costs of the trial). However, the cost to the patient varies depending on the trial, who is sponsoring the trial, what portion of the trial-related expenses the sponsor has agreed to cover, and the patient's health insurance coverage. Patients should ask their doctor about the potential costs of participating in any clinical trial under consideration and what clinical trials may be most appropriate for them. Here are some additional sources of clinical trial information:

- The Lymphoma Research Foundation's Clinical Trials Information Service at (800) 500-9976 or helpline@lymphoma.org.
- The NCI's Cancer Information Center at (800) 4-CANCER or the NCI's Clinical Trials Referral Office at (888) NCI-1937.
- The NIH websites at www.cancer.gov and www.clinicaltrials.gov.
- Local cancer centers and institutions affiliated with universities.

Questions to Ask About a Clinical Trial

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

Part 1 — Learning the Basics in Lymphoma

Chapter 9: Hospital Admission

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

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

Treatment teams conduct daily visitation rounds to check on their patients. The nurse can tell patients when their doctor will come to see them that day. It is a good idea for family members to know when the doctor is likely to be coming so they can be there to ask questions.

Whether admitted through the emergency room or a direct admission, patients may be first evaluated by a hospitalist, resident physician or a nurse practitioner. Hospitalists are doctors employed by or consulting for the hospital. Their specialty is typically internal medicine (that covers a wide range of conditions affecting the internal organs) or in some cases for pediatric patients, they are pediatricians. Patients are also assigned a case manager (usually a nurse) who works with the patient's healthcare team.

What Should Patients Bring With Them to the Hospital?

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

What to Bring if You Are Being Admitted to the Hospital

- Identification (driver's license, student ID) and emergency contact information (relatives' and friends' names and phone numbers).
- List of all allergies and the reaction that occurs in response to exposure (especially important for latex and medication allergies).
- List of all current prescription medications (name, dosage, and frequency) as well as other products taken such as over-the-counter medications and vitamins (instead of making a list, you can also place all medications in a bag and bring them with you).
- List of all medical conditions other than lymphoma, such as hypertension, epilepsy, or an active ulcer.
- List of all surgeries (even elective plastic surgeries) regardless of how long ago they occurred.
- List of all physicians currently treating you.
- Copy of any completed advanced directives (a legal document that explains how you want medical decisions about you to be made if you cannot make the decisions yourself).
- All insurance cards, a checkbook, a credit card, and a minimal amount of cash.

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

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

What Are Patients' Rights?

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

Your Rights As a Patient

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

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

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

PATIENT TIP

What to Look for in the Hospital Informed Consent Document

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

What Do Patients Need to Know at Discharge?

When the patient is ready to be discharged, make sure the case manager addresses the subjects identified in the following patient tips. Patients should receive a list of symptoms that will prompt them to contact their doctors if they develop.

Topics for the Case Manager to Address Before Discharge

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

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

Part 2 — Non-Hodgkin Lymphoma

Chapter 10: What is Non-Hodgkin Lymphoma

What Is Non-Hodgkin Lymphoma?

Non-Hodgkin lymphoma (NHL) is not a single disease but rather a large group of closely related cancers that come from abnormal (cancerous) lymphocytes. In the United States, NHL (including chronic lymphocytic leukemia [CLL] and small lymphocytic lymphoma [SLL]) is the seventh most common type of cancer.

The World Health Organization (WHO) classifies more than 80 types of NHL, and ongoing research continues to identify new types. While these various types share many common features (characteristics), certain characteristics set them apart from each other, including:

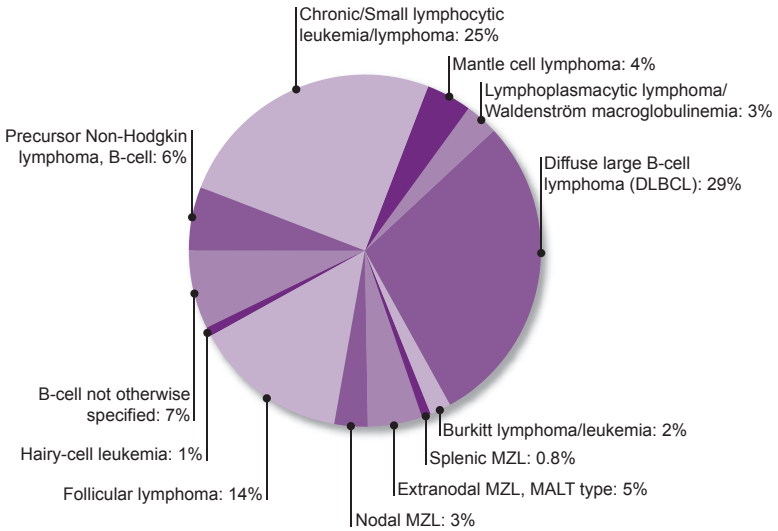
- How do cells appear when viewed under a microscope and what proteins appear on the surface of the cancer cells.
- How and where they grow in the body.
- How their growth and spread affects patients.
- How the disease should be treated.
- Likely outcome of treatment (curable vs not curable, but treatable).
- Genetic mutations (permanent change in the DNA [deoxyribonucleic acid]; the molecule that carries genetic information inside the cells) in the cells that make them become cancerous.

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

- B-cell lymphomas — These lymphomas develop from abnormal B lymphocytes and are the most common, comprising about 85 percent of NHL in the United States.
- T/NK-cell lymphomas — These lymphomas develop from abnormal T lymphocytes or NK cells. They are less common and constitute up to 15 percent of patients with an NHL diagnosis.

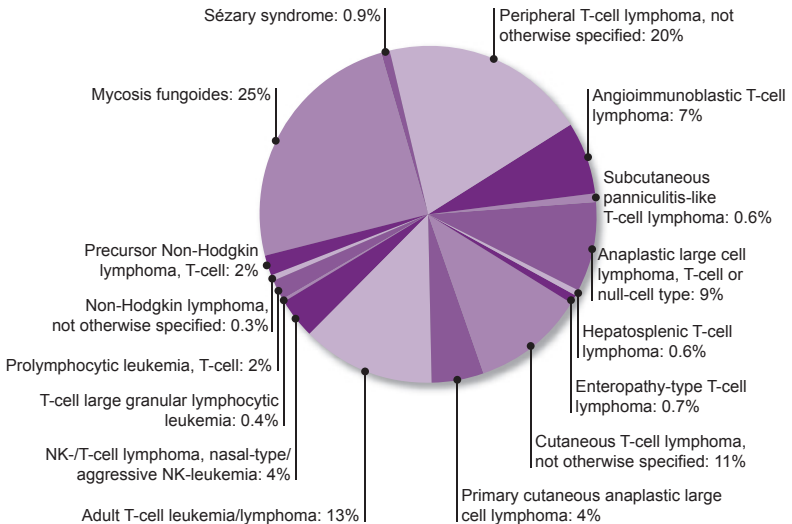
The following charts show how common or uncommon B- and T-cell NHLs are.

RELATIVE FREQUENCIES OF B-CELL LYMPHOMAS IN THE UNITED STATES



Percentages are based on the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) data, 2008-2017. Some very rare types are not shown in the graph.

RELATIVE FREQUENCIES OF T-CELL LYMPHOMAS IN THE UNITED STATES



Percentages are based on the National Cancer Institute's SEER data, 2008-2017. Some very rare types are not shown in the graph.

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

- *Indolent* (also called low-grade) lymphomas usually grow slowly and initially exhibit few symptoms. Indolent lymphomas are usually highly treatable. Patients can live a long time with these types of lymphomas because they tend to respond well to treatment and can remain in *remission* (disappearance of signs and symptoms) for many years or even decades. However, they are usually considered incurable because they can come back over time after the initial treatment. Some indolent lymphomas may transform (change) into aggressive lymphomas.
- *Aggressive* lymphomas grow and spread more quickly than indolent lymphomas. However, aggressive lymphomas can often be cured by treatments that kill rapidly dividing tumor cells.

The main types of indolent and aggressive NHLs are described in Table 10.1.

Pathologists (doctor who specializes in the diagnosis of diseases by studying the cells from a patient's body fluids and tissue samples) can tell the difference among the many different types of NHL by examining tissue, blood, and/or bone marrow (the spongy tissue inside the bones) samples under a microscope and by carrying out various laboratory tests. This information is critically important in deciding how to treat the disease in each patient.

Table 10.1. Main Types of Indolent and Aggressive NHLs (Listed Alphabetically)

Indolent NHLs	Aggressive NHLs
<ul style="list-style-type: none"> ■ Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). ■ Follicular lymphoma (FL). ■ Lymphoplasmacytic lymphoma/Waldenström macroglobulinemia (WM). ■ Marginal zone lymphoma (MZL). ■ Mycosis fungoides (MF) (subtype of cutaneous T-cell lymphoma). 	<ul style="list-style-type: none"> ■ Anaplastic large cell lymphoma (ALCL). ■ Angioimmunoblastic T-cell lymphoma (AITL). ■ Burkitt/Burkitt-like lymphomas. ■ Diffuse large B-cell lymphoma (DLBCL) ■ Lymphoblastic leukemia/lymphoma. ■ Mantle cell lymphoma (MCL) (can also present as indolent). ■ Peripheral T-cell lymphoma not otherwise specified (PTCL-NOS). ■ Primary mediastinal large B-cell lymphoma (PMBL) (subtype of DLBCL). ■ Sézary syndrome (advanced subtype of cutaneous T-cell lymphoma). ■ High-grade B-Cell Lymphoma (HGBCL).

NHL, non-Hodgkin lymphoma.

While NHL subtypes are separated into two categories (indolent or aggressive), in some cases an indolent lymphoma may become aggressive. This is called *transformed lymphoma* and occurs when an indolent lymphoma turns into a more aggressive one—for example, when FL transforms into DLBCL. In this case, slow-growing cells (FL cells) might be mixed with a few faster-growing cells (DLBCL cells). If the number of fast-growing cells increases, the lymphoma can begin to behave more like an aggressive type (grows faster). For more information about transformed lymphomas please see *Transformed Lymphoma* Fact Sheet on LRF's website at lymphoma.org/publications.

Indolent B-Cell Lymphomas

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

Chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) are types of NHL involving small lymphocytes that can be primarily in the bone marrow and blood (leukemia) or in the lymph nodes (lymphoma). While these used to be considered two separate diseases, recent research has shown that CLL and SLL are essentially the same disease. If the

malignant lymphocytes are found mainly in the lymph nodes, the disease is called SLL. If more than 5,000 malignant lymphocytes per microliter of blood are found in the bloodstream, then the disease is called CLL. Because they are essentially the same disease presenting in different parts of the body, the two terms are grouped together as CLL/SLL. The most common signs and symptoms of CLL/SLL are swollen lymph nodes, fatigue, shortness of breath, anemia, bruising easily, and frequent infections. However, many patients may not experience any signs or symptoms, so CLL/SLL is often discovered during routine blood tests and/or a physical examination. Half of CLL/SLL cases occur in people over the age of 68. Over time, CLL may occasionally progress to a more aggressive type of lymphoma, typically diffuse large B-cell lymphoma (DLBCL); this is called a Richter transformation (transformed lymphoma).

For a more detailed description of CLL/SLL, see Part 4 of this guide. Additional information about CLL is also available by viewing or reading our *Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma* or the *Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: Relapsed/Refractory* fact sheets on LRF's website at lymphoma.org/publications.

Follicular Lymphoma

Follicular lymphoma (FL) is the second most common type of NHL diagnosed each year in the United States. Although it can affect people at any age, the average age at diagnosis is 60. FL usually appears in lymph nodes throughout the body, causing them to swell. Often one of the first signs is painless swelling in the neck, underarms, or groin caused by these enlarged lymph nodes. FL sometimes transforms into a more aggressive form of disease, like DLBCL or highgrade B-cell lymphoma (HGBCL).

For more information on FL, please visit LRF's website at lymphoma.org/FL, or view the *Follicular Lymphoma* and *Follicular Lymphoma: Relapsed/Refractory* fact sheets on LRF's website at lymphoma.org/publications.

Lymphoplasmacytic Lymphoma/Waldenström Macroglobulinemia

Lymphoplasmacytic lymphoma is an uncommon B-cell lymphoma, with about 1,000 to 1,500 people newly diagnosed in the United States each year. The term Waldenström macroglobulinemia (WM) is also used to describe this type of lymphoma specifically characterized by abnormally

high levels of a protein called macroglobulin or immunoglobulin M (IgM) in the blood, which causes the blood to thicken (hyperviscosity). The disease usually is more common in older adults and is mainly found in the bone marrow, although it can sometimes be found in the lymph nodes and spleen. Symptoms include fatigue, increased bleeding or bruising easily, headache, dizziness, vision changes, abdominal pain, and swollen lymph nodes.

For more information on WM, view the *Waldenström Macroglobulinemia* fact sheet on LRF's website at lymphoma.org/publications.

Marginal Zone Lymphoma

Marginal zone lymphoma (MZL) is a B-cell lymphoma that accounts for approximately 9 percent of all B-cell NHLs. The median age at diagnosis is 67 and it is more common in men. There are three categories of MZL based on location in the body, however, for many patients more than one of these areas are involved:

(1) Extranodal MZL (ENMZL; also called mucosa-associated lymphoid tissue [MALT]) occurs outside the lymphatic system (such as the skin or stomach) and is the most common form of MZL; (2) nodal MZL occurs within the lymph nodes; and (3) splenic MZL (SMZL) occurs mostly in the spleen, blood, and bone marrow.

Many people who develop ENMZL have a history of inflammation, infection, or autoimmune disorders. For example, chronic inflammation associated with *Helicobacter pylori* (*H. pylori*; a bacteria that can cause *gastritis* (inflammation in the stomach) and stomach ulcers (a break in the lining of the stomach)) may increase the risk of developing ENMZL of the stomach lining (also called gastric MALT).

Patients with SMZL may have an enlarged spleen. These lymphomas have been associated with hepatitis C virus (HCV) infection, and they may improve or even completely resolve after treatment for the HCV infection.

For more information on MZL, view the *Marginal Zone Lymphoma* fact sheet on LRF's website at lymphoma.org/publications.

Indolent T-Cell Lymphomas

Cutaneous T-Cell Lymphoma

Cutaneous T-cell lymphoma (CTCL) is a general term for a group of T-cell lymphomas that originate in the skin. The disease affects men more often than women and usually occurs in patients over 50 years old. Most forms of CTCL begin as indolent diseases and involve only skin symptoms, although some more aggressive forms of CTCL can involve the blood, lymph nodes, and other organs.

Mycosis fungoides is the most common type of CTCL. This type of lymphoma is indolent and usually progresses very slowly. Patients with mycosis fungoides may have various types of lesions, including:

- Patches, which are usually flat, possibly scaly, and look like a rash.
- Plaques, which are thicker, raised, usually itchy lesions that are often mistaken for eczema, psoriasis, or dermatitis.
- Tumors, which are raised bumps that may ulcerate (become an open sore).

Sézary syndrome, which is an aggressive form of CTCL in which there are abnormal T-cells circulating in the blood, is discussed on page 91.

Primary cutaneous anaplastic large cell lymphoma (ALCL) limited to the skin is an uncommon type of CTCL and tends to be very indolent. The characteristic features of primary cutaneous ALCL include the appearance of single or multiple raised, red skin lesions that do not go away, have a tendency to ulcerate, and may itch. These ALCL lesions are tumors, and they can appear on the skin on any part of the body, often grow very slowly, and may be present for a long time before being diagnosed. Only about 5 to 10 percent of the time does primary cutaneous ALCL spread beyond the skin to lymph nodes or organs. If this occurs, it is usually treated like systemic (throughout the body) ALCL.

For more information on CTCL, view the *Cutaneous Lymphoma* fact sheet on LRF's website at lymphoma.org/publications.

Aggressive B-Cell Lymphomas

Burkitt Lymphoma

Burkitt lymphoma is a rare, highly aggressive B-cell NHL. There are three main types:

- Endemic Burkitt lymphoma is the most common type and is primarily found in Africa, where it is the most common childhood cancer. This type is rare outside of Africa. This type of lymphoma often starts as a tumor of the jaw or other facial bones.
- Sporadic Burkitt lymphoma occurs throughout the world. The sporadic form, seen in the United States, accounts for about one third of all childhood NHL. This type of lymphoma usually starts in the belly, causing a mass to develop in the abdomen.
- Immunodeficiency-related Burkitt lymphoma can occur in patients who have human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS); in those who have inherited immune deficiencies; and in those who take immunosuppressive medications to prevent rejection after organ transplant.

The Epstein-Barr virus (EBV) has been linked to the development of endemic and some cases of sporadic Burkitt lymphoma. However, not all with a history of EBV will develop Burkitt lymphoma.

Symptoms include weight loss, loss of appetite, fatigue, fever, and night sweats. Burkitt lymphoma is potentially curable when treated aggressively.

For more information on Burkitt lymphoma, view the *Burkitt Lymphoma* fact sheet on LRF's website at lymphoma.org/publications.

Diffuse Large B-Cell Lymphoma

Diffuse large B-cell lymphoma (DLBCL) is the most common type of lymphoma in the United States, accounting for about 30 percent of patients with NHL. The frequency of DLBCL generally increases with age, and more than half of patients are over the age of 60 at diagnosis. The first sign of DLBCL is usually rapid swelling in the neck, underarms, or groin or abdominal pain and swelling caused by enlarged lymph nodes. Other

symptoms include night sweats, chills, unexplained fevers, and weight loss, a cluster of symptoms called B symptoms.

DLBCL can develop in the lymph nodes or outside the lymphatic system, and often spreads throughout the body. Each variant of DLBCL may need a different treatment. Despite being aggressive, some patients have no signs of the disease after initial treatment, and many are cured.

For more information on DLBCL, view the *Diffuse Large B-Cell Lymphoma* and the *Diffuse Large B-Cell Lymphoma: Relapsed/Refractory* fact sheets on LRF's website at lymphoma.org/publications.

Primary Mediastinal B-Cell Lymphoma

Primary mediastinal B-cell lymphoma (PMBCL) is a form of DLBCL that appears in the thymus gland and is usually limited to the mediastinum (a compartment in the central part of the chest that includes the heart, thymus, esophagus, and trachea). Most patients are 30 to 40 years of age at diagnosis, and the disease is more common in women. Teenagers may also develop PMBCL. Symptoms include cough, chest pain, fever, weight loss, night sweats, shortness of breath, and superior vena cava syndrome, which is a swelling of the face and arms caused by compression of the major vein that delivers blood to the heart. Patients with PMBCL usually have a better prognosis than those with other subtypes of DLBCL, and most patients can be cured.

High-Grade B-Cell Lymphoma

High-grade B-cell lymphoma is a type of aggressive B-cell NHL that has two subtypes. The first is DLBCL/HGBCL with *MYC* and *BCL2* rearrangements, which occur when parts of *genes* (small portions of DNA that determine a person's traits) switch places within chromosomes. Other HGBCLs that do not have *MYC* and *BCL2* rearrangements are called HGBCL-NOS (not otherwise specified). While its appearance under the microscope usually resembles DLBCL, HGBCL is a very aggressive type of lymphoma and requires intensive treatment. HGBCL can arise from indolent lymphomas, in a process called transformation. Molecular tests (such as fluorescence in situ hybridization [FISH]) that allow doctors to check for abnormalities under a microscope are used to confirm a diagnosis of HGBCL.

For more information on HGBCL, view the *High-Grade B-Cell Lymphoma* fact sheet on LRF's website at lymphoma.org/publications.

Mantle Cell Lymphoma

Mantle cell lymphoma (MCL) accounts for 3 to 5 percent of all patients with NHLs. This type of lymphoma more frequently happens in men, and the median age at diagnosis is 60. At the time of diagnosis, MCL is often present in several lymph nodes, in one or more organs (often the intestines), and in the bone marrow. In a small number of patients, MCL may follow an indolent course that does not require therapy initially. Most cases, however, are more aggressive and require treatment as an aggressive lymphoma.

For more information on MCL, please view the *Mantle Cell Lymphoma* and *Mantle Cell Lymphoma: Relapsed/Refractory* fact sheets on LRF's website at lymphoma.org/publications.

Aggressive T-Cell Lymphomas

Peripheral T-Cell Lymphoma

Peripheral T-cell lymphoma (PTCL) is a group of T-cell lymphomas that account for over 50 percent of all cases of T-cell NHL in the United States. The most common subtypes include PTCL, not otherwise specified (PTCL- NOS), angioimmunoblastic T-cell lymphoma (AITL), and anaplastic large cell lymphoma (ALCL). PTCLs typically develop in tissues outside of the bone marrow (which is why they are called peripheral) such as the lymph nodes, spleen, gastrointestinal tract, and skin. Most are aggressive lymphomas. Some of these subtypes are described in more detail on the following pages.

For more information on all the subtypes of PTCL, visit LRF's website at lymphoma.org/PTCL, and view the *Peripheral T-Cell Lymphoma* fact sheet at lymphoma.org/publications.

Anaplastic Large Cell Lymphoma

Anaplastic large cell lymphoma (ALCL) is more common in younger people (children included), accounting for 2 percent of all NHLs and about 10-20 percent of all T-cell lymphomas. Initial symptoms of ALCL can

include fever, backache, painless swelling of lymph nodes, loss of appetite, and fatigue. ALCL occurs either systemically (throughout the body) or cutaneously (on the surface of the skin). Primary cutaneous ALCL is an indolent form of ALCL and is discussed on page 90. A rare type called breast implant associated ALCL can develop in women who have had silicone implants.

Patients with systemic ALCL are divided into two groups, depending on whether their cells contain an abnormal form of a protein called anaplastic lymphoma kinase (ALK). Systemic ALCL that is ALK positive, is more common in younger people, responds well to chemotherapy and may be curable. While ALK negative disease may initially respond to chemotherapy, it tends to relapse (disease returns after treatment) and often needs additional therapy such as stem cell transplantation (for more information, see the *Cellular Therapy* guide on LRF's website at lymphoma.org/publications).

For more information on ALCL, visit LRF's website at lymphoma.org/ALCL, and view the *Anaplastic Large Cell Lymphoma* fact sheet on LRF's website at lymphoma.org/publications.

Angioimmunoblastic T-Cell Lymphoma

Angioimmunoblastic T-cell lymphoma (AITL) affects approximately seven percent of all patients with T-cell NHL in the United States. Most patients are middle-aged to elderly and are diagnosed at a median age of 65 years old with advanced-stage disease. Symptoms may include high fever, night sweats, skin rash, and some types of autoimmune disorders, such as autoimmune hemolytic anemia (AIHA) and immune thrombocytopenia (ITP). As a result of these autoimmune disorders, the body's immune system destroys its own red blood cells (in the case of AIHA) or platelets (in the case of ITP). Initially, AITL may be treated with steroids to relieve symptoms such as joint inflammation, joint pain, and skin rash.

For more information on AITL, view the *Angioimmunoblastic T-Cell Lymphoma* fact sheet on LRF's website at lymphoma.org/publications.

Peripheral T-Cell Lymphoma, Not Otherwise Specified

Peripheral T-cell lymphoma not otherwise specified (PTCL-NOS) refers to a group of diseases that do not fit into any of the other PTCL subtypes. It is the second most common T-cell lymphoma, accounting for about 20 percent of all T-cell NHLs. It is also the most common subtype of PTCL. PTCL-NOS usually occurs in adults in their 60s. Although most patients with PTCL-NOS are diagnosed when their disease is still limited to the lymph nodes, sites outside the lymph nodes such as the liver, bone marrow, gastrointestinal tract, and skin may also be involved. This group of PTCLs is very aggressive, requires immediate treatment, and tends to relapse.

Sézary Syndrome

Sézary syndrome is a rare form of CTCL that affects both the skin and the blood. Most cases occur in adults older than 60. The most common symptoms are swollen lymph nodes and a red, very itchy rash that covers large portions of the body. Other common signs and symptoms of Sézary syndrome include hair loss, thickened skin on the palms of the hands and soles of the feet, and abnormalities of the fingernails and toenails. Abnormal T-cells, called Sézary cells, can be found in both the skin and the blood.

For more information about Sézary syndrome, please view the *Cutaneous T-Cell Lymphoma* fact sheet on LRF's website at lymphoma.org/publications.

Lymphoblastic Lymphoma

Lymphoblastic lymphoma is relatively rare and can originate from both B-cells and T-cells, but about 90 percent of all cases involve T-cells. T-cell lymphoblastic lymphoma cases represent about 30 percent of pediatric NHLs and tend to occur in males more often than females.

Lymphoblastic lymphoma is typically aggressive, and often occurs as a large mass in the chest. Experts suggest that lymphoblastic lymphoma and acute lymphoblastic leukemia (ALL) may come from the same type of cell and are different manifestations of the same disease. For this reason, lymphoblastic lymphoma is treated basically the same way as ALL. Symptoms include swollen lymph nodes, fever, night sweats,

unexplained weight loss, fatigue, and bruising easily. The complete remission (disappearance of signs and symptoms) rate after combination chemotherapy is usually very high.

What Are the Signs and Symptoms of NHL?

Some patients with NHL do not have any obvious signs or symptoms of the disease. Their doctors might detect the lymphoma during routine blood tests and/or a physical examination. For others, lymphoma is discovered when symptoms occur and patients go to the doctor because they are worried, uncomfortable, or not feeling well.

As shown in Table 10.2, NHL may cause different signs and symptoms depending on the type of NHL and where it is located in the body. Keep in mind that many of these signs and symptoms are not specific to NHL and can be caused by other conditions.

Table 10.2. Signs and Symptoms Commonly Found in Patients With NHL

Sign or Symptom	Possible Reason
<ul style="list-style-type: none">■ Lumps under the skin on the sides of the neck, above the collarbone, or in the underarms, elbows, or groin. Lumps are usually not painful.	<ul style="list-style-type: none">■ Lymph nodes, or “glands” swell up due to lymphoma. They can also swell in response to an infection or injury.
<ul style="list-style-type: none">■ Swollen, tender abdomen (“belly” or “stomach”)	<ul style="list-style-type: none">■ Enlarged lymph nodes in the abdomen.■ Accumulation (increase) of fluid in the abdomen.■ Enlarged liver or spleen.

Sign or Symptom	Possible Reason
<ul style="list-style-type: none"> ■ Abdominal pain, nausea, vomiting, decreased appetite, or feeling full more easily 	<ul style="list-style-type: none"> ■ Enlarged lymph nodes or an enlarged spleen pressing on nearby normal structures (for example, the diaphragm [a muscle below the lungs that is essential for the breathing process], nerves, or spine). ■ Enlarged spleen pressing on the stomach, which can make a person feel full after eating only a small amount of food. ■ Pain in the spleen (an organ of the immune system that stores white blood cells and helps fight infections). ■ Lymphoma in the intestine (or causing swelling near the intestine) possibly blocking bowel movements. ■ Lymphoma of the stomach or abdominal lymph nodes.
<ul style="list-style-type: none"> ■ Coughing, trouble breathing, or chest pain or pressure 	<ul style="list-style-type: none"> ■ Lymphoma in the chest, which may press on the windpipe or <i>bronchi</i> (tubes leading to the lungs). ■ Fluid around the lungs (<i>pleural effusion</i>).
<ul style="list-style-type: none"> ■ Headache, trouble thinking, weakness in extremities (legs or arms), personality changes, double or blurred vision, facial numbness, trouble speaking, or seizures (sudden, uncontrolled burst of electrical activity in the brain) 	<ul style="list-style-type: none"> ■ Lymphoma of the brain or spinal cord, or lymphoma originating in other parts of the body that has spread to or near the brain or spinal cord.
<ul style="list-style-type: none"> ■ Rash or itchy red or purple lumps or nodules under the skin 	<ul style="list-style-type: none"> ■ Lymphoma of the skin.
<ul style="list-style-type: none"> ■ “B symptoms,” including fever for no known reason, unexplained drastic weight loss, or drenching night sweats that soak clothing and sheets 	<ul style="list-style-type: none"> ■ Increased levels of inflammatory chemicals in the blood (molecules that initiate immune and inflammation responses called cytokines) that are released by lymphoma cells or by the immune system reacting to the lymphoma cells.
<ul style="list-style-type: none"> ■ Severe or frequent infections 	<ul style="list-style-type: none"> ■ Reduced ability to fight infection because of decreased numbers of certain types of white blood cells or low levels of gamma globulins (antibodies).

Why Do Some People Develop NHL?

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

Known risk factors for NHL include:

- A weakened immune system caused by an inherited (passed from parent to child) immune disorder (inability to produce an adequate immune response); for example, hypogammaglobulinemia (Wiskott-Aldrich syndrome) or infection with human immunodeficiency virus (HIV; the virus that causes AIDS).
- An autoimmune disease (the immune system attacks the body's own organs, tissues or cells; for example, Crohn's disease, rheumatoid arthritis, systemic lupus erythematosus, Sjogren's syndrome, or psoriasis).
- Treatment for autoimmune diseases, especially with methotrexate and tumor necrosis factor (TNF)-inhibitor therapy as immunosuppression therapies.
- Treatment with certain drugs used after solid organ (such as the liver or kidney) transplantation.
- Infections with certain viruses (for example, human T-cell lymphotropic virus type 1 [HTLV-1], EBV or HCV).
- Infections with certain bacteria such as with *Helicobacter pylori*.
- Family history of lymphoma (first degree relative, like parent, child or sibling).
- Older age (like most cancers, NHL is much more common in adults older than 60, although NHL also occurs in children and younger adults).
- Male sex (for unknown reasons, NHL is slightly more common in men than in women).

- Exposure to certain chemicals (like benzene), herbicides (for example, Agent Orange) and pesticides, and some chemotherapy drugs used to treat other cancers or autoimmune diseases.
- Treatment with radiation therapy for other cancers, including NHL.

NHL cannot be caused by injury and cannot be caught by someone who has the disease. While parents, children, and siblings of patients with NHL have a slightly increased risk of developing this disease compared with the general population, there are not clearly identifiable genetic or hereditary factors that can predict this slightly increased risk. Therefore, routine screening for NHL among the immediate family members of patients with NHL is not recommended.

What Are Prognostic Factors?

Favorable or good prognostic factors (characteristics that predict how well the patient will do) tend to be associated with better outcomes (like survival or good response to treatment), while unfavorable or poor prognostic factors tend to be associated with worse outcomes. Various prognostic indicators have been developed for different forms of NHL.

What Is the International Prognostic Index?

The International Prognostic Index (IPI) was first developed for aggressive lymphomas such as DLBCL. The IPI is based on five factors represented by the acronym APLES: age, performance status (PS; measurement of level of body function and capacity for self-care), lactate dehydrogenase (LDH; protein that rises in the blood in case of fast-growing NHL) level, number of extranodal sites (lymphoma cells located outside of the lymph nodes), and stage (as shown in Table 10.3 below). The IPI score assigns 1 point for the presence of each negative prognosis factor, which adds up to make a final score (from 0 to 5). Risk groups are based on the final score and are categorized as low risk (0/1), low-intermediate risk (2), high-intermediate risk (3) and high risk (4/5). Updated versions of this score include the revised IPI (R-IPI) and the National Comprehensive Cancer Network IPI (NCCN-IPI). Other prognostic indicators have been developed for specific NHL subtypes. The Follicular Lymphoma International Prognostic Index (FLIPI) is based on the original IPI but excludes PS and adds hemoglobin

(protein present in red blood cells that transports oxygen) level as a risk factor. Other indicators have been developed for MCL and MZL.

Table 10.3. International Prognostic Index for Diffuse Large B-cell Lymphoma and NHL

Factor	Better Prognostic Factors	Worse Prognostic Factors
Age	60 years or younger	Older than 60 years
Performance Status (PS)	ECOG score ≤ 1 (Patient able to function normally)	ECOG score ≥ 2 (Patient needs help with daily activities)
Lactate Dehydrogenase (LDH) Level	Normal	Above upper limit of normal
Extranodal Sites	Lymphoma is only in the lymph nodes or in only one area outside of the lymph nodes	Lymphoma is in two or more organs outside of the lymph nodes
Stage	I or II	III or IV

What Is Relapsed or Refractory NHL?

In some patients who receive treatment, NHL can relapse (come back after treatment) or become refractory (disease does not respond to treatment). There are many treatment options for patients with relapsed or refractory NHL. Exactly what type of treatment is best for individual patients with relapsed or refractory NHL depends on such factors as the subtype of NHL, the patient’s age and overall health, the extent and location of disease, the type of previous therapies received, and the length of response to previous therapies.

Many of the therapies for newly diagnosed NHL can be effective in patients with relapsed or refractory NHL. Many treatment centers will also consider using autologous or allogeneic stem cell transplantation for patients with relapsed or refractory NHL, especially aggressive NHL, depending on the patient’s age, overall health, and other characteristics (see page 59 in Chapter 7 for further information on stem cell transplantation).

Patients who do not go into complete remission (CR, no signs or symptoms of disease) following treatment or who do not respond to treatment should not lose hope. Lasting responses to therapy may be achieved after a diagnosis of relapsed or refractory disease. Many patients seek second opinions when newly diagnosed, and some choose to do so if their disease relapses or is considered refractory.

While clinical trials can be a good option for patients at all stages of disease, they are often especially useful for patients with relapsed or refractory NHL, because many of the novel therapeutic agents (new drugs) most recently approved by the U.S. Food and Drug Administration (FDA; organization responsible for the approval of drugs and making sure that drugs are safe and effective) and those being investigated in clinical trials are used specifically for these patients. Lymphoma research continually evolves as doctors and scientists discover new therapies and more effective ways of giving existing treatments. Chapter 8 in Part 1 further describes clinical trials and some of the options currently under investigation.

Part 2 — Non-Hodgkin Lymphoma

Chapter 11: Treatments for Non-Hodgkin Lymphoma

This chapter reviews the most common therapies currently used in the treatment of NHL. Keep in mind that new therapies may have been approved by the FDA since this guide was published. Read Chapter 12 to learn more about emerging treatments under investigation.

There are important differences between different types of NHL, and a treatment that works for one type of NHL may not necessarily be the best treatment choice for another type. There are also small but important differences in the lymphoma cells found in different patients diagnosed with the same type of NHL. Because of these differences, a treatment that may work very well in one patient may not have the same positive effect in another.

What Types of Treatments Are Used in Patients With NHL?

There are four general types of approaches and treatments for patients with NHL:

- *Active surveillance*, also known as *watchful waiting* (observation with no treatment given), in which the patient is closely monitored to see if/when treatment should be started.
- Drug therapy, including one or more of the following types of drugs:
 - Chemotherapy, which affects general cell growth and *proliferation* (the ability of cells to multiply). Most patients with lymphoma receive combination chemotherapy (two or more drugs) instead of a single drug (monotherapy). The most common chemotherapy regimens are detailed in Table 11.1.
 - Immunotherapy, which helps the body's immune system attack lymphoma cells (monoclonal antibodies, antibody-drug conjugates [antibody combined with treatment drug], bispecific antibodies, immune checkpoint inhibitors, immunomodulatory drugs and radioimmunotherapy).

- Targeted therapies, which affect special characteristics or internal workings of lymphoma cells. These drugs may kill, slow down, stop the growth of cancer cells or help the immune system fight against cancer cells.
- Radiation therapy, which uses high-energy radiation to kill lymphoma cells.
- Cellular therapy (such as stem cell transplantation and chimeric antigen receptor [CAR] T-cell therapy).

Each of these types of therapies is described in detail in this chapter. Treatment side effects are detailed in Part 5 of this guide (pages 180-207).

Active Surveillance

With the active surveillance approach (watchful waiting), patients' health and disease are monitored, but they do not receive any anti-lymphoma treatments. For more information about active surveillance see Chapter 7 of this guide.

This approach is used in patients with indolent, non-aggressive NHLs (i.e., FL, MZL, or SLL) who have no significant symptoms and would not yet benefit from treatment. Patients with non-aggressive disease continue to remain untreated if they do not show any signs or symptoms and there is no evidence that the lymphoma is growing or of significant concern. This approach may be used after the initial diagnosis of NHL or after relapse, depending on the situation, but once a patient's disease demonstrates a need for therapy, a treatment course would begin. Active surveillance may also be used for advanced NHL without indications for treatment. As there are a number of reasons that your team may recommend initiation of treatment, it is important to report any new or ongoing symptoms or other medical concerns during follow-up visits with your oncology team.

Although active surveillance or watchful waiting may not be what a patient is expecting after the diagnosis of a lymphoma, many patients can safely delay initiation of treatment for long periods of time. As a result, it is important to discuss with your physicians what concerns you may have related to active surveillance so that these can be addressed.

Active surveillance most often is not a treatment option for patients with aggressive NHL or Hodgkin lymphoma (HL). Usually, treatment for these patients should start as soon as possible after diagnosis.

Chemotherapy

For the treatment of some B-cell lymphomas, a standard combination chemotherapy regimen is known as CHOP, which includes the drugs cyclophosphamide (Cytoxan, Neosar), doxorubicin/hydroxydaunorubicin (Rubex, Adriamycin PFS), vincristine (Oncovin and others), and prednisone (Deltasone and others). CHOP has been administered for more than 25 years in patients with lymphoma. In some cases, your team may recommend a modified version of CHOP based on your age, other medical conditions, or factors associated with your specific lymphoma case.

In the vast majority of cases of B-cell NHL, doctors add a fifth agent, an anti-CD20 monoclonal antibody (an engineered molecule that is not considered a chemotherapy) called rituximab (Rituxan), to this combination to create R-CHOP. Many of the chemotherapy treatment regimens in Table 11.1 are combined with rituximab (Rituxan) to treat B-cell NHL. In these cases, the treatment regimens have an “R” added to their name (not shown in the table). Rituximab is discussed in greater detail on page 106.

Sometimes other chemotherapy regimens and anti-CD20 antibodies (such as obinutuzumab [Gazyva]) are used. Some of these alternative regimens are shown in Table 11.1.

For T-cell lymphomas, CHOP is the most frequently used frontline (initial) treatment, but CHOEP or CHP, with the antibody-drug conjugate (a monoclonal antibody attached to a chemotherapy drug) brentuximab vedotin (Adcetris), may also be used.

Table 11.1 lists the common chemotherapy drugs and regimens used for NHL. This list is subject to change as the FDA approves new lymphoma treatments.

Table 11.1. Common Chemotherapy Regimens For NHL

Drug or Regimen Abbreviation	Generic Name of Drugs (Brand Name)	How Treatment is Given
B	■ Bendamustine (Treanda, Bendeka)	IV infusion
BV	■ Brentuximab vedotin (Adcetris)	IV infusion
C	■ Cyclophosphamide (Cytoxan, Neosar)	IV infusion or oral tablets
CDOP	■ Cyclophosphamide (Cytoxan, Neosar) ■ Liposomal doxorubicin (Doxil) ■ Vincristine (Oncovin and others) ■ Prednisone (Deltasone and others)	IV infusion IV infusion IV infusion Oral tablets
CEOP	■ Cyclophosphamide (Cytoxan, Neosar) ■ Vincristine (Oncovin and others) ■ Prednisone (Deltasone and others) ■ Epirubicin (Ellence)	IV infusion IV infusion Oral tablets IV infusion
CEPP	■ Cyclophosphamide (Cytoxan, Neosar) ■ Etoposide (VePesid, Toposar, Etopophos) ■ Prednisone (Deltasone and others) ■ Procarbazine (Mutalane)	IV infusion IV infusion or oral capsules Oral tablets Oral capsules
CHOP	■ Cyclophosphamide (Cytoxan, Neosar) ■ Doxorubicin/hydroxydaunorubicin (Rubex, Adriamycin PFS) ■ Vincristine (Oncovin and others) ■ Prednisone (Deltasone and others)	IV infusion IV infusion IV infusion Oral tablets
CHOEP	■ Cyclophosphamide (Cytoxan, Neosar) ■ Doxorubicin (Adriamycin) ■ Vincristine (Oncovin and others) ■ Etoposide (VePesid, Toposar, Etopophos) ■ Prednisone (Deltasone and others)	IV infusion IV infusion IV infusion IV infusion or oral capsules Oral tablets
CHP	■ Cyclophosphamide (Cytoxan, Neosar) ■ Doxorubicin (Adriamycin) ■ Prednisone (Deltasone and others)	IV infusion IV infusion Oral tablets

Drug or Regimen Abbreviation	Generic Name of Drugs (Brand Name)	How Treatment is Given
CODOXM-IVAC	<ul style="list-style-type: none"> ■ Cyclophosphamide (Cytoxan, Neosar) ■ Vincristine (Oncovin and others) ■ Liposomal doxorubicin (Doxil) ■ Cytarabine/high-dose Ara-C (Cytosar-U, Tarabine PFS) ■ Methotrexate (Mexate and others) ■ Ifosfamide (Ifex) ■ Etoposide (VePesid, Toposar, Etopophos) 	<p>IV infusion</p> <p>IV infusion</p> <p>IV infusion</p> <p>IV infusion</p> <p>IV infusion</p> <p>IV infusion</p> <p>IV infusion or oral capsules</p>
CVP (COP)	<ul style="list-style-type: none"> ■ Cyclophosphamide (Cytoxan, Neosar) ■ Vincristine (Oncovin and others) ■ Prednisone (Deltasone and others) 	<p>IV infusion</p> <p>IV infusion</p> <p>Oral tablets</p>
DHAP	<ul style="list-style-type: none"> ■ Dexamethasone (Decadron and others) ■ Cytarabine/high-dose Ara-C ■ Cisplatin (Platinol, Platinol-AQ) 	<p>Oral tablets or IV infusion</p> <p>IV infusion</p> <p>IV infusion</p>
DHAX	<ul style="list-style-type: none"> ■ Dexamethasone (Decadron and others) ■ Cytarabine (Cytosar) ■ Oxaliplatin (Eloxatin) 	<p>Oral tablets or IV infusion</p> <p>IV infusion</p> <p>IV infusion</p>
DICE	<ul style="list-style-type: none"> ■ Dexamethasone (Decadron and others) ■ Ifosfamide (Ifex) ■ Cisplatin (Platinol) ■ Etoposide/VP16 (VePesid, Toposar, Etopophos) 	<p>Oral tablets or IV infusion</p> <p>IV infusion</p> <p>IV infusion</p> <p>IV infusion or oral capsules</p>
EPOCH	<ul style="list-style-type: none"> ■ Etoposide/VP16 (VePesid, Toposar, Etopophos) ■ Prednisone (Deltasone and others) ■ Vincristine (Oncovin and others) ■ Cyclophosphamide (Cytoxan, Neosar) ■ Doxorubicin/hydroxy daunorubicin (Adriamycin/Adriamycin PFS) 	<p>IV infusion or oral capsules</p> <p>Oral tablets</p> <p>IV infusion</p> <p>IV infusion</p> <p>IV infusion</p>

Drug or Regimen Abbreviation	Generic Name of Drugs (Brand Name)	How Treatment is Given
ESHAP	<ul style="list-style-type: none"> ■ Etoposide/VP16 (VePesid, Toposar, Etopophos) ■ Methylprednisolone (Medrol and others) ■ Cytarabine/high-dose Ara-C (Platinol, Platinol-AQ) ■ Cisplatin (Platinol) 	<p>IV infusion or oral capsules</p> <p>Oral tablets</p> <p>IV infusion</p> <p>IV infusion</p>
F	<ul style="list-style-type: none"> ■ Fludarabine (Fludara) 	IV infusion
FC	<ul style="list-style-type: none"> ■ Fludarabine (Fludara) ■ Cyclophosphamide (Cytoxan, Neosar) 	<p>IV infusion</p> <p>IV infusion</p>
FND	<ul style="list-style-type: none"> ■ Fludarabine (Fludara) ■ Mitoxantrone (Novantrone) ■ Dexamethasone (Decadron and others) 	<p>IV infusion</p> <p>IV infusion</p> <p>Oral tablets or IV Infusion</p>
G	<ul style="list-style-type: none"> ■ Gemcitabine (Gemzar) 	IV infusion
GCVF	<ul style="list-style-type: none"> ■ Gemcitabine (Gemzar) ■ Cyclophosphamide (Cytoxan, Neosar) ■ Vincristine (Oncovin and others) ■ Prednisolone (Orapred ODT) 	<p>IV infusion</p> <p>IV infusion</p> <p>IV infusion</p> <p>Oral tablet</p>
GDP	<ul style="list-style-type: none"> ■ Gemcitabine (Gemzar) ■ Dexamethasone (Decadron and others) ■ Cisplatin (Platinol) 	<p>IV infusion</p> <p>Oral tablets or IV infusion</p> <p>IV infusion</p>
GemOX	<ul style="list-style-type: none"> ■ Gemcitabine (Gemzar) ■ Oxaliplatin (Eloxatin) 	<p>IV infusion</p> <p>IV infusion</p>
HDMP	<ul style="list-style-type: none"> ■ High-dose methylprednisolone (Solu-Medrol) 	IV infusion or IM injection
HD MTX and HD Ara-C	<ul style="list-style-type: none"> ■ High-dose methotrexate (Mexate and others) ■ Cytarabine/high-dose Ara-C 	<p>IV infusion, IM injection, or Oral tablets</p> <p>IV infusion</p>

Drug or Regimen Abbreviation	Generic Name of Drugs (Brand Name)	How Treatment is Given
HyperCVAD/ MTX-Ara-C	<ul style="list-style-type: none"> ■ Cyclophosphamide (Cytoxan, Neosar) ■ Vincristine (Oncovin and others) ■ Doxorubicin/hydroxydaunorubicin (Adriamycin/Adriamycin PFS) ■ Dexamethasone (Decadron and others) ■ Methotrexate (Mexate and others) ■ Cytarabine/high-dose Ara-C (Platinol, Platinol-AQ) 	<p>IV infusion</p> <p>IV infusion</p> <p>IV infusion</p> <p>Oral tablets or IV infusion</p> <p>IV infusion, IM injection, or oral tablets</p> <p>IV infusion</p>
ICE	<ul style="list-style-type: none"> ■ Ifosfamide (Ifex) ■ Carboplatin (Paraplatin) ■ Etoposide/VP16 (VePesid, Toposar, Etopophos) 	<p>IV infusion</p> <p>IV infusion</p> <p>IV infusion or oral capsules</p>
O	<ul style="list-style-type: none"> ■ Obinutuzumab (Gazyvaro) 	IV infusion
P	<ul style="list-style-type: none"> ■ Pralatrexate (Folotyng) 	IV infusion
Pola-R-CHP	<ul style="list-style-type: none"> ■ Polatuzumab vedotin-piiq (Polivy) ■ Rituximab (Rituxan) ■ Cyclophosphamide (Cytoxan, Neosar) ■ Doxorubicin (Doxil) ■ Prednisone (Deltasone and others) 	<p>IV infusion</p> <p>IV infusion</p> <p>IV infusion</p> <p>IV infusion</p> <p>Oral tablets</p>
R	<ul style="list-style-type: none"> ■ Rituximab (Rituxan, Rituxan Hycela) 	IV infusion or subcutaneous injection
SMILE	<ul style="list-style-type: none"> ■ Methotrexate (Mexate and others) ■ Leucovorin/Levoleucovorin (Wellcovorin) ■ Ifosfamide (Ifex) ■ Mesna (Mesnex) ■ Dexamethasone (Decadron and others) ■ Etoposide/VP16 (VePesid, Toposar, Etopophos) ■ Pegaspargase (Oncaspar) 	<p>IV infusion, IM injection, or oral tablets</p> <p>IV infusion</p> <p>IV infusion</p> <p>IV infusion or oral tablets</p> <p>Oral tablets or IV infusion</p> <p>IV infusion or oral capsules</p> <p>IV infusion or IM injection</p>

IV, intravenous; IM, intramuscular

What Other Types of Drugs Are Used to Treat Patients With NHL?

In addition to chemotherapy, there are many types of other drugs used to treat NHL. These can be divided into two main categories: immunotherapy and targeted therapies. Most of these drugs have been developed relatively recently, and ongoing studies are continually testing new drugs in these categories.

Immunotherapy

Currently used FDA-approved immunotherapies for NHL can be subdivided into six types:

- The monoclonal antibodies rituximab (Rituxan), obinutuzumab (Gazyva), ofatumumab (Arzerra), tafasitamab-cxix (Monjuvi), and mogamulizumab-kpkc (Poteligeo).
- The antibody-drug conjugates (ADCs) brentuximab vedotin (Adcetris), polatuzumab vedotin-piiq (Polivy), and loncastuximab tesirine-lpyl (Zynlonta).
- The bispecific antibodies epcoritamab (Epkinly), mosunetuzumab (Lunsumio), and glofitamab-gxbm (Columvi).
- The immune checkpoint inhibitor pembrolizumab (Keytruda).
- The immunomodulatory drug (IMiD) lenalidomide (Revlimid).
- The radioimmunotherapy ibritumomab tiuxetan (Zevalin).

For detailed information about treatment see Chapter 7, and the *Immunotherapy and Other Targeted Therapies* fact sheet on LRF's website at lymphoma.org/publications. Approved immunotherapies for NHL are described below.

Monoclonal antibodies

Rituximab (Rituxan), obinutuzumab (Gazyva), and ofatumumab (Arzerra) are directed against different parts of CD20, an antigen (marker) that is almost universally present on the surface of B-cells.

Tafasitamab-cxix (Monjuvi) binds to the CD19 antigen on B lymphocytes to promote cell death. Some cancer cells have large amounts of PD-L1 protein, which helps them “hide” from immune cells, and the anti-PD1

immune checkpoint inhibitors like pembrolizumab (Keytruda) are used in these unique lymphoma subtypes. Mogamulizumab-kpkc (Poteligeo) is a monoclonal antibody that disrupts lymphocyte movements through the body.

Rituximab (Rituxan), Rituximab and Hyaluronidase Human (Rituxan Hycela), Rituximab-abbs (Truxima), and Rituximab-pvvr (Ruxience)

Rituximab (Rituxan) is the most commonly used antibody for B-cell NHL. In 1997, rituximab became the first monoclonal antibody approved by the FDA for the treatment of patients with lymphoma. As of 2022, rituximab is approved by the FDA for treatment of adult patients with NHL in the following settings:

- Previously untreated follicular CD20-positive B-cell NHL in combination with first-line chemotherapy, and in patients achieving a complete (no signs of lymphoma after treatment) or partial remission (tumor responded to treatment and shrunk to less than one-half of its original size), as single-agent maintenance therapy (ongoing treatment of patients whose disease has responded well to treatment).
- Non-progressing (including stable disease) low-grade CD20-positive B-cell NHL as a single agent after first-line chemotherapy (commonly R-CVP [rituximab, cyclophosphamide, vincristine, prednisone], R-CHOP [rituximab, cyclophosphamide, vincristine, doxorubicin, prednisone] or BR [bendamustine and rituximab]).
- Relapsed or refractory low-grade or follicular CD20-positive B-cell NHL as a single agent.
- Previously untreated CD20-positive DLBCL in combination with CHOP or other anthracycline-based chemotherapy regimens.

Rituximab (Rituxan) is also approved for pediatric patients over 6 months with previously untreated, CD20-positive mature B-cell NHL, including DLBCL, BL or Burkitt-like lymphoma (high grade B-cell lymphoma, NOS), in combination with chemotherapy.

The original form of rituximab (Rituxan) is given as an IV infusion, and the schedule varies depending on the type of combination regimen used. When combined with chemotherapy, rituximab is usually given during the

first day of each chemotherapy cycle (regular treatment schedule that consists of treatment periods followed by a rest period).

A subcutaneous form (injection just below the skin) of rituximab (Rituxan Hycela or “rituximab and hyaluronidase human”) was approved by the FDA in 2017 for the treatment of adult patients with NHL in the following settings:

- Relapsed or refractory FL as a single agent.
- Previously untreated FL in combination with first line chemotherapy and in patients achieving a complete or partial remission, as single-agent maintenance therapy.
- Non-progressing (including stable disease) FL as a single agent after first line CVP chemotherapy.
- Previously untreated DLBCL in combination with CHOP chemotherapy or other anthracycline-based chemotherapy regimens.

Subcutaneous administration allows the drug to be given in a shorter period of time. Before patients can receive rituximab and hyaluronidase human (Rituxan Hycela), they must first have at least one full dose of rituximab by IV infusion. Dosing of subcutaneous rituximab varies depending on the type of lymphoma being treated.

Rituximab-abbs (Truxima), a *biosimilar*, is a biologic therapy that is modeled after an existing biologic therapy or reference (an already approved drug with a similar effect in the body) product that has already been approved by the FDA. Biosimilar therapy is expected to be just as effective as its reference product with the potential benefit of reducing the cost of treatment. Rituximab-abbs (Truxima), approved by the FDA in 2018, and rituximab-pvvr (Ruxience), approved by the FDA in 2019, are biosimilars to rituximab (Rituxan) for use in patients with untreated, relapsed or refractory, or non-progressing CD20- positive B-cell NHL. Rituximab-abbs and rituximab-pvvr are delivered intravenously.

Obinutuzumab (Gazyva)

Obinutuzumab (Gazyva) was first approved by the FDA in 2013 and is indicated for use in the following situations:

- In combination with bendamustine (Treanda, Bendeka) followed by monotherapy for the treatment of patients with FL that has relapsed after, or is refractory to, a regimen containing rituximab (Rituxan).
- In combination with chemotherapy followed by monotherapy for the treatment of adult patients achieving at least a partial remission for the treatment of previously untreated stage II bulky, stage III, or stage IV FL.

Obinutuzumab (Gazyva) is also being investigated in other types of NHL. In patients with FL, obinutuzumab (Gazyva) is given as an IV infusion in six 28-day treatment cycles in combination with bendamustine (Treanda), six 21-day cycles (in combination with CHOP, followed by 2 additional 21-day cycles of obinutuzumab [Gazyva] alone) or eight 21-day cycles in combination with CVP.

Mogamulizumab-kpkc (Poteligeo)

Mogamulizumab-kpkc was approved by the FDA in 2018 for the treatment of relapsed or refractory mycosis fungoides or Sézary syndrome (a type of T-cell NHL) in adult patients after at least one prior *systemic* (throughout the body) therapy. Mogamulizumab-kpkc blocks the C-C chemokine receptor type 4 (CCR4) receptor resulting in cell death of the targeted T-cells. It is delivered intravenously once a week for the first 28-day cycle and then once every two weeks for each subsequent cycle.

Tafasitamab-cxix (Monjuvi)

Tafasitamab-cxix was approved by the FDA in 2020 to be used in combination with lenalidomide for the treatment of adult patients with relapsed or refractory DLBCL, NOS (including DLBCL arising from low grade lymphoma) who are not eligible for stem cell transplantation. Tafasitamab-cxix binds to CD19 that is expressed on B-cells—including neoplastic B lymphocytes—and promotes cell *lysis* (the breakdown of cells) resulting in cell death. Tafasitamab-cxix is delivered intravenously 5 times during the first 28-day cycle of treatment, 4 times during the second and third 28-day cycles of treatment, and on days 1 and 15 of each subsequent 28-day cycle.

Antibody-Drug Conjugates

An antibody-drug conjugate is a chemotherapy drug attached to a monoclonal antibody. The three antibody-drug conjugates approved for use in NHL are described below:

Brentuximab Vedotin (Adcetris)

Brentuximab vedotin (Adcetris) is a combination of a small molecule, monomethyl auristatin E (MMAE or vedotin), attached to a monoclonal antibody against CD30 (brentuximab). The monoclonal antibody part of this drug is like a “guided missile” that is directed against and attaches to lymphoma cells that express the CD30 antigen. Once the monoclonal antibody is attached to the lymphoma cell, it is taken inside the cell (internalized). MMAE is then released, where it attacks the inner parts of the cell and causes it to stop multiplying and die.

As of 2018, Brentuximab vedotin (Adcetris) is approved by the FDA for the treatment of adult patients with NHL in the following situations:

- Systemic (throughout the body) ALCL after failure of at least one previous combination chemotherapy regimen.
- Previously untreated systemic ALCL or other CD30-expressing PTCL, including AITL and PTCL – NOS, in combination with CHP (cyclophosphamide, doxorubicin, and prednisone) chemotherapy.
- Primary cutaneous ALCL or CD30-expressing mycosis fungoides.

Brentuximab vedotin (Adcetris) is given as an IV infusion once every three weeks.

Polatuzumab vedotin-piiq (Polivy)

Polatuzumab vedotin-piiq (Polivy) is a combination of the small molecule drug monomethyl auristatin E (MMAE or vedotin) attached to a monoclonal antibody targeting CD79b (polatuzumab), a component (piece) of the NHL B-cell receptor. After the antibody binds CD79b, it is internalized and MMAE is released to kill the cancer cell by blocking cell division.

Polatuzumab vedotin-piiq (Polivy) was approved by the FDA in 2019 for the treatment of adult patients with:

- Relapsed or refractory DLBCL and DLBCL-not otherwise specified (NOS), after at least two prior therapies, in combination with bendamustine (Treanda) and a rituximab product.
- Previously untreated DLBCL, DLBCL-NOS or high-grade B-cell lymphoma (HGBCL) and who have an IPI score of 2 or greater, in combination with R-CHP.

Polatuzumab vedotin-piiq (Polivy) is given as an IV infusion once every 21 days in combination with bendamustine (Treanda) and a rituximab product. Premedication (prior treatment) with an antihistamine and fever reducer is recommended to prevent infusion-related reactions (like fever, chills, flushing and muscle pain).

Loncastuximab tesirine-lpyl (Zynlonta)

Loncastuximab tesirine-lpyl (Zynlonta) is a conjugate of a small molecule called tesirine (or SG3199, an anti-cancer agent) with a monoclonal antibody (loncastuximab) targeting CD19, a protein expressed at the surface of NHL B-cells. Upon binding to CD19, the conjugate is internalized and tesirine is released inside the B-cell, where it binds to the DNA and leads to cell death.

Loncastuximab tesirine-lpyl was approved by the FDA in 2021 for the treatment of adult patients with relapsed or refractory DLBCL-NOS, DLBCL arising from low-grade lymphoma, and HGBCL, after at least two or more lines of systemic therapy. It is given as an IV infusion once every 3 weeks. Premedication with dexamethasone is recommended to prevent reactions such as edema (swelling) and effusions (accumulation of fluid in the body).

Bispecific Antibodies

Bispecific antibodies (bsAbs) approved to treat NHL work by linking cancer cells to cells from the immune system that fight cancer. These bsAbs combine regions that bind to CD20 on malignant B-cells and CD3 on cancer-fighting T-cells. For this reason, they are also called “T-cell engagers”.

This group of drugs may be valuable therapeutic alternatives for patients with relapsed/refractory NHL who have not responded to or are not eligible cellular therapy.

Epcoritamab (Epkiny)

Epcoritamab (Epkiny) is a T-cell engaging bsAb that binds to the CD3 and CD20. It is indicated for the treatment of adult patients with relapsed or refractory DLBCL, DLBCL-NOS, including DLBCL arising from indolent lymphoma (transformed lymphoma), and HGBCL after two or more lines of systemic therapy. Epcoritamab is administered by subcutaneous injection weekly for the first 3 cycles, followed by every 2 weeks for cycles 4-9 and then once every 4 weeks. Each cycle is 28 days.

Mosunetuzumab (Lunsumio)

Mosunetuzumab (Lunsumio) is a T-cell engaging bsAb that binds to CD3 and CD20. It is indicated for the treatment of adult patients with relapsed or refractory FL after two or more lines of systemic therapy. Mosunetuzumab is given weekly as an IV infusion for the first cycle and then every 3 weeks in 21-day cycles for 8-17 cycles based on response.

Glofitamab-gxbm (Columvi)

Glofitamab (Columvi) is a bsAb that binds CD20 and CD3. It is indicated for the treatment of adult patients with relapsed or refractory DLBCL, DLBCL-NOS or large B-cell lymphoma (LBCL) arising from FL, after two or more lines of systemic therapy. Glofitamab is given by IV infusion on days 8 and 15 of cycle 1. Before initiating glofitamab, all patients receive pretreatment with obinutuzumab on day 1 of the cycle. From cycle 2, it is administered every 3 weeks for a maximum of 12 cycles.

Immune checkpoint inhibitors

An immune checkpoint inhibitor binds to PD-1 or PD-L1, located on the surface of the lymphoma cell, and prevents it from escaping the body's immune response. Only one immune checkpoint inhibitor is approved for use in NHL, as described on the next page.

Pembrolizumab (Keytruda)

In 2018, pembrolizumab (Keytruda) was approved by the FDA for treatment of primary mediastinal large B-cell lymphoma (PMBCL) in adult and pediatric patients with refractory or relapsed disease following two or more prior lines of therapy. Urgent reductive surgery (therapy that reduces the number of cancer cells) is rarely performed in PMBCL, but in those cases treatment with pembrolizumab (Keytruda) is not recommended.

Pembrolizumab is a checkpoint inhibitor that blocks the PD-1 receptor on T-cells to allow the immune system to better identify and attack lymphoma cells. Pembrolizumab is given as an IV infusion every 3 or 6 weeks (for adults) or every 3 weeks (for children).

Immunomodulatory Drugs

Immunomodulatory drugs have many ways of working against cancer cells. They cause tumor cells to die, help keep tumors from getting nutrients from the blood, and stimulate the immune system to help destroy cancer cells. The only immunomodulatory drug (IMiD) approved for use in NHL is lenalidomine (Revlimid).

Lenalidomide (Revlimid)

Lenalidomide (Revlimid) is a novel therapeutic agent that inhibits the growth and causes the death of some types of malignant blood cells. For this reason, lenalidomide is FDA approved for treatment of adult patients with NHL in the following situations:

- Patients with MCL whose disease has relapsed or progressed after two prior therapies, one of which included bortezomib (Velcade).
- Previously treated FL and MZL in combination with a rituximab product.
- In combination with tafasitamab for patients with relapsed or refractory DLBCL
- Lenalidomide comes as an oral tablet. It is given once a day for three weeks of a four-week cycle.

Radioimmunotherapy

Radioimmunotherapy (RIT) consists of a radioactive *isotope* (molecule) attached to a monoclonal antibody. The monoclonal antibody recognizes and attaches to antigens on lymphoma cells, thereby exposing them to radiation. The only currently available RIT that is FDA-approved for lymphoma is ibritumomab tiuxetan (Zevalin).

Ibritumomab Tiuxetan (Zevalin)

Ibritumomab tiuxetan consists of three parts: the CD20-targeted monoclonal antibody ibritumomab, a radioactive isotope called yttrium-90 (Y90), and tiuxetan, a molecule that links them together. The ibritumomab component of the drug binds to CD20-positive NHL B-cells. Once bound, the radiation from the Y90 damage the cell, triggering its destruction. Y90 ibritumomab tiuxetan was first approved by the FDA in 2002 and is indicated for the treatment of:

- Relapsed or refractory low-grade or follicular B-cell NHL.
- Previously untreated follicular NHL in patients who have achieved partial or complete responses to first line chemotherapy.

Ibritumomab tiuxetan is given through an IV injection in combination with rituximab (Rituxan). Treatment time is very short. Radioimmunotherapy treatment requires two infusions given about one week apart.

Targeted Therapies

This term refers to drugs that target molecules that cancer cells use to survive, multiply, and spread in the body. To learn more about targeted therapies, please view Chapter 7 of this guide (page 57).

FDA-approved targeted therapies used in the treatment of NHL include:

- Histone deacetylase (HDAC) inhibitors belinostat (Beleodaq), romidepsin (Istodax), and vorinostat (Zolinza).
- The proteasome inhibitor bortezomib (Velcade).
- The Bruton tyrosine kinase (BTK) inhibitors: acalabrutinib (Calquence), ibrutinib (Imbruvica), zanubrutinib (Brukinsa), and pirtobrutinib (Jaypirca).
- The tyrosine kinase inhibitor crizotinib (Xalkori).

- The enhancer of zeste homolog 2 (EZH2) inhibitor tazemetostat (Tazverik).
- The nuclear export inhibitor selinexor (Xpovio).
- The retinoid X receptor (RXR) activator bexarotene (Targretin).

Belinostat (Beleodaq)

Belinostat (Beleodaq) is a HDAC inhibitor, approved to treat adult patients with relapsed or refractory PTCL. It is given as an IV infusion on the first five days of a 21-day treatment cycle.

Romidepsin (Istodax)

Romidepsin (Istodax) is an HDAC inhibitor approved for the treatment of CTCL in adult patients who have received at least one prior systemic therapy. It is given as an IV infusion over a 4-hour period on days 1, 8, and 15 of a 28-day cycle.

Vorinostat (Zolinza)

Vorinostat (Zolinza) is an HDAC inhibitor approved for treatment of patients with CTCL whose disease has progressed or has not responded to other therapies, or for whom the disease has persisted or returned after two systemic therapies. Vorinostat (Zolinza) is given as a tablet once daily with food.

Bortezomib (Velcade)

Bortezomib (Velcade) is a proteasome inhibitor, a class of drugs that cause an abnormal build-up of proteins in a cancerous cell, resulting in cell death. Bortezomib (Velcade) is approved for the treatment of adult patients with MCL. It is given by IV infusion twice weekly for two weeks, followed by 10-day rest period every 3 weeks.

Acalabrutinib (Calquence)

Acalabrutinib (Calquence) inhibits the BTK signaling protein to block the growth and survival of cancerous B-cells in some types of NHL. It is approved for the treatment of adult patients with MCL who have received at least one prior therapy. It comes in capsules that are taken twice daily and should be swallowed whole with water.

Ibrutinib (Imbruvica)

Ibrutinib (Imbruvica) inhibits the signaling protein BTK to block the growth and survival of the cancerous B-cells in some types of NHL. Ibrutinib (Imbruvica) is approved for the treatment of adult patients with WM, as a single agent or in combination with rituximab (Rituxan). It is also approved in adult and pediatric patients aged 1 year or older with chronic graft versus host disease (GVHD, where the graft attacks the patient's healthy cells) after failure of one or more lines of systemic therapy.

Ibrutinib (Imbruvica) comes in capsules and tablets that should be swallowed whole with a glass of water once daily.

Zanubrutinib (Brukinsa)

Zanubrutinib (Brukinsa) inhibits the BTK signaling protein to block the growth and survival of the cancerous B-cells in some types of NHL. It is approved for the treatment of adult patients with MCL who have received at least one prior therapy, WM, and relapsed or refractory MZL who have received at least one anti-CD20-based regimen. It is taken as an oral tablet once or twice a day with water.

Pirtobrutinib (Jaypirca)

Pirtobrutinib (Jaypirca) inhibits the BTK signaling protein to block the growth and survival of cancerous B-cells in some types of NHL. Pirtobrutinib (Jaypirca) is indicated for the treatment of adult patients with relapsed or refractory MCL after at least two lines of systemic therapy, including a BTK inhibitor. It is taken as an oral tablet once a day with water.

Crizotinib (Xalkori)

Crizotinib (Xalkori) is a multi-kinase inhibitor, including anaplastic lymphoma kinase (ALK), which promotes the growth of some forms of NHL. By inhibiting ALK, it stops the proliferation (multiplication) and induces the death of ALK-positive NHL cells. Crizotinib (Xalkori) is approved for the treatment of pediatric patients (over 1 year of age) and young adults with relapsed or refractory systemic ALCL that is ALK-positive. It is taken as an oral tablet twice a day.

Tazemetostat (Tazverik)

Tazemetostat (Tazverik) inhibits the EZH2 enzyme to decrease overgrowth of cancer cells. It is approved for the treatment of adult patients with relapsed or refractory FL whose tumors are positive for an EZH2 mutation as detected by an FDA-approved test and who have received at least two prior systemic therapies, and for adult patients with relapsed or refractory FL who have no satisfactory alternative treatment options. It is taken as an oral tablet twice a day.

Selinexor (Xpovio)

Selinexor (Xpovio) blocks the movement of several proteins inside the cell promoting anti-cancer activity and prevent uncontrolled growth of cancer cells. It is approved for the treatment of adult patients with relapsed or refractory DLBCL-NOS, including DLBCL arising from FL, after at least 2 lines of systemic therapy. Selinexor (Xpovio) is taken as a tablet on days 1 and 3 each week with anti-nausea medicines.

Bexarotene (Targretin)

Bexarotene (Targretin) activates retinoid X that regulates (controls) cell division and multiplication, preventing tumor growth. Bexarotene (Targretin) has two different forms of administration - gel and capsules. The gel is indicated for the topical treatment of cutaneous lesions of patients with refractory or persistent disease after other therapies, or who have not tolerated other therapies for CTCL. A generous amount of gel should be applied over the surface of each lesion using a clean washed finger. Bexarotene (Targretin) capsules are indicated for the treatment of cutaneous manifestations (skin symptoms) of CTCL in patients who are refractory to at least one prior systemic therapy. Capsules should be taken as a single oral daily dose with a meal.

Radiation Therapy

Radiation therapy (also called radiotherapy) uses high-energy X-rays or other types of radiation to kill cancer cells and shrink tumors. The term is generally used to describe external-beam radiotherapy, in which a radiation beam is delivered from a machine. For detailed information about radiation therapy, see Chapter 7 of this guide. The most common types of radiation therapy and delivery methods used for NHL are described below.

Image-Guided Radiation Therapy (IGRT)/Tomography

This technique uses repeated imaging scans to monitor changes in tumor size and location throughout the radiation treatment. Imaging scans include computed tomography (CT), magnetic resonance imaging (MRI), and/or positron emission tomography (PET) scans. The aim is to direct radiation to the areas affected by the cancer, sparing healthy tissues.

Three-Dimensional Conformal Radiation Therapy (3D-CRT)

Very sophisticated computer software and advanced machines deliver radiation to a precisely shaped area of the body.

Electron Beam Radiation

A machine sends electrons (negatively charged particles) directly to the area where the lymphoma was found and sometimes to nearby lymph nodes.

Proton Therapy

Uses positively charged particles called protons delivered by an external beam. This can reduce the radiation exposure of nearby healthy tissues, allowing higher doses to be delivered to the tumor. It may be useful to treat tumors near places that are difficult to treat (e.g., heart, lungs, or esophagus).

Total Skin Electron Beam Therapy

A weak radiation beam that only penetrates the outer layers of the skin is directed to the entire surface of the body.

Photopheresis or Extracorporeal Photochemotherapy

A fraction of the patient's blood is removed from the body, treated with a chemical that makes lymphocytes more likely to die when exposed to ultraviolet radiation, and re-infused back into the patient.

Cellular Therapy

Cellular therapy is the introduction of autologous (from the patient) or allogeneic (from a donor) healthy human cells into the patient's body for medical purposes to replace or repair damaged tissue and/or cells. Allogeneic transplants require immunosuppressant therapy (drugs that

prevent the immune system from attacking healthy cells and tissues) to reduce the risk of rejection of the transplanted cells (“graft”) and GVHD.

Both stem cell transplantation and CAR T-cell therapy are forms of cellular therapy, and many of the steps in the procedures are similar. While both procedures require prior chemotherapy, the regimen used in CAR T-cell therapy is associated with fewer side effects. Further information on Cellular Therapy is described in Chapter 7.

CAR T-Cell Therapy

CAR T-cells are a special type of cellular immunotherapy that uses patient’s T-cells that were modified to help fight cancer. For more information on CAR T-cell therapy see Chapter 7 of this guide (page 57) and the *Cellular Therapy* guide on LRF’s website at lymphoma.org/publications. CAR T-cell therapies approved to treat NHL are described below.

Axicabtagene Ciloleucel (Yescarta)

Axicabtagene ciloleucel (Yescarta) is a CAR T-cell therapy directed to the CD19 antigen, which is present on almost all B lymphoma cells, making it an ideal target for cellular therapy. It is approved for the treatment of adult patients with:

- Large B-cell lymphoma that is refractory to first line chemoimmunotherapy or that relapses within 12 months of first line chemoimmunotherapy
- Relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy, including DLBCL-NOS, PMBCL, HGBCL, and DLBCL arising from FL.
- Relapsed or refractory FL after two or more lines of systemic therapy (efficacy observed in early studies is being confirmed in larger studies called confirmatory clinical trials).

Axicabtagene ciloleucel (Yescarta) is for autologous use only and is given through central venous access over 30 minutes. Dosing is based on the number of CAR-positive viable T-cells, and the patient’s weight.

Tisagenlecleucel (Kymriah)

Tisagenlecleucel (Kymriah) is also directed against CD19. It is for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy including DLBCL-NOS, HGBCL, and DLBCL arising from FL, and relapsed or refractory FL after two or more lines of systemic therapy. Tisagenlecleucel (Kymriah) is for autologous use only and is given as a single-dose by IV infusion.

Brexucabtagene Autoleucel (Tecartus)

Brexucabtagene autoleucel (Tecartus) is a CAR T-cell therapy directed against the CD19 antigen. It is approved for the treatment of adult patients with relapsed or refractory MCL. Brexucabtagene autoleucel (Tecartus) is for autologous use only and is given through central venous access (a catheter introduced inserted into a vein in the neck, chest, arm or groin) over 30 minutes. Dosing is based on the number of CAR-positive viable T-cells, and the patient's weight.

Lisocabtagene maraleucel (Breyanzi)

Lisocabtagene maraleucel (Breyanzi) is a CAR T-cell therapy directed against the CD19 antigen. It is approved for the treatment of adult patients with large B-cell lymphoma including DLBCL-NOS (including DLBCL arising from indolent lymphoma), HGBCL, PMBCL, and FL grade 3B, who have:

- Refractory disease to first-line chemoimmunotherapy or relapse within 12 months of first-line chemoimmunotherapy.
- Relapsed or refractory disease to first-line chemoimmunotherapy or are not eligible for stem cell transplantation due to comorbidities (other existing diseases) or age.
- Relapsed or refractory disease after two or more lines of systemic therapy.

Lisocabtagene maraleucel (Breyanzi) is for autologous use only and is given as single dose by IV infusion. Dosing is based on the number of CAR-positive viable (alive and healthy) T-cells.

Stem Cell Transplantation

A stem cell transplant adds new stem cells (blood-forming cells) back into the body after chemotherapy with or without radiation, replacing the cells that were destroyed and restoring the bone marrow's ability to make new blood cells. In deciding if transplantation is a good option, doctors consider the patient's health status, age, medical history, cancer stage, and responses to previous therapy.

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

Autologous Stem Cell Transplant

In an autologous stem cell transplant, patients are their own donor. Autologous stem cell transplantation is used in patients with cancers that are responding to chemotherapy. The ability to transplant the patient's own stem cells (autologous stem cell transplant) allows doctors to use higher doses of chemotherapy than the body would normally tolerate, increasing the probability of treatment success.

Allogeneic Stem Cell Transplant

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

Syngeneic Stem Cell Transplant

In a syngeneic stem cell transplant, the donor is the patient's identical twin.

For additional information about the process of stem cell transplantation, please view Chapter 7 of this guide (page 59) and the *Understanding Cellular Therapy* guide on LRF's website at lymphoma.org/publications.

Part 2 — Non-Hodgkin Lymphoma

Chapter 12: Clinical Trials and Advances in Treatment of Patients with Non-Hodgkin Lymphoma

Overview of Clinical Trials

Drugs that are not yet approved for sale by the FDA are said to be investigational. Some of these investigational drugs are being studied in laboratory experiments. This stage is often referred to as the preclinical phase (before testing in humans). The drugs in more advanced stages of research are being studied in patients in clinical trials; these are referred to as being in the clinical phase of development. The most common way for a patient to receive an investigational drug is through a clinical trial.

A *clinical trial* is a carefully designed research study that involves patients who volunteer to participate. The purpose of cancer clinical trials is to answer specific questions about new ways to prevent, diagnose, treat, or manage a disease or the side effects caused by a new or existing treatment. The investigators in clinical trials want to determine the safety and effectiveness of the treatment being investigated by making specific assessments before, during, and after the trial.

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

To find out more about getting access to investigational drugs and clinical trials, visit the National Cancer Institute’s (NCI’s) website at www.cancer.gov and search for “access to investigational drugs.” Alternatively, visit www.clinicaltrials.gov to search for trials using a particular drug or to find clinical trials nearby. Patients should check with their doctor or the Lymphoma Research Foundation (LRF) Helpline

“Clinical Trials Information Service” (call (800) 500-9976 or email helpline@lymphoma.org) for additional information and recent updates.

See Chapter 8 of this guide (page 69) for more general information about the topics below:

- What is a clinical trial?
- Why is a placebo (a substance that contains no medicine and/or has no effect) sometimes used in Phase III trials?
- Should I participate in a clinical trial?
- What is informed consent in a clinical trial?
- What is the cost of participating in a clinical trial?

Advances in Treatment of Patients With NHL

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

Today’s science is moving very quickly. Patients should check with their doctor or the Lymphoma Research Foundation (LRF) Helpline/ Clinical Trials Information Service for additional information and recent updates.

For a detailed description of currently approved treatment options, please see Chapter 11 of this guide (pages 98-120).

Chemotherapy

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

Stem Cell Transplantation

Ongoing research in stem cell transplantation is focused on finding better ways to collect stem cells from the bone marrow or peripheral blood; reducing or eliminating GVHD in allogeneic transplants in which donor cells recognize the normal organs of the patient as foreign and attack them; improving ways to remove all lymphoma cells from stem cell samples drawn from the patient's bone marrow and used for autologous transplants; and developing more effective regimens for reduced-intensity (use of lower doses of chemotherapy and radiation) stem cell transplantation.

Immunotherapy

Monoclonal Antibodies

The success of the monoclonal antibody rituximab (Rituxan) inspired researchers to develop other monoclonal antibodies to treat patients with various types of NHL, such as the receptor tyrosine kinase-like Orphan Receptor 1 (ROR1) inhibitor cirmtuzumab for MCL and MZL. Another example of a type of monoclonal antibody being developed for treatment of NHL are bsAbs. Odronektamab (REGN1979) showed promising results in patients with aggressive relapsed or refractory B-cell NHL. Other bsAbs being investigated for NHL are AFM13 for the treatment of relapsed or refractory ALCL, MF, and relapsed or refractory PTCL, and blinatumomab for B-cell NHL. These drugs have thus emerged as a new class of immunotherapy with potential to treat aggressive lymphoma as second- or third-line agents.

Antibody-Drug Conjugates

Antibody-drug conjugates in development for NHLs include zilovetamab vedotin (targeting receptor tyrosine kinase-like orphan receptor 1 [ROR1]) for the treatment of DLBCL, MCL, and FL.

Radioimmunotherapy

Betalutin (177Lu lilotomab satetraxetan) is a radioimmunotherapy that targets CD37 and is currently under investigation for the treatment of NHL (DLBCL and FL).

Checkpoint Inhibitors

A newer class of immunotherapies called checkpoint inhibitors has been developed more recently. Nivolumab (Opdivo), which is FDA-approved for the treatment of HL, has shown encouraging results in clinical trials for patients with B-cell NHL. Other checkpoint inhibitors are also under investigation for the treatment of NHL, such as:

- Durvalumab (Imfinzi) for DLBCL, FL, MCL, and CTCL.
- Ipilimumab (Yervoy) for B-cell and T-cell NHL.
- Atezolizumab (Tecentriq) for DLBCL, FL, and other NHLs.
- Ontoppacept for B-cell and T-cell NHL.

Targeted Therapies

Many targeted therapies for NHL are being studied in laboratories and in clinical trials. Examples include:

- HDAC inhibitors such as chidamide for PTCL, entinostat for B-cell NHL, abexinostat for FL, and vorinostat (Zolinza) for recurrent B-cell and T-cell NHL.
- Inhibitors of B-cell lymphoma-2 (BCL2) such as BGB-11417 for relapsed and refractory MCL.
- Kinase inhibitors, including:
 - BTK inhibitors such as orelabrutinib (Inokai) for DLBCL, BL, FL, and MCL, and nemtabrutinib for WM, MCL, DLBCL, FL, and MZL.
 - PI3K inhibitors such as pascalisib and liperlisib for relapsed and refractory PTCL, amdizalisib for FL and MZL, and BGB-10188 for DLBCL.
 - ALK inhibitor such as brigitanib (Alunbrig) for ALCL, and ensartinib for NHL.
- Proteasome inhibitors such ixazomib (Ninlaro) for relapsed and refractory FL, PTCL, BL, DLBCL and MCL.
- Cereblon targeting drugs such as CELMoDs (like golcadomide) for FL.

CAR T-Cell Therapy

CAR T-cell therapies that target the CD19, CD20, CD22, and CD30 antigens are currently being investigated for several types of lymphoma. Examples include:

- IMPT-314 for relapsed and refractory NHL.
- ALLO-501A for relapsed and refractory large B-cell lymphoma.
- Azercabtagene zapreleucel for NHL.
- ATLCAR.CD30 for PTCL.
- MB-106 for refractory B-cell lymphoma, FL, recurrent MCL, and recurrent WM.

Vaccines

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

- EO2463 for indolent NHL.
- Oncoquest-L for FL.
- DPX-Survivac for DLBCL.

Part 3 — Hodgkin Lymphoma

Chapter 13: What is Hodgkin Lymphoma

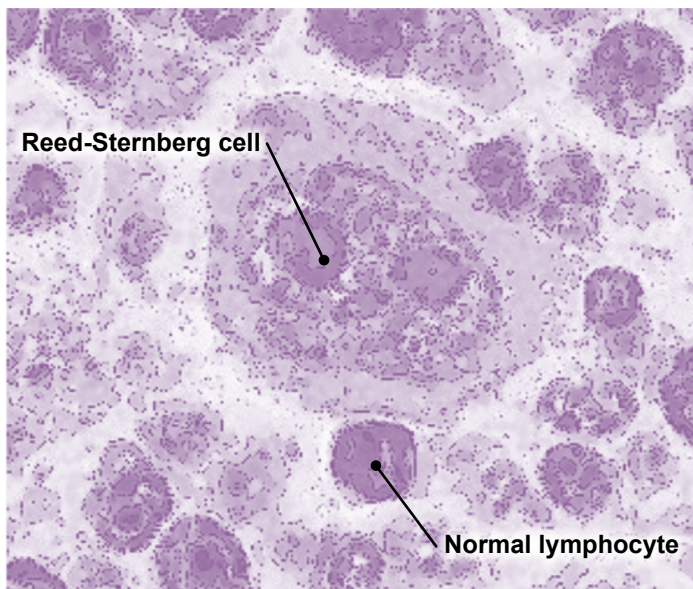
What is Hodgkin Lymphoma?

Hodgkin lymphoma (HL), previously called Hodgkin's disease or Hodgkin disease, is a type of cancer that starts in the lymphatic system (tissues and organs that produce, store and carry white blood cells). HL is named after Dr. Thomas Hodgkin, a British physician who first described the disease in 1832. In the United States, approximately 8,830 people a year are diagnosed with HL. In 2020, there were an estimated 223,512 people living with HL in the United States. Both children and adults can develop HL, but the disease is most common among young adults aged 20 to 34.

How Does HL Develop?

HL develops when abnormal (cancerous) B-cells called Reed-Sternberg (RS) cells start to multiply and grow in an unregulated (uncontrolled) manner and make lymph nodes grow bigger than normal. Most patients with HL have either RS cells or RS cell variants (RS cells that have some differences in their shape, size, and structure compared to typical RS cells) in their lymphatic system. When examined under a microscope, RS cells are usually surrounded by large numbers of inflammatory cells (cells that respond to damage and help the body fight off infections) such as T-cells, histiocytes (a type of large white blood cell), eosinophils (a type of white blood cell), and neutrophils (a type of white blood cell). For this reason, HL was not initially recognized as a cancer; for years doctors thought HL was a type of infection. HL looks different from other cancers in that only a few of the cells (1-2%) in the lymph nodes are cancerous, and the rest help cancerous RS cells stay alive.

A REED-STERNBERG CELL



The presence of cells that look like RS cells does not necessarily mean that a person has HL. In fact, RS-like cells can be found in many other conditions, mainly other types of cancer. A unique characteristic of most types of HL is that the RS cells have an antigen (marker) on their surfaces called CD30. To make an HL diagnosis, a hematopathologist (a doctor who specializes in the diagnosis of blood diseases) examines a sample of the affected lymph node under a microscope and uses tests to determine whether (1) the RS cells are surrounded by inflammatory cells, and (2) the CD30 antigen and CD15 antigen are present on the RS cells. The hematopathologist may also use more sophisticated molecular tests to help confirm the diagnosis.

HL usually starts in the lymph nodes, and the first signs a patient notices may be swelling in the neck, above or below the collarbone, under the arms, in the chest, or in the groin. The lymphoma can then spread throughout the body via lymphatic vessels (tube-like structures that carry a fluid called lymph) and all lymphatic system. HL may also spread to other areas and organs outside of the lymphatic system.

What Distinguishes HL From NHL?

The RS cells seen in patients with HL are not present in patients with non-Hodgkin lymphoma (NHL). Also, HL tends to spread from one group of lymph nodes to adjacent nodes, while NHL may spread to lymph nodes anywhere in the body in an unpredictable manner.

The different types and subtypes of HL are distinguished by how they look under a microscope. The two main forms are classical HL (cHL) and nodular lymphocyte-predominant HL (NLPHL).

Classical HL and Its Subtypes

About 95% of patients with HL are cHL. There are four subtypes of cHL, as described in Table 13.1. However, it is important to remember that these four subtypes are generally treated similarly.

Table 13.1. Subtypes of cHL

Nodular Sclerosis HL	<ul style="list-style-type: none">■ Affects 70% of patients with cHL.■ Involved lymph nodes often form <i>nodules</i> (lumps) separated by broad bands of <i>fibrotic</i> (fiber-like) or <i>sclerotic</i> (hardened) tissue.■ More common in young adults and women.■ Most frequently involves lymph nodes in the neck or chest.
Mixed Cellularity HL	<ul style="list-style-type: none">■ Affects 20-40% of patients with cHL.■ Characterized by many classic RS cells mixed with other types of inflammatory cells.■ More common in older adults, children under 10 years, and people with underlying immunodeficiency disorders (diseases that weaken the immune system and cause infections and other health problems). Often associated with an infection of Epstein Barr virus (EBV, the virus that causes mono).
Lymphocyte-Rich HL	<ul style="list-style-type: none">■ Affects 5% of patients with cHL.■ Characterized by many normal lymphocytes and relatively few RS cells.■ More common in men.
Lymphocyte-Depleted HL	<ul style="list-style-type: none">■ Affects less than 1% of patients with cHL.■ Characterized by very few normal lymphocytes and many RS cells.■ More common in older adults or people living with human immunodeficiency virus (HIV, a virus that weakens the body's immune system by destroying cells that fight off infections).■ Often not diagnosed until the disease is in an advanced stage.

Nodular Lymphocyte-Predominant Hodgkin Lymphoma (NLPHL)

This type of HL accounts for about 5 percent of all HL cases. It is indolent (slow-growing) and characterized by a different type of RS cells, called lymphocyte-predominant (LP) cells. These are also called “popcorn cells,” because the cell nuclei (structure in the center of the cell) resemble popped kernels of corn. The antigens on cell surfaces of LP cells are different from those found on RS cells in cHL. For example, LP cells are positive for the CD20 antigen (often found in B-cell NHL) and typically negative for the CD30 antigen seen in cHL. This form of HL is often found in the lymph nodes of the neck, groin, or underarms. The treatment for NLPHL differs from the treatment for cHL. NLPHL should not be confused with lymphocyte-rich HL, which is a subtype of cHL described in Table 13.1.

Do Certain People Develop HL?

The reasons why certain people develop HL are not totally understood. However, scientists have found that people with particular characteristics called “risk factors,” have a slightly higher chance of developing HL compared with people who do not have these risk factors. Having one or more HL risk factors does not mean a person will definitely develop the disease. In fact, most people with the known risk factors never develop HL, and many people diagnosed with HL do not have any of these risk factors. However, there does seem to be a link between the risk factors described in Table 13.2 and the development of HL.

Table 13.2. Risk Factors for HL

Age	<ul style="list-style-type: none">■ People who are 15-40 years of age or over 55 years have a higher risk of developing HL than people in other age groups.
Family History	<ul style="list-style-type: none">■ A family history of HL, especially among first-degree relatives (parent, sibling, or child), increases the risk of developing HL (but still a very low risk overall).■ Siblings of patients with HL have a 3- to 7-fold increased risk of developing this disease, and the risk is higher in identical twins. However, the risk of a first-degree relative developing HL is still very rare.■ Fewer than 1% of patients with HL have a family history of the disease.
Gender	<ul style="list-style-type: none">■ Men have a slightly higher risk of developing HL than women.■ Women are more likely to be diagnosed with the nodular sclerosis subtype.
Immunodeficiency Disorders	<ul style="list-style-type: none">■ People with inherited (for example, common variable immunodeficiency disorder, X-linked lymphoproliferative disorder) or acquired (for example, chronic immunosuppression following a solid organ transplant or treatment of certain immune conditions such as juvenile rheumatoid arthritis) immunodeficiency disorders are at an increased risk of developing HL.
Infection by Certain Viruses	<ul style="list-style-type: none">■ People infected with the Epstein-Barr virus (EBV; the virus that can cause infectious mononucleosis) or the human immunodeficiency virus (HIV; the virus that can cause acquired immunodeficiency syndrome [AIDS]) have a higher risk of developing HL compared with people who have not been infected with these viruses.

HL cannot be caused by injury and cannot be caught from someone who has the disease. While parents, children, and siblings of patients with HL have a slightly increased risk of developing this disease compared with the general population, there are no clearly identifiable genetic or hereditary factors that can predict this slightly increased risk. Therefore, routine screening for HL among the immediate family members of patients with HL is not recommended as most will never develop HL.

What Are the Signs and Symptoms of HL?

Most patients present with enlarged lymph nodes that continue to grow over several months to more than 3 centimeters in size (roughly the size of a banana slice). Enlarged lymph nodes are extremely common, so there is nothing to do or worry about if a person is feeling healthy and well until they are too big to be considered normal. Some patients with HL do not have any obvious signs or symptoms of the disease at the time of diagnosis. Their doctors might detect the lymphoma during routine blood tests and/or a physical examination. For others, lymphoma is discovered when symptoms occur and patients go to the doctor because they are worried, uncomfortable, or not feeling well.

As shown in Table 13.3, HL may cause different signs and symptoms depending on where it is located in the body. Keep in mind that many of these signs and symptoms are not specific to HL and may be due to other conditions.

Table 13.3. Signs and Symptoms Commonly Found in Patients with HL

Sign or Symptom	Possible Reasons
<ul style="list-style-type: none"> ■ Lumps under the skin on the sides of the neck, above the collarbone, or in the underarms, elbows, or groin 	<ul style="list-style-type: none"> ■ Lymph nodes, or “glands,” that swell when the lymphocytes respond to an infection or because of an increased number of abnormal lymphocytes
<ul style="list-style-type: none"> ■ “B symptoms,” including fevers for no known reason, unexplained drastic weight loss, and drenching night sweats that soak clothing and sheets 	<ul style="list-style-type: none"> ■ Increased levels of inflammatory chemicals in the blood that are released by lymphoma cells or by the immune system reacting to the lymphoma cells
<ul style="list-style-type: none"> ■ Unexplained itching (sometimes severe) 	<ul style="list-style-type: none"> ■ Unknown cause but often associated with “B symptoms” or reactivation of viruses
<ul style="list-style-type: none"> ■ Coughing, trouble breathing, or chest pain or pressure 	<ul style="list-style-type: none"> ■ Lymphoma in the chest, which may press on the windpipe or <i>bronchi</i> (tubes leading to the lungs) ■ <i>Pleural effusion</i> (fluid surrounding the lungs)
<ul style="list-style-type: none"> ■ Feeling tired 	<ul style="list-style-type: none"> ■ <i>Anemia</i> (low red blood cell count) or the cancer process in general
<ul style="list-style-type: none"> ■ Increased sensitivity to alcohol, or pain in the lymph nodes after drinking alcohol 	<ul style="list-style-type: none"> ■ Poorly understood cause, but thought to be due to increased blood flow through the lymph nodes in response to alcohol

What is Relapsed or Refractory HL?

Relapsed HL means that the disease has returned after responding to treatment, which is sometimes also called a *recurrence*. *Refractory* HL means that the patient's disease does not respond to a specific treatment or that the response to treatment does not last very long.

Chapter 14: Treatment of Hodgkin Lymphoma

This chapter reviews the most common therapies currently used in the treatment of HL. Keep in mind that new therapies may have been approved by the U.S. Food and Drug Administration (FDA) since this guide was published. Read Chapter 15 to learn more about emerging treatments under investigation in clinical trials.

There are important differences between different types of HL, and a treatment that works for one type of HL may not necessarily be the best treatment choice for another type. There are also small but important differences between patients diagnosed with the same type of HL. Because of these differences, a treatment that may work very well in one patient may not have the same positive effect in another.

What Types of Treatments are Used in Patients with cHL?

There are three general types of treatments for patients with cHL:

- Drug therapy, including one or more of the following types of drugs
 - Chemotherapy, which affects general cell growth and *proliferation* (the ability of cells to multiply). Chemotherapy is the main treatment for most people with HL (except for some people with NLPHL).
 - Immunotherapy, which helps the body's immune system attach to lymphoma cells (immune checkpoint inhibitors).
- Radiation therapy, which uses high-energy radiation to kill lymphoma cells.
- Stem cell transplantation, usually in combination with high-dose chemotherapy, which replaces the patient's immune system with healthy immune cells.

Chemotherapy

Most patients treated for cHL receive combination chemotherapy (two or more drugs), with or without radiation therapy, as their *frontline* (first) treatment. Most chemotherapy for HL is given by IV. In North America, the

standard frontline chemotherapy regimen is known as ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine); this regimen and other common frontline regimens for adults are listed in Table 14.1.

Table 14.1. Common Frontline Chemotherapy Regimens for Adults with cHL

Chemotherapy regimen (abbreviation)	Generic Name of Drugs (Brand Names)
ABVD	<ul style="list-style-type: none"> ■ Doxorubicin/hydroxydaunorubicin (Rubex, Adriamycin PFS) ■ Bleomycin (Blenoxane) ■ Vinblastine (Velban) ■ Dacarbazine (DTIC-Dome)
AVD	<ul style="list-style-type: none"> ■ Doxorubicin (Adriamycin) ■ Vinblastine (Velban) ■ Dacarbazine (DTIC-Dome)
BV-AVD (A-AVD)	<ul style="list-style-type: none"> ■ Brentuximab vedotin (Adcetris) ■ Doxorubicin (Adriamycin) ■ Vinblastine (Velban) ■ Dacarbazine (DTIC-Dome)
Escalated BEACOPP	<ul style="list-style-type: none"> ■ Bleomycin (Blenoxane) ■ Etoposide/VP16 (VePesid, Toposar, Etopophos) ■ Doxorubicin (Adriamycin) ■ Cyclophosphamide (Cytoxan, Neosar) ■ Vincristine (Oncovin and others) ■ Procarbazine (Matulane) ■ Prednisone
MOPP	<ul style="list-style-type: none"> ■ Mechlorethamine (Mustargen) ■ Vincristine (Oncovin and others) ■ Procarbazine (Matulane) ■ Prednisone
Stanford V	<ul style="list-style-type: none"> ■ Mechlorethamine (Mustargen) ■ Doxorubicin (Adriamycin) ■ Vinblastine (Velban) ■ Vincristine (Oncovin and others) ■ Bleomycin (Blenoxane) ■ Etoposide/VP16 (VePesid, Toposar, Etopophos) ■ Prednisone

Patients usually receive 2 chemotherapy cycles, followed by positron emission tomography-computed tomography (PET-CT, a scan that uses a special dye to show where the cancer is located) imaging to evaluate how the lymphoma is responding to the treatment. The results are used to determine whether any of the chemotherapy drugs (most often bleomycin) can be eliminated, or if radiation therapy will be required as part of treatment. Even if a patient has a *complete response* (no signs of cancer on scans or tests) it is important to complete all of the prescribed cycles of therapy in order to achieve a “cure”.

The ABVD regimen is the most widely used first-line combination chemotherapy regimen for cHL. All four agents are given intravenously every two weeks in 28-day cycles. Patients may receive 2 to 6 cycles depending on the disease stage (how severe the disease is), prognosis (how well the patient will do), other treatments, and tolerability. Bleomycin may be stopped after the third cycle to prevent lung complications. Some regimens today are more effective and less toxic, so you should ask your provider if there are other regimens that are an option for you.

Common frontline chemotherapy regimens used in children with cHL are listed in Table 14.2.

Table 14.2. Common Frontline Chemotherapy Regimens for Children with cHL

Chemotherapy regimen (abbreviation)	Generic Name of Drugs (Brand Names)
ABVE-PC	<ul style="list-style-type: none"> ■ Doxorubicin (Adriamycin) ■ Bleomycin ■ Vincristine (Oncovin and others) ■ Etoposide (Vepesid, Toposar, Etopophos) ■ Prednisone ■ Cyclophosphamide
OEPA/COPDac	<ul style="list-style-type: none"> ■ Doxorubicin (Adriamycin) ■ Vincristine (Oncovin and others) ■ Etoposide (VePesid, Toposar, Etopophos) ■ Prednisone ■ Doxorubicin (Adriamycin) ■ Cyclophosphamide (Cytoxan, Neosar) ■ Dacarbazine (DTIC-Dome)

Pediatric patients usually receive 2 chemotherapy cycles, followed by PET-CT imaging to determine whether any chemotherapy can be eliminated and/or a radiotherapy regimen is needed.

What Other Types of Drugs Are Used to Treat Patients With HL?

In addition to chemotherapy, immunotherapy, radiation therapy and stem cell transplantation can be used to treat HL.

Immunotherapy

The term *immunotherapy* refers to treatments that help boost the body's own immune response (see Chapter 7). Immunotherapy drugs used to treat cHL include antibody-drug conjugates and immune checkpoint inhibitors.

For more information, read the sections below about types of immunotherapy and see the *Immunotherapy and Other Targeted Therapies* fact sheet on LRF's website at lymphoma.org/publications.

Antibody-Drug Conjugates

An antibody-drug conjugate is a chemotherapy drug attached to a monoclonal antibody (see Chapter 7). Antibody-drug conjugates used to treat cHL are described below.

Brentuximab vedotin (Adcetris)

Brentuximab vedotin (Adcetris) is a combination of the chemotherapy drug monomethyl auristatin E (MMAE or vedotin) and a monoclonal antibody against CD30 (brentuximab). The CD30 antigen is present on the surface of all RS cells (the cancer cells in HL). Thus, the monoclonal antibody part of this drug is like a “guided missile” that is directed against and attaches itself to RS cells. Once the antibody is attached to the lymphoma cell, it is taken inside the cell (internalized). The MMAE is then released inside the HL cell, causing it to stop multiplying and die.

Brentuximab vedotin (Adcetris) is approved by the FDA to treat:

- Adult patients with previously untreated Stage III or IV cHL, in combination with doxorubicin, vinblastine, and dacarbazine.
- Pediatric patients 2 years and older with previously untreated high risk cHL, in combination with doxorubicin, vincristine, etoposide, prednisone, and cyclophosphamide.
- Adult patients with cHL at high risk of relapse or progression after autologous stem cell transplantation consolidation.
- Adult patients with cHL after failure of autologous stem cell transplantation or after failure of at least two prior multi-agent (including two or more drugs) chemotherapy regimens in patients who are not candidates for stem cell transplantation.

Brentuximab vedotin (Adcetris) in monotherapy is given as an IV infusion once every 3 weeks until disease progression or unacceptable toxicity. Doctors may use this drug in monotherapy after bone marrow transplantation as maintenance to try and keep patients in *remission* (no signs or symptoms of cancer). When combined with chemotherapy in previously untreated stage III or IV cHL, it is given every 2 weeks for a maximum of 12 doses.

Immune Checkpoint Inhibitors

Immune checkpoint inhibitors are monoclonal antibodies that restore the immune system's ability to attack the cancer cells and rid them from the body (see Chapter 7). Immune checkpoint inhibitors used to treat cHL are given intravenously every 3 or 6 weeks, target the PD-1/PD-L1 protein on the lymphoma cell and are described below.

Nivolumab (Opdivo)

Nivolumab (Opdivo) is approved by the FDA for adult patients with cHL that has relapsed or progressed after autologous stem cell transplantation and post-transplantation treatment with brentuximab vedotin (Adcetris) or 3 or more lines of systemic therapy that includes autologous stem cell transplantation.

Pembrolizumab (Keytruda)

Pembrolizumab (Keytruda) is approved by the FDA for adult and pediatric patients with relapsed or refractory cHL, or pediatric patients with cHL that has relapsed after 2 or more previous lines of therapy.

Radiation Therapy

Radiation therapy (also called *radiotherapy*) uses high-energy X-rays or other types of radiation to kill cancer cells and shrink tumors. This was the first cure for HL and works very well for this cancer. The term is generally used to describe *external-beam radiotherapy*, in which a radiation beam is delivered from a machine. In the past, common areas of the body that received radiation included lymph nodes in the neck, chest, and underarms (called the “mantle field”); lymph nodes in the abdomen and possibly spleen; and lymph nodes in the pelvis and groin. In certain circumstances, extended-field radiation was given to both the mantle and upper abdominal fields. However, these fields are no longer used in the modern treatment of HL. The most common types of radiation therapy and delivery methods used for HL are described below.

Involved-field Radiation Therapy (IFRT)

IFRT includes the lymph node regions that contain HL and is usually given after chemotherapy.

Involved-Site Radiation Therapy (ISRT)

The radiation field is narrower than IFRT so that nearby healthy tissues and organs are not affected.

Proton Therapy

Uses positively charged particles called protons delivered by an external beam. This can reduce the radiation exposure of nearby healthy tissues, allowing higher doses to be delivered to the tumor. It may be useful to treat tumors near places that are difficult to treat (e.g. heart, lungs, or esophagus).

Total Body Irradiation

The whole body is exposed to radiation along with high-dose chemotherapy (to kill all lymphoma cells in the body). It may be given to patients who are preparing for a stem cell transplant.

Stem Cell Transplantation

A stem cell transplant adds new stem cells (blood-forming cells) back into the body after chemotherapy with or without radiation, replacing the cells that were destroyed and restoring the bone marrow's ability to make new blood cells (see Chapter 7). In deciding if transplantation is a good option, doctors consider the patient's health status, age, medical history, cancer stage, and responses to previous therapy.

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

Autologous Stem Cell Transplant

In an autologous stem cell transplant, patients are their own donor. Autologous stem cell transplantation is used in patients with cancers that are responding to chemotherapy. The ability to transplant the patient's own stem cells (autologous stem cell transplant) allows doctors to use higher doses of chemotherapy than the body would normally tolerate, increasing the probability of treatment success. The curative part of this process is that it resets the patient's immune system and increases the chance that their body will kill and clear these cancer cells in the future.

Allogeneic Stem Cell Transplant

In an allogeneic stem cell transplant, the donor is another person who is genetically similar to the patient; this person is often a brother or sister. Donor stem cells may also come from the patient's child, the patient's parent, an unrelated person, or donated umbilical cord blood. This gives the patient a new immune system if their own continues to allow cancer to grow.

Syngeneic Stem Cell Transplant

In a syngeneic stem cell transplant, the donor is the patient's identical twin.

For additional information about the process of stem cell transplantation, please view the *Understanding Cellular Therapy* guide on LRF's website at lymphoma.org/publications.

Treatment of Patients With Relapsed or Refractory cHL

Patients with cHL whose disease does not go into complete remission (CR, disappearance of all signs of cancer) after initial therapy or whose disease relapses after achieving CR are often treated with second-line treatment. The preferred second-line treatment for transplant-eligible patients with relapsed HL is another chemotherapy regimen (typically different from the frontline therapy) or immunotherapy, followed by high-dose chemotherapy with autologous stem cell transplantation. Table 14.3 shows examples of second-line chemotherapy regimens used in patients with relapsed or refractory cHL.

Table 14.3. Common Second-line Chemotherapy Regimens for Adults with Relapsed or Refractory cHL

Chemotherapy regimen (abbreviation)	Generic Name of Drugs (Brand Names)
BVB	<ul style="list-style-type: none">■ Brentuximab vedotin (Adcetris)■ Bendamustine (Treanda)
BEGEV	<ul style="list-style-type: none">■ Bendamustine (Treanda)■ Gemcitabine (Gemzar)■ Vinorelbine (Navelbine)

Chemotherapy regimen (abbreviation)	Generic Name of Drugs (Brand Names)
ChIVPP	<ul style="list-style-type: none"> ■ Chlorambucil (Leukeran) ■ Vinblastine (Velban) ■ Procarbazine (Matulane) ■ Prednisone
DHAP	<ul style="list-style-type: none"> ■ Dexamethasone ■ Cytarabine/high-dose Ara-C (Cytosar-U, Tarabine PFS) ■ Cisplatin (platinol)
DICE	<ul style="list-style-type: none"> ■ Dexamethasone ■ Ifosfamide (Ifex) ■ Cisplatin (Platinol) ■ Etoposide/VP 16 (VePesid, Toposar, Etopophos)
ESHAP	<ul style="list-style-type: none"> ■ Etoposide/VP16 (VePesid, Toposar, Etopophos) ■ Methylprednisolone ■ Cytarabine (high-dose Ara-C) ■ Cisplatin (Platinol)
GCD	<ul style="list-style-type: none"> ■ Gemcitabine (Gemzar) ■ Carboplatin (Paraplatin) ■ Dexamethasone
GDP	<ul style="list-style-type: none"> ■ Gemcitabine (Gemzar) ■ Dexamethasone ■ Cisplatin (Platinol)
GEMOX	<ul style="list-style-type: none"> ■ Gemcitabine (Gemzar) ■ Oxaliplatin (Eloxatin)
GVD	<ul style="list-style-type: none"> ■ Gemcitabine (Gemzar) ■ Vinorelbine (Navelbine) ■ Liposomal doxorubicin(Doxil)
ICE	<ul style="list-style-type: none"> ■ Ifosfamide (Ifex) ■ Carboplatin (Paraplatin) ■ Etoposide/VP16 (VePesid, Toposar, Etopophos)
IGEV	<ul style="list-style-type: none"> ■ Ifosfamide (Ifex) ■ Gemcitabine (Gemzar) ■ Vinorelbine (Navelbine)

Regimens commonly used in the treatment of pediatric cHL include gemcitabine (Gemzar) plus vinorelbine (Navelbine), and ifosfamide (Ifex) plus vinorelbine (Navelbine).

For some patients with relapsed cHL, including those who are not good candidates for a stem cell transplant, other second line treatment options include the following:

- Radiation therapy alone.
- Chemotherapy alone.
- Chemotherapy combined with radiation therapy.
- An antibody-drug conjugate (brentuximab vedotin [Adcetris], see page 137).
- A checkpoint inhibitor (nivolumab [Opdivo] or pembrolizumab [Keytruda], see page 138).
- A clinical trial.

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

Clinical trials are also an important option for patients at all stages of disease, including from the start. They offer a chance to receive new treatments that may be more effective or tolerable. Many of the novel therapeutic agents (new treatments) being investigated in clinical trials are used specifically for patients with relapsed or refractory disease. Chapter 15 describes some of the options currently under investigation. For more information about clinical trials for patients with cHL, please contact the LRF Helpline at (800) 500-9976 or helpline@lymphoma.org and ask about the LRF “Clinical Trials Information Service”.

When Should a Clinical Trial Be Considered?

Clinical trials are appropriate for patients at all stages of disease, whether newly diagnosed or relapsed/refractory disease. See Chapter 8 for more general information about Clinical Trials.

If patients are interested in participating in a clinical trial, they should ask their doctor if there is an appropriate trial for them and what the potential risks and benefits may be. For more information about clinical trials for patients with HL, please contact the LRF Helpline at (800) 500-9976 or helpline@lymphoma.org and ask about the LRF “Clinical Trials Information Service”.

What Types of Treatments are Used in Patients with NLPHL?

NLPHL tends to grow slowly and may relapse later in life, no matter what type of treatment a patient receives. This form of HL is treated more like *indolent* (slow-growing) NHL than like cHL. In addition to chemotherapy and radiation therapy, immunotherapy with monoclonal antibodies and radioimmunotherapy can be used to treat NLPHL. Table 14.4 shows treatments used for various stages of NLPHL.

Active Surveillance

With the active surveillance approach (watchful waiting), patients' health and disease are monitored through regular checkups and periodic evaluation procedures, such as laboratory and imaging tests, but they do not receive any anti-lymphoma treatments. These patients continue to remain untreated as long as they do not show any signs or symptoms and there is no evidence that the lymphoma is growing or spreading. Active surveillance is an option for some patients who have early- stage or advanced-stage disease that is not bulky (no tumor greater than 10 centimeters) or with complete resection (removal through surgery) of a single involved node. For more information about active surveillance see Chapter 7 of this guide.

Doctors recommend active surveillance for selected patients with early-stage NLPHL. This approach may be used after the initial diagnosis or after relapse, depending on the situation. Patients are switched from active

surveillance to active treatment if they begin to develop lymphoma-related symptoms or if there are signs that the disease is progressing.

Active surveillance is not a treatment option for patients with symptomatic NLPHL.

Monoclonal Antibodies

Monoclonal antibodies are molecules that have been engineered in a laboratory to attach to one specific target (antigen) on the surface of cancer cells and they are effective for patients with cancer cells expressing that specific antigen (see Chapter 7). Once injected in the patient, the monoclonal antibodies travel through the blood and attach themselves to the cells that have the antigen they recognize, most of which are HL cells. This can either stop or slow down the growth of the cancer cell, or it can trigger an “alarm” that makes it easier for other immune cells to recognize and destroy the cancer cell.

The monoclonal antibody rituximab (Rituxan) used in the treatment of NLPHL is described below.

Rituximab (Rituxan)

Rituximab is a monoclonal antibody that targets the antigen CD20, a specific molecule found on the surface of almost all B-cells and other cancer cells in NLPHL (but not cHL).

While not approved by the FDA to treat HL, rituximab is sometimes given either as monotherapy (without other drugs) or in combination with chemotherapy to patients with NLPHL. Rituximab treatment is given as an IV infusion usually once weekly for a certain number of cycles, but the schedule varies depending on the type of combination regimen used. When combined with chemotherapy, rituximab is usually given during the first day of each chemotherapy cycle.

In patients with relapsed (disease comes back) or refractory (does not respond to treatment) NLPHL whose disease responds well to rituximab monotherapy, rituximab may also be used as maintenance therapy (ongoing treatment to prevent cancer from returning) for up to two years.

Whether used as monotherapy, combination therapy, or maintenance therapy, any use of rituximab for patients with NLPHL is considered off-label, meaning that the FDA has not specifically approved using rituximab for this purpose. However, it is listed as an option in the National Comprehensive Cancer Network (NCCN) guidelines. You may consult with your doctor to determine whether this is an option for you.

Radioimmunotherapy

Radioimmunotherapy consists of a targeted antibody attached to a radioisotope (a particle that emits radiation). These drugs act as a “guided missile” to destroy lymphoma cells by attaching to them and delivering small doses of radiation.

Table 14.4. Treatment for Various Stages of NLPHL

Stage	Commonly Used Treatments
Early Disease	<ul style="list-style-type: none"> ■ Observation/active surveillance ■ Involved-site radiation therapy (ISRT) ■ Rituximab (Rituxan) ■ ISRT plus ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) chemotherapy, with or without rituximab ■ AVPC (doxorubicin, vincristine, prednisone, cyclophosphamide) or CVP (cyclophosphamide, vincristine, prednisone) for pediatric patients
Advanced Disease	<ul style="list-style-type: none"> ■ Rituximab (Rituxan) ■ ABVD chemotherapy plus rituximab, with or without ISRT ■ CHOP chemotherapy plus rituximab ■ Local radiation therapy ■ ABVE-PC (doxorubicin, bleomycin, vincristine, etoposide, prednisone, procarbazine) with or without ISRT for pediatric patients
Relapsed or Refractory Disease	<ul style="list-style-type: none"> ■ Clinical trial ■ Observation/active surveillance if recurrence is limited and there are no symptoms ■ ABVD chemotherapy, rituximab (Rituxan), or involved-field radiation therapy (IFRT) alone or in any combination ■ Chemotherapy regimens used for aggressive NHL ■ Radioimmunotherapy (RIT)

In some rare cases, NPLHL can transform into aggressive NHL. Rapid growth of one or more lymph nodes is a clear indication for a biopsy to see if such a transformation has occurred. If transformation occurs, treatment of the resulting NHL is necessary.

Table 14.4 shows treatments used for various stages of NPLHL.

Alternative and Complementary Therapies for HL

Alternative therapy refers to any treatment used instead of a standard therapy (the proper treatment that is widely used by healthcare professionals and accepted by medical experts). Alternative therapies are not recognized as effective by the medical profession. **Currently, there are no proven alternative therapies to conventional cancer care for patients with HL. Patients should not use alternative remedies to replace the care suggested by their doctors.**

Complementary therapy can be used in addition to standard therapy to help improve a patient's quality of life and to relieve the effects of drug therapy, radiation, and surgery.

For more information about complementary therapies, please view Chapter 7 of this guide and the *Integrative Oncology* fact sheet on LRF's website at lymphoma.org/publications.

Some forms of complementary therapy, also known as integrative medicines or integrative oncology are described as follows.

Chiropractic and Massage Therapy

These are the most used complementary therapies to help relieve side effects and stress. A special type of massage called oncology massage for patients with cancer can help manage stress, pain, swelling and other side effects without causing harm or interfering with cancer treatments.

Acupuncture

Uses ultra-thin needles applied to specific points on the body. It may help to relieve some side effects associated with chemotherapy like pain, nausea, fatigue, hot flashes (sudden feeling of warmth in the upper body), and neuropathy (numbness or tingling in the hands or feet).

Herbal Therapy

Uses herbal medicines made with active ingredients from plant parts, such as leaves, roots or flowers. Patients should talk to their doctor before using herbal therapies, because some may interfere with cancer treatments (e.g. vitamin C, St. John's wort). Some vitamins can actually clear the chemotherapy from the body and therefore decrease its effect. It is important to talk to your provider before taking any supplements.

Mind/Body Therapies

Meditation, guided imagery and self-hypnosis may help patients manage stress. Other practices like Tai Chi and yoga may also help improve balance and flexibility.

Part 3 — Hodgkin Lymphoma

Chapter 15: Clinical Trials and Advances in Treatment of Patients with HL

Overview of Clinical Trials

Drugs that are not yet approved for sale by the FDA are said to be investigational. Some of these investigational drugs are being studied in laboratory experiments. This stage is often referred to as the preclinical phase. The drugs in more advanced stages of research are being studied in patients in clinical trials; these are referred to as being in the clinical phase of development. The most common way for a patient to receive an investigational drug is through a clinical trial.

A *clinical trial* is a carefully designed research study that involves patients who volunteer to participate. The purpose of cancer clinical trials is to use information from all the patient outcomes (how the patients responded to treatment) on past trials and design specific questions about new ways to prevent, diagnose, treat, or manage a disease or the side effects caused by a new or existing treatment. The goal is to “do better” than the previous trial. The investigators in clinical trials want to determine the safety and effectiveness of the treatment being investigated by making specific assessments before, during, and after the trial.

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

To find out more about getting access to investigational drugs and clinical trials, visit the National Cancer Institute’s (NCI’s) website at www.cancer.gov and search for “access to investigational drugs.”

Alternatively, visit www.clinicaltrials.gov to search for trials using a particular drug or to find clinical trials nearby. Patients should check with their doctor or the Lymphoma Research Foundation (LRF) Helpline “Clinical Trials Information Service” for additional information and recent updates.

See Chapter 8 of this guide for more general information about the topics below:

- What is a Clinical Trial?
- Why Is a Placebo Sometimes Used in Phase III Trials?
- Should a Patient Participate in a Clinical Trial?
- What Is Informed Consent in a Clinical Trial?
- Questions to Ask About a Clinical Trial
- What Is the Cost of Participating in a Clinical Trial?

Advances in Treatment of Patients With HL

Doctors and scientists around the world are working very hard to improve currently available treatment options and find better and safer drugs to treat patients with HL. Advances are being made in different areas including genetics, molecular biology, immunology, treatments, and supportive care. In particular, recent developments have provided a better understanding of the biology of the disease. Ongoing research and advances in treatment of patients with HL are described below.

Chemotherapy

Researchers are trying to develop new chemotherapy drugs, improve existing drugs, and find better ways to combine different dosages and sequences of existing drugs. The goal is to develop treatment regimens that are better at killing HL cells while leaving healthy cells alone, decreasing the chance of side effects. Researchers are also investigating the best way to use imaging techniques to evaluate responses to therapy and to determine future doses.

Stem Cell Transplantation

Ongoing research in stem cell transplantation is focused on finding better ways to collect stem cells from the bone marrow or peripheral blood; reducing or

eliminating *graft-vs-host disease* (where the graft attacks the patient's healthy cells) in allogeneic transplants; improving ways to remove all lymphoma cells from stem cell samples used for autologous transplants; and developing more effective regimens for reduced-intensity stem cell transplantation (uses less chemotherapy and radiation than a standard transplant).

Immunotherapy

Monoclonal antibodies

Monoclonal antibodies under study for HL include magrolimab, a first-in-class therapy against CD47, and favelezimab, directed against the inhibitory receptor lymphocyte activation gene-3 protein (LAG3). Although they have different targets, both these monoclonal antibodies activate the body's mechanisms of defense against the HL cells. Another example of a monoclonal antibody under study for HL is axatilimab (SNDX-6352), which inhibits colony stimulating factor-1 receptor (CSF-1R) and blocks mechanisms that cancer cells use to survive and spread.

Bispecific antibodies

Bispecific antibodies bind to two different antigens at once and bring together cells that have these two targets. An example of a bispecific antibodies under study for relapsed and refractory HL is AFM13, which binds to both natural killer (NK) cells (cells of the immune system) that express CD16A and HL cells that express CD30. Blinatumomab (Blinicyto), a bispecific CD19-directed CD3 T-cell engager, is also being studied in patients with HL.

Radioimmunotherapy

Yttrium-90-labeled basiliximab is a monoclonal antibody which targets the CD25 receptor. It is being studied in clinical trials as a potential vehicle to deliver radioactive substances to HL cells and kill them.

Checkpoint inhibitors

Just like the HL therapies nivolumab (Opdivo) and pembrolizumab (Keytruda), other checkpoint inhibitors that target the PD-1/PD-L1 pathway—avelumab (Bavencio), camrelizumab (SHR-1210), sintilimab (Tyvyt), and tislelizumab (BGB-A317)—are currently being investigated for use in patients with HL. Another checkpoint inhibitor called ipilimumab

(Yervoy) that targets the CTLA-4 checkpoint is also in clinical trials for the treatment of HL. Ipilimumab is currently approved by the FDA to treat melanoma (skin cancer), but it has also shown promise as an HL therapy. Vudalimab (XmAb20717) is a bispecific antibody that inhibits both PD-1 and CTLA-4 checkpoints and is also in clinical trials for HL.

Immunomodulatory drugs

Immunomodulatory drugs (IMiDs) interact with the immune system to encourage the destruction of cancer cells. The IMiD agent lenalidomide (Revlimid), which is already approved for the treatment of other blood cancers such as multiple myeloma and mantle cell lymphoma (MCL), is currently being evaluated for use in the treatment of patients with HL, both alone and in combination with other therapies such as checkpoint inhibitors.

CAR T-Cell Therapy

Chimeric antigen receptor (CAR) T-cells are a special type of cellular immunotherapy that uses a modified version of the patient's T-cells to fight cancer. These are being studied to treat patients with relapsed and refractory HL. Some patients have had very good responses to CAR T-cell therapy, with no malignant tumor cells detected after treatment. However, this therapy can sometimes result in serious side effects such as cytokine release syndrome, which is characterized by mild to moderate flu-like symptoms, reduced blood pressure, heart arrhythmias, and difficulty breathing, as well as neurologic toxicity. Medicines are now available to prevent or alleviate many of these symptoms. Research is ongoing to improve this novel therapy.

Targeted therapies

A better understanding of the biology and genetics of HL is helping researchers identify specific molecules in lymphoma cells that may be good targets for new drugs. These molecules usually have important roles in controlling the growth and survival of lymphoma cells. The drugs that target these molecules are called *targeted therapies*. Targeted therapies attack cancer cells in a more specific way than chemotherapy drugs and are less likely to kill or damage healthy cells, making it less likely for these agents to cause serious side effects.

Examples of targeted therapies, some of which have been FDA-approved for use in other types of lymphoma, leukemia, and solid cancers, that are being studied for HL in clinical trials include:

- Histone deacetylase (HDAC) inhibitors and vorinostat (Zolinza)
- Kinase inhibitors, including:
 - Bruton tyrosine kinase (BTK) inhibitors such as ibrutinib (Imbruvica)
 - Janus-associated kinase (JAK) inhibitors such as ruxolitinib (Jakafi) and itacitinib (INCB039110)
 - Mammalian target of rapamycin (mTOR) inhibitors such as everolimus (Afinitor)

Other Systemic Therapies

Systemic drugs are therapies that work throughout the body. Ongoing investigation of many novel non-chemotherapeutic agents may lead to the development of HL treatments that may attack HL cells that are resistant to conventional chemotherapy and radiation therapy. These therapies are being tested for use in both newly diagnosed and relapsed/refractory HL and include a modified interleukin-2 (a type of protein) (THOR-707) and regenerative medicine (that replaces and repairs the normal function of cells, organs, and tissues) (AB-205). The research being conducted today is changing the entire landscape of HL treatment now and in the future. The promise of this research is a compelling reason for patients with HL to consider participating in a clinical trial at any stage of treatment.

Radiation Therapy

Researchers are working to continue reducing the size of radiation therapy treatment fields and the dose of radiation delivered, with the goal of limiting radiation exposure to normal organs and tissues and hopefully reducing long-term risks of radiation therapy.

Part 4 — Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

Chapter 16: What is CLL/SLL?

What is CLL/SLL?

Until the 1990s, doctors believed that chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) were two different diseases. However, recent research has shown that CLL and SLL are actually the same disease. If the cancer cells are found mainly in the lymph nodes, the disease is called SLL. If high levels of cancer cells are found in the bloodstream, then the disease is typically called CLL. Cancer cells are often found in both the lymph nodes and the bone marrow (the spongy tissue inside the bones) of patients with SLL and CLL, and patients with CLL can also have enlarged lymph nodes at the time of diagnosis. Over time, a patient with *relapsed* (disease returns after treatment) CLL may develop enlarged lymph nodes like a patient with SLL, and a patient with relapsed SLL may have cancer cells in the blood like a patient with CLL. In fact, most cases of SLL become CLL over time. Because they are essentially the same disease presenting in different parts of the body, the two terms are now grouped together as a single condition known as “CLL/SLL”. Since patients with CLL and SLL receive the same treatments and the prognosis is similar, the rest of this guide will use the term CLL/SLL, unless a distinction needs to be made between the two conditions.

Although CLL is a leukemia, CLL and SLL are in the family of B-cell lymphomas within the larger category of non-Hodgkin lymphoma (NHL). Doctors consider CLL/SLL to be an *indolent* (slow-growing) type of lymphoma because it may remain inactive (with no symptoms) over an extended period of time and can be managed like a chronic disease (long-lasting medical condition that can be controlled but not cured).

Occasionally, CLL/SLL may progress or transform to a more aggressive (fast-growing) type of lymphoma. This transformation from CLL/SLL to a more aggressive lymphoma (usually diffuse large B-cell lymphoma) is called Richter syndrome or Richter transformation.

How Common is CLL/SLL?

About 19% of patients with a B-cell lymphoma have CLL/SLL, making it the third most common type of B-cell lymphoma. According to the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) data, approximately 18,740 people in the United States are diagnosed with CLL/SLL each year. In 2020, there were approximately 207,463 people living with CLL in the US. This disease is rare in people younger than 40 years. The median age at diagnosis is 70.

What Causes CLL/SLL?

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

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

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

Why Do Some People Develop CLL/SLL?

The reasons why certain people develop CLL/SLL are not totally understood. However, scientists have found that people with particular

characteristics, called *risk factors*, have a slightly higher chance of developing CLL/SLL. Having one or more risk factors for CLL/SLL does not mean a person will develop the disease. In fact, most people with the known risk factors never develop CLL/SLL, and many people diagnosed with CLL/SLL do not have any of these risk factors. However, there does seem to be a correlation between the risk factors described below and the development of CLL/SLL.

Known risk factors for CLL/SLL include:

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

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

What Are the Signs and Symptoms of CLL/SLL?

Approximately 50-75% of patients with CLL/SLL do not have any obvious signs or symptoms of the disease at the time of diagnosis. Their doctors might detect the disease during routine blood tests and/or a physical examination. Besides a higher than normal number of white blood cells, the immune system of people with CLL may also produce antibodies against their own red blood cells and/or platelets (*autoantibodies*, your immune system mistakes your red blood cells and platelets for foreign cells). For

others, CLL/SLL is discovered when symptoms occur and they go to the doctor because they are worried, uncomfortable, or not feeling well.

As shown in Table 16.1, CLL/SLL may cause different signs and symptoms depending on the location of the tumor in the body. Keep in mind that many of these signs and symptoms are not specific to CLL/SLL or other types of NHL and may be due to other conditions.

Table 16.1. Signs and Symptoms Commonly Found in Patients With CLL/SLL

Sign or Symptom	Possible Reason
Shortness of breath, <i>fatigue</i> (extreme tiredness), and pale skin	Low red blood cell counts (<i>anemia</i>)
Severe or frequent infections	Reduced ability to fight infection due to low white blood cell counts or a reduced ability to make antibodies that fight infections (<i>hypogammaglobulinemia</i>)
Frequent nosebleeds, bleeding from the gums, tiny red marks on the skin caused by minor bleeding under the skin (<i>petechiae</i>), and bruising easily	Low platelet counts (<i>thrombocytopenia</i>)
“B symptoms” including fever for no known reason, unexplained drastic weight loss, or drenching night sweats that soak clothing and sheets. Patients may also experience chills.	Increased levels of inflammatory chemicals (substances that cause redness, swelling and pain) in the blood that are released by cancer cells or by the immune system
Lumps under the skin on the sides of the neck, above the collarbone, or in the underarms, elbows, or groin	Lymph nodes, or “glands,” that swell because of an increased number of abnormal lymphocytes

When Should a Patient Seek Medical Attention?

Anyone who has an enlarged lymph node in the absence of an infection that does not return to normal size within a few weeks and/or persistent symptoms should see a doctor to make sure that CLL/SLL or another serious condition is not present. A good rule of thumb is to seek medical attention if any of the signs or symptoms listed in Table 16.1 last longer than 2 weeks, or sooner if the symptoms are intense enough to impact a person’s daily life. It is important to note that most patients with these

symptoms do not have CLL/SLL, as other diseases or conditions may cause many of these symptoms.

What Does the Doctor Look For During the Visit?

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

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

If the doctor suspects CLL/SLL, they will order tests to confirm the diagnosis. For CLL, it may be best to consult with a hematologist oncologist, a doctor who specializes in diagnosing and treating blood cancers.

These tests should include a complete blood count, a comprehensive metabolic panel (a group of 14 tests that measure different substances in blood) and assessing the performance status (ability to carry out day to day activities through a scoring system). Specific laboratory tests and

imaging tests (including scans) may also be required. A lymph node biopsy (a procedure that collects a small sample of the affected lymph node) may be needed for patients with suspected SLL. Doctors do not always need a bone marrow (the spongy tissue inside the bones) test to make the CLL/SLL diagnosis, but they may find it useful prior to treatment and/or to assess the response to therapy. These tests and procedures will be further discussed in more detail in this chapter.

How Is CLL/SLL Diagnosed?

CLL/SLL is diagnosed by testing the blood. Rarely are a bone marrow biopsy, or a lymph node biopsy necessary. Typically, once the diagnosis is made, there is no need to confirm it from additional sites. Most cases of CLL/SLL are diagnosed based on abnormal blood test results in people who do not have any symptoms of the disease. The doctor might also suspect that a patient has CLL/SLL because of reported symptoms or results of the physical examination. The following tests are usually used to confirm the diagnosis:

- Complete blood count with differential, a test in which the number of the different blood cells are measured. The diagnosis of CLL is characterized by a high white blood cell counts, and sometimes low levels of red blood cell and platelet counts
- Hematopathologic examination of blood smears and sometimes of a bone marrow biopsy
- Immunophenotyping by flow cytometry of the lymphocytes in the blood and lymph nodes. In these tests, chemicals or dyes are used to understand if certain proteins on the outside of the cell (*cell surface proteins*) are present. This information distinguishes CLL from other types of leukemia. Classic markers found in CLL/SLL include CD5, CD19, CD23 and dimCD20. To learn more about immunophenotyping, see Table 3.2 in Chapter 3 of this guide (page 16).
- Histopathologic examination of a lymph node biopsy (needed for diagnosis of SLL if flow cytometry from the blood does not provide enough information).

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

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

- Genetic tests (like *Fluorescence in situ hybridization* [FISH] or cytogenetic analyses) to look for acquired changes in specific regions of the chromosomes (thread-like structures that contain the genetic material). To learn more about FISH and cytogenetic analysis, see Table 3.3 in Chapter 3 of this guide (page 20).
- Molecular analysis to check on the mutation status of the immunoglobulin heavy chain variable region (*IGHV*) gene. Patients who have mutations in the *IGHV* gene usually do better than patients who do not have these mutations.
- Sequencing (determining the order of *nucleotides*, a component of DNA) of the TP53 gene to see if it contains mutations (changes)
- Blood levels of a protein called Beta-2 microglobulin
- Other tests that the doctor may deem to be useful for determining therapy

Prognostic Factors for CLL/SLL

Prognosis is the medical term for predicting how a patient will ultimately do with their disease.

The characteristics that help predict a patient's prognosis are called *prognostic factors*. Favorable or good prognostic factors tend to be associated with better outcomes (overall longevity or good response to any treatment), while unfavorable or poor prognostic factors tend to be associated with worse outcomes. Scientists have known about several prognostic factors, called traditional (most commonly used) prognostic factors, for many years or even decades, while novel (new) prognostic factors have only been recently identified (Table 16.2).

Table 16.2. Known Prognostic Factors for CLL/SLL

Traditional Prognostic Factors	Modern Prognostic Factors
<ul style="list-style-type: none">■ Rai stage■ Sex■ Age■ Beta-2 microglobulin levels in the blood	<ul style="list-style-type: none">■ FISH■ Immunoglobulin heavy chain variable (<i>IGHV</i>) gene mutation status■ <i>TP53</i> mutation

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

FISH

FISH (Fluorescence in situ Hybridization) is a way to study the chromosomes inside CLL cells. Chromosomes contain genes that are made of very long strands of DNA (genetic material). Normal human cells have 23 pairs of chromosomes. CLL cells from some patients have a normal number of chromosomes, but some have too many or too few chromosomes, or they may have abnormal chromosomes that have undergone a genetic change. These changes can cause CLL cells to multiply. The most common types of chromosome abnormalities that occur in CLL/SLL are described below and in Table 16.3.

- *Deletion*: A common chromosomal abnormality in CLL/SLL is called a *deletion*, which happens when part of a chromosome is missing. The most common deletions, abbreviated as “del,” in CLL/SLL are seen in chromosomes 11, 13, and 17. Deletions in these chromosomes are written as del(11q), del(13q), and del(17p) in a patient’s FISH or karyotype testing report. Some patients’ cancer cells might have no detectable deletions at first, but they can develop deletions in chromosome 17 over time (called *clonal evolution*). Of all the prognostic markers (markers that indicate how well the patient will do), the most important to know is whether deletions in chromosome 17 are present, as this affects treatment selection.

- **Trisomy:** Another type of chromosomal abnormality that may be present in the DNA of CLL/SLL lymphocytes is trisomy, which indicates the presence of an extra copy of a chromosome. Normally there are two pairs of each chromosome, but if a mistake occurs during cell division, a third copy of the chromosome can be created.

Table 16.3. Chromosomal Changes and Genetic Mutations Most Commonly Found in CLL/SLL

Chromosome or Gene Mutation	Prevalence in Patients With CLL/SLL ^a
Del(13q14)	50% to 60%
Trisomy 12	10% to 20%
Del(11q23)	15% to 20%
Del(17p)	5% to 10%

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

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

IGHV (Immunoglobulin Heavy Chain Variable)

To assess IGHV (Immunoglobulin Heavy Chain Variable) status, pathologists sequence (determine the order of the building-blocks that form the genetic material) the DNA inside the CLL cells to determine how similar the DNA in these cells is to the other cells in the body. If the DNA is very similar (2% or less difference) that is called “unmutated IGHV”, and if the DNA is less similar (>2% difference) that is called “mutated”. CLL cells from patients with unmutated IGHV CLL typically grow faster, so patients with this type of CLL often need treatment sooner. Patients with mutated IGHV CLL tend to have slower growing CLL which often takes longer before treatment is needed. Historically, chemotherapy-based regimens were not as effective for patients with unmutated IGHV, leading to shorter survival. Fortunately, the targeted therapies developed for CLL over the last decade are highly effective for patients with unmutated IGHV, so the prognosis for these patients has improved dramatically in recent years.

TP53 Mutations

Mutations in the TP53 gene (located on chromosome 17) can also be found in CLL. TP53 provides instructions for the cells to produce a tumor suppressor protein (a protein that controls cell division and causes the

death of cancer cells) called p53. In CLL, mutations in the TP53 have historically been associated with a poor prognosis. Note that to assess TP53 mutation status (the number and type of permanent changes in the TP53 gene), a separate blood test must be sent from the FISH test, as DNA sequencing (determining the order of building-blocks that form DNA) is required. This can be confusing, because some FISH results will report deletion TP53, but this is not the same thing as *TP53* mutation. Often, both del(17p) and *TP53* mutation are both present, but about 5% of patients with CLL will have *TP53* mutation alone at diagnosis. As with unmutated IGHV, the prognosis for patients with *TP53* mutation has improved dramatically in the last few years with the use of targeted therapies.

In summary, given the complexity of these molecular tests and their impact on prognosis, it is important for patients to discuss the interpretation of diagnostic tests with their doctor. Some important considerations when interpreting diagnostic tests are listed below.

Additionally, two important features of prognostic markers to remember are:

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

Cautions About Interpreting Diagnostic Reports

- If patients wish to look at their written or electronic test reports, it is important for them to review and interpret the findings carefully with their doctor
- Some test results may be reported as "normal" even though CLL/SLL is present

- Some test results may be reported as “abnormal” even though CLL/SLL is not present
- Other conditions can produce signs and symptoms similar to CLL/SLL
- The interpretation of test results, such as imaging studies and scans, can be lengthy, complex, and difficult in some situations
- Follow-up tests are often needed to determine the significance of previous results, and additional biopsies may be needed to clarify the results

Part 4 — Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

Chapter 17: Treatment of CLL/SLL

This chapter reviews the most common therapies currently used in the treatment of CLL/SLL. Keep in mind that new therapies may have been approved by the U.S. Food and Drug Administration (FDA) since this guide was published. See Chapter 17 to learn more about emerging treatments under investigation.

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

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

There are 3 general types of treatments approved for patients with CLL/SLL:

- *Active surveillance* (observation with no treatment), in which the patient is closely monitored to see if/when treatment should be started.
- Drug therapy, including one or more of the following types of drugs:
 - Targeted therapies, which affect special characteristics or internal workings of CLL cells
 - Immunotherapy, which helps the body's immune system attack CLL cells
 - Chemotherapy, which affects general cell growth and proliferation (the ability of cells to multiply). It is important to add that chemotherapy currently plays a very limited role in the treatment of CLL/SLL.
- Stem cell transplantation, which replaces the patient's immune system with healthy immune cells.

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

What Is Active Surveillance?

With the active surveillance (or *watchful waiting*) approach, patients' health and disease are monitored through regular checkups and evaluation procedures, such as laboratory and imaging tests, but they do not receive any CLL treatments. These patients continue to remain untreated as long as they do not show any signs or symptoms and there is no evidence that the CLL is growing or spreading. If the lymphocyte counts doubles in less than 6 months, this can be a sign that the CLL is becoming more active, but in and of itself does not lead to a need for CLL treatment.

Doctors use established criteria to help determine when the disease is becoming more active and the patient should no longer remain on active surveillance. These criteria include:

- Progressive bone marrow failure; indicated by anemia (low levels of red blood cells; Rai stage III) or thrombocytopenia (low platelet levels; Rai stage IV). To learn more about Rai staging for CLL/SLL, see Chapter 5 of this guide (page 33).
- Development of large (bulky) lymph nodes
- Enlargement of the spleen (splenomegaly)
- Autoimmune cytopenias (body attacks its own blood cells) that is not resolved by treatment with steroids
- B symptoms (fever and/or chills for no known reason, unexplained weight loss, and drenching night sweats that soak clothing and sheets)
- Severe fatigue (extreme tiredness) due to progressing CLL/SLL
- A threat caused by the CLL to one or more organs

Though doctors may recommend active surveillance for selected patients with *indolent* CLL/SLL, it is not a treatment option for patients with advanced CLL/SLL (when CLL cells outnumber the healthy cells in the bone marrow and the disease becomes more severe). While the decision to start treatment depends on the clinical judgment of the treating physician, treatment for patients with advanced CLL/SLL should generally start soon after patients reach this stage. For more information about active surveillance see Chapter 7 of this guide (page 52).

What Drugs Are Used to Treat CLL/SLL?

Patients with CLL/SLL are commonly given either a single drug or a combination of drugs. The purpose of combining drugs is to increase how effectively they damage or kill cancer cells, to diminish the chances of the cancer cells becoming resistant to treatment, or to allow lower doses of each drug to be used to minimize side effects. Some patients receive treatment in cycles at specific intervals (followed by rest periods), and other patients may be treated daily for an indefinite amount of time (for some oral drugs like pills, tablets or capsules).

Drugs may be combined to create a *treatment regimen*—a specific schedule that determines which drugs are given in which doses on which days of each treatment cycle.

Treatment regimens for CLL/SLL may include chemotherapy, immunotherapy, and/or targeted therapy. Most chemotherapy and monoclonal antibody drugs used to treat CLL/SLL are given intravenously (as a liquid that is infused directly into a vein, commonly known as an “IV”). Table 17.1 lists the drug regimens currently FDA approved for the treatment of CLL/SLL. This list is subject to change as the FDA approves new CLL/SLL treatments.

Table 17.1. Drug regimens currently FDA approved for the treatment of CLL/SLL

Medication or Regimen Abbreviation	Generic Name of Medications (Brand Name)	Delivery Method
Acalabrutinib alone	Acalabrutinib (Calquence)	Oral capsules
Acalabrutinib plus obinutuzumab	Acalabrutinib (Calquence) Obinutuzumab (Gazyva)	Oral capsules IV infusion
Alemtuzumab ^a alone	Alemtuzumab (Campath)	IV infusion
Alemtuzumab ^a with rituximab	Alemtuzumab (Campath) Rituximab (Rituxan)	IV infusion IV infusion
Bendamustine plus obinutuzumab	Bendamustine (Bendeka, Treanda) Obinutuzumab (Gazyva)	IV infusion IV infusion
Bendamustine plus ofatumumab ^b	Bendamustine (Bendeka, Treanda) Ofatumumab (Arzerra)	IV infusion IV infusion

Medication or Regimen Abbreviation	Generic Name of Medications (Brand Name)	Delivery Method
Bendamustine plus rituximab	Bendamustine (Bendeka, Treanda) Rituximab (Rituxan)	IV infusion IV infusion
BR plus ibrutinib	Bendamustine (Bendeka, Treanda) Rituximab (Rituxan) Ibrutinib (Imbruvica)	IV infusion IV infusion Oral capsules/tablets/oral suspension
Chlorambucil plus obinutuzumab	Chlorambucil (Leukeran) Obinutuzumab (Gazyva)	Oral tablets IV infusion
Chlorambucil plus ofatumumab ^b	Chlorambucil (Leukeran) Ofatumumab (Arzerra)	Oral tablets IV infusion
Chlorambucil plus rituximab	Chlorambucil (Leukeran) Rituximab (Rituxan)	Oral tablets IV infusion
Duvelisib	Duvelisib (Copiktra)	Oral capsules
FC plus ofatumumab ^b	Fludarabine (Fludara) Cyclophosphamide (Cytoxan) Ofatumumab (Arzerra)	IV infusion Oral tablets or IV infusion IV infusion
FCR	Fludarabine (Fludara) Cyclophosphamide (Cytoxan) Rituximab (Rituxan) or Rituximab hyaluronidase (Rituxan Hycela)	IV infusion Oral tablets or IV infusion IV infusion or SC injection
FR	Fludarabine (Fludara) Rituximab (Rituxan)	IV infusion IV infusion
HDMP-R	High-dose methylprednisolone (Solu-Medrol and others) Rituximab (Rituxan)	IV infusion or intramuscular (IM) injection IV infusion
Ibrutinib alone	Ibrutinib (Imbruvica)	Oral capsules/tablets/oral suspension
Ibrutinib plus obinutuzumab	Ibrutinib (Imbruvica) Obinutuzumab (Gazyva)	Oral capsules/tablets/oral suspension IV infusion

Medication or Regimen Abbreviation	Generic Name of Medications (Brand Name)	Delivery Method
Ibrutinib plus rituximab	Ibrutinib (Imbruvica)	Oral capsules/tablets/oral suspension
	Rituximab (Rituxan)	IV infusion
Idelalisib alone	Idelalisib (Zydelig)	Oral tablets
Idelalisib plus rituximab	Idelalisib (Zydelig)	Oral tablets
	Rituximab (Rituxan)	IV infusion
Lenalidomide alone	Lenalidomide (Revlimid)	Oral capsules
Lenalidomide plus rituximab	Lenalidomide (Revlimid)	Oral capsules
	Rituximab (Rituxan)	IV infusion
Obinutuzumab alone	Obinutuzumab (Gazyva)	IV infusion
Ofatumumab ^b alone	Ofatumumab (Arzerra)	IV infusion
Rituximab alone	Rituximab (Rituxan)	IV infusion
	Rituximab-abbs ^c (Truxima)	IV infusion
Rituximab and hyaluronidase human ^d	Rituximab and hyaluronidase human (Rituxan Hycela)	SC injection
Venetoclax alone	Venetoclax (Venclexta)	Oral tablets
Venetoclax plus obinutuzumab	Venetoclax (Venclexta)	Oral tablets
	Obinutuzumab (Gazyva)	IV infusion
Venetoclax plus rituximab	Venetoclax (Venclexta)	Oral tablets
	Rituximab (Rituxan)	IV infusion
Zanubrutinib alone	Zanubrutinib (Brukinsa)	Oral capsules

^aAlemtuzumab is provided only through the Campath Distribution Program; it is no longer commercially available.

^bOfatumumab is provided only through the Arzerra Oncology Access Program; it is no longer commercially available.

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

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

IV, intravenous; SC, subcutaneous.

Immunotherapy

The term immunotherapy refers to treatments that use the body's own immune response to fight cancer (see Chapter 6). There are many different types of immunotherapy, but only a specific type called monoclonal antibodies are approved to treat patients with CLL/SLL. The three monoclonal antibodies that are approved to treat CLL are described below.

For more information, read the sections below about types of immunotherapy and see the *Immunotherapy and Other Targeted Therapies* fact sheet on LRF's website at lymphoma.org/publications.

Monoclonal Antibodies

Monoclonal antibodies are molecules that have been engineered in a laboratory to attach to one specific target (antigen). This target is specifically chosen to be useful for the treatment of the cancer. Antibodies generated in the laboratory are all identical in their protein sequence (order of the building blocks that form proteins). Once injected in the patient, the monoclonal antibodies travel through the blood and attach themselves to the cells that have antigens they recognize, most of which are CLL/SLL cells. This can either stop or slow down the growth of the cancer cell, or it can trigger an "alarm" that makes it easier for other cells in the immune system to recognize and destroy the cancer cell.

The monoclonal antibody therapies used to treat CLL/SLL are given as IV infusions or subcutaneous (under the skin) injections. Two monoclonal antibodies are used in the treatment of CLL/SLL: rituximab (Rituxan) and obinutuzumab (Gazyva). Alemtuzumab (Campath) and ofatumumab (Arzerra) are no longer commercially available but can be obtained for clinical use. Alemtuzumab is provided only through the Campath Distribution Program, while ofatumumab (Arzerra) is provided only through the Arzerra Oncology Access Program. With the exception of alemtuzumab (Campath), these treatments are directed against different parts of CD20, an antigen that is almost universally present on the surface of B-cells, including the malignant lymphocytes in CLL/SLL. Because they target different parts of CD20, each of these drugs work a bit differently.

Obinutuzumab (Gazyva)

Obinutuzumab (Gazyva) is approved by the FDA for the treatment of patients with previously untreated CLL in combination with chlorambucil (Leukeran). It may also be used in combination with venetoclax (Venclexta), ibrutinib (Imbruvica) or acalabrutinib (Calquence).

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

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

In 1997, rituximab (Rituxan) became the first monoclonal antibody approved by the FDA for the treatment of patients with lymphoma. Rituximab is approved by the FDA for the treatment of adult patients with previously untreated or treated CD20-positive CLL/SLL in combination with FC chemotherapy (fludarabine and cyclophosphamide).

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

A subcutaneous formulation of rituximab (Rituxan Hycela or “rituximab and hyaluronidase human”) was approved by the FDA in 2017 for use in patients with previously untreated or treated CLL in combination with FC (fludarabine and cyclophosphamide) chemotherapy. Subcutaneous administration allows the drug to be given in a shorter period of time. Before patients can receive rituximab and hyaluronidase human (Rituxan Hycela), they must first have at least one full dose of IV rituximab.

Targeted Therapies

This term refers to drugs that target molecules that cancer cells use to survive, multiply, and spread in the body. To learn more about targeted therapies, please view Chapter 7 of this guide (page 57).

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

- The Bruton tyrosine kinase (BTK) inhibitors ibrutinib (Imbruvica), acalabrutinib (Calquence), zanubrutinib (Brukinsa), and pirtobrutinib (Jaypirca). These drugs inhibit the signaling protein BTK to block the growth and survival of cancer cells.
- The phosphatidylinositol 3-kinase (PI3K) inhibitor idelalisib (Zydelig) and duvelisib (Copiktra). These drugs block the signaling protein PI3K to block the growth and cause the death of cancer cells.
- The B-cell lymphoma 2 (Bcl2) inhibitor venetoclax (Venclexta). This drug targets the Bcl2 protein, which is essential for cancer cell survival.

Ibrutinib (Imbruvica)

Ibrutinib (Imbruvica) is approved for treatment of adult patients with CLL/SLL, with or without del(17p). It can be used as single agent or in combination with other drugs approved for the treatment of CLL/SLL (See Table 17.1). Ibrutinib (Imbruvica) comes in the form of capsules, tablets or oral suspension taken orally once a day. Capsules and tablets must be swallowed whole.

Acalabrutinib (Calquence)

Acalabrutinib (Calquence) is approved for treatment of adult patients with CLL/SLL. It can be used in monotherapy or in combination with obinutuzumab (Gazyva). Acalabrutinib (Calquence) is taken orally twice a day and comes in a tablet form that should be swallowed whole.

Zanubrutinib (Brukinsa)

Zanubrutinib (Brukinsa) is approved as monotherapy for treatment of adult patients with CLL/SLL. Zanubrutinib (Brukinsa) is taken orally twice a day, or once a day, and comes in the form of capsules that should be swallowed whole.

Pirtobrutinib (Jaypirca)

Pirtobrutinib (Jaypirca) is indicated for the treatment of adult patients with CLL/SLL who have received at least two prior lines of therapy, including a BTK inhibitor and a Bcl-2 inhibitor. It is taken as an oral tablet once a day with water.

Idelalisib (Zydelig)

Idelalisib (Zydelig) is approved in combination with rituximab, for the treatment of patients with CLL for whom rituximab alone would be considered appropriate therapy due to other co-morbidities (other diseases or medical conditions of the patient).

Idelalisib may only be used in patients who have received other lymphoma treatments; it is not intended to be used as frontline (initial) therapy. Idelalisib (Zydelig) is taken orally twice a day and comes in the form of tablets that should be swallowed whole.

Duvelisib (Copiktra)

Duvelisib (Copiktra) is approved for the treatment of adult patients with relapsed or refractory CLL/SLL after at least two prior therapies. Duvelisib (Copiktra) is taken orally twice a day and comes in the form of capsules that should be swallowed whole.

Venetoclax (Venclexta)

Venetoclax (Venclexta) is approved as monotherapy or in combination with obinutuzumab (Gazyva) for the frontline treatment of adult patients with CLL/SLL. It is also approved in combination with rituximab (Rituxan) in the treatment of patients with previously treated CLL/SLL which has relapsed or become refractory. Venetoclax (Venclexta) is taken orally once daily and comes in the form of tablets that must be swallowed whole. Venetoclax is typically given in a *ramp up schedule* (doses are gradually increased over the course of 4 weeks) until the ideal dose is attained. You will need your labs monitored around the dose ramp-up of venetoclax to monitor a severe complication of venetoclax called tumor lysis syndrome (see page 195).

Chemotherapy

Chemotherapy drugs work by attacking cells that grow and multiply very quickly, which is a common characteristic of cancer cells. To learn more about chemotherapy, see Chapter 7 of this guide (page 54)

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

agents bendamustine (Bendeke, Treanda), fludarabine (Kudara), and chlorambucil (Leukeran). Most patients with CLL/SLL that are treated with chemotherapy receive treatment as an outpatient (patient receives treatment in the clinic or hospital but is not hospitalized overnight).

Combined Therapies

Some treatment strategies for CLL/SLL use treatment combinations (e.g. chemotherapy or targeted therapy plus monoclonal antibody). For example, monoclonal antibodies like rituximab (Rituxan) or obinutuzumab (Gazyva) are frequently combined with targeted therapy. Other combination therapies used to treat CLL/SLL are listed on Table 17.1. The treating physician will evaluate which combination will provide the best treatment results and lowest risk for each patient.

Stem Cell Transplantation

A stem cell transplant adds new stem cells (blood-forming cells) back into the body after chemotherapy with or without radiation, replacing the cells that were destroyed and restoring the bone marrow's ability to make new blood cells (see Chapter 7). In deciding if transplantation is a good option, doctors consider the patient's health status, age, medical history, cancer stage, and responses to previous therapy.

There are three types of stem cell transplantation that differ based on the source of the stem cells: autologous, allogeneic and syngeneic. Autologous stem cell transplantation is not used in patients with CLL/SLL because their stem cells are often contaminated with the disease. Therefore, this type of stem cell transplantation is not discussed below.

Allogeneic Stem Cell Transplant

In an allogeneic stem cell transplant, the donor is another person who is genetically similar to the patient; this person is often a brother or sister. Donor stem cells may also come from the patient's child, the patient's parent, an unrelated person, or donated umbilical cord blood (blood from the placenta and umbilical cord that is collected after birth and is rich in stem cells).

Syngeneic Stem Cell Transplant

In a syngeneic stem cell transplant, the donor is the patient's identical twin.

For additional information about the process of stem cell transplantation, please view the *Cellular Therapy* guide on LRF's website at lymphoma.org/publications.

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

Part 4 — Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

Chapter 18: Clinical Trials and Advances in Treatment of Patients with CLL/SLL

Overview of Clinical Trials

Drugs that are not yet approved by the FDA are said to be investigational. Some of these investigational drugs are being studied in laboratory experiments. This stage is often referred to as the preclinical phase. The drugs in more advanced stages of research are being studied in patients in clinical trials; these are referred to as being in the clinical phase of development. The most common way for a patient to receive an investigational drug is through a clinical trial.

A *clinical trial* is a carefully designed research study that involves patients who volunteer to participate. The purpose of cancer clinical trials is to answer specific questions about new ways to prevent, diagnose, treat, or manage a disease or the side effects caused by a new or existing treatment, or the cancer. The investigators in clinical trials want to determine the safety and effectiveness of the treatment being investigated by making specific assessments before, during, and after the trial.

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

To find out more about getting access to investigational drugs and clinical trials, visit the National Cancer Institute’s (NCI’s) website at www.cancer.gov and search for “access to investigational drugs.” Alternatively, visit www.clinicaltrials.gov to search for trials using a particular drug or to find clinical trials nearby. Patients should check with their doctor

or the Lymphoma Research Foundation (LRF) Helpline “Clinical Trials Information Service” for additional information and recent updates.

See Chapter 8 of this guide for more general information about the topics below:

- What is a Clinical Trial?
- Why Is a Placebo Sometimes Used in Phase III Trials?
- Should a Patient Participate in a Clinical Trial?
- What Is Informed Consent in a Clinical Trial?
- Questions to Ask About a Clinical Trial
- What Is the Cost of Participating in a Clinical Trial?

Advances in Treatment of Patients With CLL/SLL

Doctors and scientists around the world are working very hard to improve currently available treatment options and find better and safer drugs to treat patients with CLL/SLL. Advances are being made in different areas including genetics, molecular biology, immunology, treatments, and supportive care. In particular, recent developments have provided a better understanding of the biology of the disease (how and why the disease develops and spreads). Ongoing research and advances in treatment of patients with CLL/SLL described below.

CAR T-Cell Therapy

Chimeric antigen receptor (CAR) T-cells are a special type of cellular immunotherapy that uses a modified (changed in the laboratory) version of the patient’s T-cells to fight cancer. For more information on CAR T-cell therapy, see Chapter 7 of this guide (page 57). CAR T-cells are currently being studied to treat patients with relapsed or refractory CLL/SLL.

Lisocabtagene maraleucel (Breyanzi) and rapcabtagene autoleucel (YTB-323) are examples of CD19-directed CAR T-cell therapies currently under study for CLL/SLL. Other examples are CLIC-1901, MB-CART19.1 and CTX112. MB-106 is an anti-CD20 CAR T-cell therapy and is also in clinical trials for CLL/SLL.

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

Stem Cell Transplantation

Ongoing research in stem cell transplantation is focused on finding better ways to collect stem cells from the bone marrow or peripheral blood; reducing or eliminating *graft-versus-host disease* in allogeneic transplants; improving ways to remove all lymphoma/leukemia cells from stem cell samples used for autologous transplants; and developing more effective regimens for reduced-intensity stem cell transplantations. For more information on transplantation, please view LRF's Understanding Cellular Therapy booklet available at lymphoma.org/publications.

Immunotherapy

Monoclonal antibodies

Monoclonal antibodies like rituximab (Rituxan, an anti-CD20 antibody), alemtuzumab (Campath, an anti-CD52 antibody), and obinutuzumab (Gazyva, an anti-CD20 antibody) are approved by FDA for the treatment of patients with CLL/SLL. New combinations of these monoclonal antibodies and other novel medications are being investigated in clinical trials. Tafasitamab (Monjuvi, an anti-CD19 monoclonal antibody) is currently being evaluated in clinical trials for patients with CLL. Other monoclonal antibodies in clinical trials include cirmtuzumab (UC-961), targeting receptor tyrosine kinase-like orphan receptor 1 (ROR1). XmAb5574 (MOR00208), a CD19-directed monoclonal antibody, is also being tested for the treatment of patients with CLL/SLL.

Bispecific antibodies

Bispecific antibodies bind to two different antigens which can be located at the surface of the same or 2 different cells. Examples of bispecific antibodies under study for relapsed/refractory CLL include epcoritamab (Epkinyt) and mosunetuzumab (Lunsumio), which bind to the patient's

healthy T-cells (a type of white blood cell) that express CD3 and cancer cells that express CD20. Ixazomib (Tibicen), a bispecific antibody directed at two different parts of CD37 (a marker in cancerous B-cells), is also being studied in patients with relapsed or refractory CLL/SLL.

Immune Checkpoint inhibitors

Immune checkpoint inhibitors help develop or enhance the immune system's capacity to kill cancer cells that evade the immune system's response. Two checkpoint inhibitors, nivolumab (Opdivo) and pembrolizumab (Keytruda), which are FDA-approved for the treatment of Hodgkin lymphoma, are currently being investigated in CLL/SLL clinical trials. Atezolizumab (Tecentriq) is also under investigation for the treatment of CLL/SLL.

Vaccines

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

Targeted therapies

Several targeted therapies for CLL/SLL are being studied in laboratories and in clinical trials, like the BTK inhibitor nembatinib (MK-0752). MS-553, an inhibitor of protein kinase C (PKC), is also in clinical trials for the treatment of CLL/SLL. Since research in CLL/SLL advances quickly, patients should check with their doctor or LRF for additional information and updates.

Chemotherapy

Researchers are trying to develop new chemotherapy drugs, improve existing drugs, and find better ways to combine different dosages and sequences of existing drugs. The goal is to develop treatment regimens that are better at killing CLL/SLL cells while leaving healthy cells alone, decreasing the chance of side effects.

Combination Therapies

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

Part 5 — Survivorship and Living with The Side Effects of Treatment

Chapter 19: Common Treatment Side Effects

Patients being treated for lymphoma may experience various side effects or toxicities caused by their treatment. All treatments have the potential to cause side effects. Fortunately, medications and other treatment strategies can effectively prevent or lessen the severity of most side effects. Before beginning treatment, patients should ask their healthcare team about the most common treatment side effects and how to prevent and manage them. Once treatment has begun, patients need to tell their doctor, nurse, nurse practitioner, or physician assistant about all side effects they experience. This chapter explains why side effects occur, the types of side effects caused by different treatments, and steps for minimizing them.

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

Long-term effects are toxicities that occur during cancer treatment and continue for months or years. Fatigue, symptoms of menopause (the time that marks the end of a woman's menstrual cycles) and neuropathy (nerve problems) are examples of long-term effects. In contrast, *late* effects of treatment appear only after treatment has ended—sometimes months, years, or even decades after treatment is completed. Infertility, osteoporosis (disease that thins and weakens the bones), heart problems, and secondary cancers are examples of late effects.

Why Does Chemotherapy Cause Side Effects or Toxicities?

Chemotherapy causes side effects because of the nonspecific way these drugs work, which means that they affect cancer cells but also some types of healthy cells. Most chemotherapy drugs work by killing cells that grow and multiply faster than typical cells. Cancer cells are one type of cell that multiplies rapidly, which is why chemotherapy can be effective at killing them. However, a few types of normal cells in the body also multiply quickly, including the cells in hair roots, the mouth, the gastrointestinal tract (stomach and intestines), and bone marrow (the spongy tissue inside the

bones), so these may also be damaged or killed by chemotherapy. Some chemotherapy drugs can also damage cells in other organs and tissues.

The type and severity of side effects caused by chemotherapy vary widely depending on the specific drugs that are given, an individual patient's tolerance, other medical conditions, and the length of time therapy is delivered. The same drug may cause no side effects in one patient, while in others it may cause very mild to very serious side effects. Other side effects do not occur until later and may become worse over time.

What Side Effects Are Caused by Chemotherapy?

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

- Changes in taste
- Cognitive problems (trouble concentrating, impaired memory, sometimes called “chemo brain”)
- Constipation
- Decreased blood cell production (decreased red blood cells, hemoglobin, white blood cells, neutrophils, or platelets)
- Diarrhea
- Fatigue
- Hair loss
- Pain
- Heart damage (cardiotoxicity)
- Increased risk of infections
- Loss of appetite
- Lung toxicity (damage to the lungs)
- Mouth sores
- Nausea or vomiting
- Peripheral neuropathy (numbness or tingling in hands and feet)
- Problems with sexual function
- Sterility (inability to have children)

- Tumor Lysis Syndrome (TLS, a reaction to toxic substances released by dying cancer cells, which can damage the kidneys and other organs)
- Secondary cancers
- Change in skin and/or nails

Changes in Taste

Some patients receiving treatment experience a change in the way foods or beverages taste. Familiar foods may taste different (*dysgeusia*), or the flavors of foods may not taste as strong (*hypogeusia*). Some patients may also notice that foods have a metallic taste. These side effects are temporary and usually disappear after completion of chemotherapy.

Sometimes this side effect can be helped by dietary changes, such as eating foods that are frozen, cold, or at room temperature; adding extra seasonings or sugar to enhance taste and reduce bitterness; and avoiding metallic silverware.

Cognitive Problems

Chemotherapy can result in mild cognitive impairment, such as trouble concentrating, impaired memory, or issues with motor control (control over the body's movements) Some patients refer to these side effects as "chemo brain." Although these side effects can be stressful, they typically disappear over time.

Constipation

Constipation is a significant side effect observed in young and older patients with lymphoma. It can be severe in some of the regimens given to adolescents and young adults as a result of higher vincristine (Oncovin and others) doses. This can lead to nonadherence (not following directions) to regimens prescribed.

Decreased Blood Cell Production

Chemotherapy temporarily interferes with the ability of the bone marrow to produce enough red blood cells, white blood cells, and/or platelets (*myelosuppression*). Because of this, it is standard practice to space out the chemotherapy treatments and allow the bone marrow to restore its function.

To prevent and monitor myelosuppression, samples of a patient's blood are tested with a complete blood count (CBC) with differential, which measures the numbers of red blood cells and platelets, as well as all the different subtypes of white blood cells. These tests are usually done before and sometimes during the treatment process. Table 19.1 describes five of the most common conditions involving a decrease in blood cell production.

Table 19.1. Five Common Conditions Caused by Decreased Blood Cell Production

<p>Anemia</p>	<ul style="list-style-type: none"> ■ <i>Anemia</i> is a decrease in the number of red blood cells. ■ Many types of therapy cause mild or moderate anemia. ■ Anemia can make people feel tired and short of breath, especially when it is severe. ■ Drugs or red blood cell transfusions can be used in less common conditions where anemia is severe.
<p>Leukopenia</p>	<ul style="list-style-type: none"> ■ <i>Leukopenia</i> refers to a decrease in the number of leukocytes, or white blood cells. Leukocytes include lymphocytes (B-cells and T-cells), neutrophils, basophils, eosinophils, and monocytes. ■ Patients with low levels of neutrophils are at increased risk of infections.
<p>Lymphopenia</p>	<ul style="list-style-type: none"> ■ <i>Lymphopenia</i>, also called lymphocytopenia, refers to a decrease in the number of lymphocytes. Lymphocytes are white blood cells that produce antibodies and fight particular infections. About 20%-40% of white blood cells are lymphocytes. ■ Patients with low levels of lymphocytes are at increased risk of infections.

Neutropenia

- *Neutropenia* refers to a decrease in neutrophils, the primary type of white blood cells that fight bacterial infections.
- Patients with low neutrophil counts are at higher risk of serious and even life-threatening infections. Symptoms of infection often include fever and chills.
- During therapy, doctors regularly monitor the patient's absolute neutrophil count (ANC), the number of neutrophils in the peripheral blood. Because patients with an ANC below 500 cells per microliter are at particularly high risk for infections, doctors frequently modify or hold treatment in case of infection, until the ANC returns to 500 or greater.
- Some patients with neutropenia require treatment with antibiotics and hospitalization to prevent or treat infections.
- To avoid a patient missing a dose of therapy, doctors sometimes prescribe drugs like filgrastim (Neupogen, Granix, Zarxio) or pegfilgrastim (Neulasta, Fulphia) to reduce the duration and severity of neutropenia. These drugs can sometimes cause bone pain, which is usually temporary. Bone pain in the chest can mimic heart disease; patients experiencing unexplained chest pain should contact their doctor immediately.
- Unless contraindicated (not advised), bone pain can be managed with nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen (Advil and others) or naproxen (Aleve, Naprosyn), as well as the antihistamine loratadine (Claritin, Alavert). Acetaminophen (Tylenol) can also be used. Always ask your doctor about using NSAIDs, tylenol, or other medications.
- For patients with Hodgkin Lymphoma (HL), pegfilgrastim, filgrastim, and other white blood cell growth factors (substances that stimulate the growth of living cells) **SHOULD ALMOST NEVER BE GIVEN** to patients with early-stage HL receiving frontline ABVD. However, these substances can be given to patients with advanced HL who receive AVD-BV or AVD-nivolumab (Opdivo). Although these drugs can help to raise the ANC, they can also increase the chances that one of the chemotherapy drugs (for example, bleomycin) will cause lung problems. However, these growth factors can be given to patients who do not receive or who stop receiving bleomycin. Note that this is not generally a problem in the treatment of pediatric classical HL.

Thrombocytopenia

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

Diarrhea

Some types of chemotherapy may cause diarrhea. While most patients do not experience severe diarrhea, the most important point to remember is to stay hydrated. Signs of dehydration include dry mouth or skin, passing urine less often than usual, and feeling dizzy or lightheaded after standing up. The doctor should be contacted if the patient has bloody diarrhea, fever with diarrhea, or if the diarrhea lasts for a long time. Patients may follow the tips below.

PATIENT TIP

Avoiding Dehydration From Diarrhea or Vomiting

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

Fatigue

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

PATIENT TIP

Coping With Fatigue

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

Hair Loss

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

When hair loss occurs, it usually starts two to six weeks after the first chemotherapy treatment. Remember that hair loss caused by chemotherapy is usually temporary; hair will most likely grow back after the end of treatment. When the hair first grows back, it may have a slightly

different texture or color than it had before treatment. Over time, the texture and color often return to how they looked before treatment started.

Loss of hair in the nose and nasal passages may lead to *rhinorrhea* (runny nose). Loss of eyelashes may make eyes more irritated and dry.

Patients may follow the tips below for managing chemotherapy-induced hair loss. However, it is important to understand that none of these measures have been shown to prevent hair loss.

PATIENT TIP

Managing Chemotherapy-Induced Hair Loss

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

Pain

Patients may occasionally experience pain from the lymphoma itself or from the treatments and procedures. Pain is very treatable, and there is no reason for a patient to endure it without help. Patients should tell their doctors, nurses, nurse practitioners or physician assistants if they have any pain, because the healthcare team can help determine whether pain

is related to lymphoma, and potentially offer advice regarding medications and other ways to reduce and manage the pain.

Different types of pain are best controlled by different types of pain relievers, and some medications may not be appropriate for patients with lymphoma. The tips below may help for managing pain.

PATIENT TIP

Managing Pain

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

Heart Damage (Cardiotoxicity)

Cardiotoxicity refers to damage to cells in the heart or heart muscle. Long-term use of certain chemotherapy agents such as doxorubicin can cause cardiotoxicity in a small number of patients.

In general, most patients with lymphoma treated with potentially cardiotoxic chemotherapy, such as doxorubicin, receive these drugs at dosages that are not likely to cause cardiotoxicity. In addition, patients only generally receive doxorubicin during frontline chemotherapy and not later during treatment. This helps reduce their risk for developing chemotherapy-related cardiovascular disease.

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

Careful monitoring by the healthcare team can reduce the chances of patients developing cardiotoxicity. Before deciding to treat patients with a cardiotoxic drug, most doctors order either an echocardiogram (ECHO, test that uses ultrasounds to check how the heart and nearby blood vessels are working) or a multigated acquisition (MUGA, test that looks at how well the heart is pumping blood by following a special marker injected into the bloodstream) scan to measure the patient's cardiac function (the ability of the heart to meet the demands of the body). These tests ensure that patients are prescribed a safe chemotherapy dosage given their current heart function. Patients with underlying conditions that put them at high risk of cardiotoxicity may also have their heart function monitored more intensively during the course of treatment for lymphoma.

Infections

Some lymphoma treatments can lower a patient's ability to fight infections, especially when they cause myelosuppression. Patients with a fever of 100.5°F or greater should contact the doctor or their healthcare team. Chills or a chilly sensation often comes before a fever. Patients should ask their provider what to do if they have a sore throat, rash, diarrhea, cough, or redness, swelling, or pain around a wound. The doctor should also be contacted if the patient experiences any painful local rash with or without blisters, as this could indicate an infection with shingles (herpes zoster).

To reduce the risk of infections, patients may be prescribed antibiotic, antiviral, or antifungal medications. Patients may be at increased risk for viral infections such as shingles, and sometimes doctors prescribe medication to prevent a shingles outbreak during therapy. If a patient has recurrent infections, the doctor may consider the prescription of gamma immunoglobulins, to boost the patient's immunity and help to fight the invading microbes (small living organisms such as bacteria and viruses). Other ways to reduce the risk of infections are included below.

PATIENT TIP

Reducing Infection Risk During Chemotherapy

- Check with your doctor to make sure your vaccinations are up to date before starting treatment.
- Wash your hands diligently and regularly.
- Avoid crowds, especially during influenza season (October–May in North America) and other outbreaks.
- Make sure all foods are thoroughly washed and/or cooked; avoid raw foods that may carry germs.
- Do not sleep with pets.
- Consider wearing a mask in certain situations

Generally, it is not recommended to receive a vaccine while undergoing chemotherapy although your doctor may recommend it in certain situations. Vaccines generate an immune response to provide long-lasting protection against a disease. During treatment for lymphoma, the immune system may be unable to generate an appropriate response to provide that protection.

However, infection with influenza (also called the flu) can be serious and life-threatening. To protect against influenza, a flu shot with inactive (dead) flu virus is recommended. Talk with your doctor and healthcare team to receive their specific recommendations for vaccination and timing, particularly for the flu and COVID-19 vaccines.

Loss of Appetite

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

The patient's healthcare team should be notified about lack of appetite to determine the underlying cause. Loss of appetite can sometimes be treated with drugs or by changing eating habits, such as eating several small meals each day and making nutritious food choices. Patients may wish to visit a nutritionist for additional tips. For more information about nutrition, please view the Nutrition fact sheet on Lymphoma Research Foundation's website at www.lymphoma.org/publications.

Lung (Pulmonary) Toxicity

Damage to the lungs is a serious side effect of the chemotherapy drug bleomycin (Blenoxane). Patients who are receiving ABVD, escalated BEACOPP, Stanford V, ABVE-PC or any other chemotherapy regimen that contains bleomycin should tell their doctor immediately if they experience cough, chest pain, or shortness of breath. Some doctors monitor patients' lung health by regularly performing pulmonary (lung) function tests (PFTs) during the course of any chemotherapy regimen that contains bleomycin. In addition to bleomycin, other treatments may have a risk of inflammation of the lungs and if your doctor informs you this is a risk of your treatment, it is important to notify them immediately of any these symptoms.

Mouth Sores

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

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

PATIENT TIP

Preventing and Caring for Mouth Sores

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

Nausea or Vomiting

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

PATIENT TIP

Controlling or Minimizing Nausea and Vomiting

- Before chemotherapy, drink a liquid diet consisting of water-based items such as broth, gelatin, ice pops, tea, and water. Do not drink milk or have a meal in which the main ingredients are dairy products.
- Do not eat foods that are too hot or too cold, greasy or fatty, sweet or spicy.
- Eat smaller, more frequent meals instead of fewer large meals each day.
- Avoid strong or offensive smells. Get plenty of fresh air.
- Take prescribed antiemetics before chemotherapy to prevent nausea.
- If you vomit, avoid becoming dehydrated (see tips on page 185).
- Try different approaches to determine what works best for you.

Peripheral Neuropathy

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

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

Although no medications have been specifically approved by the U.S. Food and Drug Administration (FDA) to treat chemotherapy-induced peripheral neuropathy, there are several different classes of drugs that doctors may prescribe to help alleviate patients' symptoms. These include antiepileptic agents (drugs used to treat seizures) such as pregabalin (Lyrica) and gabapentin (Gralise, Horizant, Neurontin, and others); local anesthetics such as lidocaine patches; opioid pain relievers; and antidepressants that also target pain such as duloxetine (Cymbalta, Irenka) and amitriptyline (Elavil). Complementary therapy techniques such as acupuncture and massage may also help with neuropathy symptoms (see page 66). Finally, patients should avoid tight-fitting shoes or clothes and exposure to cold, as these may worsen neuropathy symptoms in the hands and feet.

A specific type of neuropathy called Raynaud phenomenon may occur in some patients receiving treatment for lymphoma, particularly bleomycin (Blenoxane). This condition is characterized by signs of poor red blood cell circulation in the blood vessels near the nose, ears, fingers, and toes in response to cold temperatures (including cool weather); symptoms include feelings of cold, numbness, tingling, discoloration of affected areas, and pain in the hands and feet in cool temperatures. Raynaud phenomenon may be managed with a class of medications called calcium channel blockers.

Problems With Sexual Function

Psychological factors such as fear about illness, altered body image due to hair loss and depression, and the physical side effects of treatment on the body and the brain, often cause a drop in *libido* (sex drive). However, a normal libido usually returns after treatment is finished. Patients should not be embarrassed to talk with their doctor about any problems or concerns they have about changes in their libido or sexual function. The doctor might order tests to track hormone levels or recommend seeing

a specialist. Doctors can also prescribe medications to restore erectile function in men, or hormone therapy to alleviate vaginal dryness and other menopausal symptoms in women. It is important for patients to discuss this issue openly with their spouses or partners.

Sterility

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

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

Tumor Lysis Syndrome (TLS)

Patients who have large, rapidly growing, or multiple tumors such as those associated with Burkitt lymphoma may experience *tumor lysis syndrome* (TLS) during treatment. This condition occurs when a drug triggers the quick death of a large number of lymphoma cells, causing the dying cells to release cellular breakdown products (substances that are stored inside the cell or that result from the decomposing of cellular materials), such uric acid, potassium, and phosphorus into the blood in high concentrations that can damage the kidneys and other organs. Certain chemotherapy agents are known to have the potential to cause TLS. If not promptly treated, TLS may lead to kidney failure.

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

Secondary Cancers

There is a risk of developing a secondary cancer (a second type of cancer that develops due to the toxicity of the treatment) as a late effect (happens a long time after the initial treatment) following chemotherapy treatment. In particular, alkylating chemotherapy drugs such as cyclophosphamide (Cytoxan, Neosar) in combination with etoposide (VePesid, Toposar, Etopophos) may have an increased risk of secondary cancer. Chemotherapy regimens have shifted to lower chemotherapy doses when possible, to potentially reduce the risk. Regular doctor visits following the completion of lymphoma treatment can help monitor for the appearance of a secondary cancer. In certain cases, your doctor may recommend additional testing such as initiation of routine cancer screening at an earlier age that may include laboratory or imaging follow up.

Other Possible Side Effects

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

What Side Effects Are Caused by Steroids?

Corticosteroids (often simply called “steroids”) are commonly given along with chemotherapy. Steroids can serve several purposes including helping to treat the lymphoma, reducing inflammation, relieving nausea, and stimulating appetite. However, corticosteroid drugs can cause insomnia (the inability to fall or stay asleep), increased appetite, mood or personality changes, anxiety, high blood pressure, fluid retention, and weight gain. Prednisone can also trigger diabetes in patients prone to that disease or

worsen diabetes in patients who already have it. Long-term steroid use can also cause osteoporosis, cataracts, and changes in appearance.

If personality changes do occur, the doctor should be informed right away, as the steroid dosage may need to be reduced.

What Side Effects Are Caused by Immunotherapy?

Monoclonal Antibodies

The monoclonal antibodies used to treat lymphoma —obinutuzumab (Gazyva), ofatumumab (Arzerra), rituximab (Rituxan), rituximab and hyaluronidase human (Rituxan Hycela), tafasitamab (Monjuvi), mogamulizumab (Poteligeo), alemtuzumab (Campath)—may cause side effects such as low blood cell counts and infusion reactions, although monoclonal antibodies are less likely than chemotherapy to cause low blood cell counts. These side effects are usually mild, but they can sometimes be severe. Other rare but potentially very serious side effects include infections, TLS, and reactivation of past infections such as hepatitis. Other important side effects that may occur while receiving monoclonal antibodies include:

■ Infusion/Injection Reactions

- An infusion/injection reaction is a reaction that typically occurs during or within 24 hours after IV infusion or administration of a subcutaneous injection. Symptoms include dizziness, fainting, headache, feeling warm or flushed, fever or chills, hives, itching, shortness of breath, changes in heart rate and blood pressure, pain in the back or abdomen, and swelling of the face, tongue, or throat. Some infusion/injection reactions are true allergic reactions that can cause low blood pressure, difficulty breathing, and anaphylactic shock (severe allergic reaction).
- To prevent infusion/injection reactions, patients are given an antihistamine such as diphenhydramine (Benadryl), as well as acetaminophen (Tylenol) and sometimes corticosteroids before or during the antibody infusion/ injection. Nurses closely monitor patients during the infusions/injections for signs of an infusion/ injection reaction. Patients should immediately report any symptom they experience during or after an infusion/injection.

■ Infections

- Treatment with CD20-directed monoclonal antibodies (i.e., obinutuzumab, ofatumumab, and rituximab) can trigger immune system changes that reactivate HBV (infection comes back), which can cause acute liver failure. To prevent HBV from reactivating, patients are screened for HBV infection before treatment. Patients who have the virus are closely monitored during and after treatment and may be given antiviral medications to control HBV infection. Patients should be mindful of signs of an active HBV infection, such as increasing fatigue, yellowing of the skin or eyes, and dark urine.
- Very rare cases of a serious and usually fatal central nervous system infection called JC virus infection or progressive multifocal leukoencephalopathy (PML) can occur with any of the monoclonal antibodies. Patients should be mindful of neurological symptoms, such as difficulty thinking, loss of balance, changes in speech or walking, weakness on one side of the body, or blurred or lost vision.

Antibody-Drug Conjugates

The most common side effects reported in patients treated with brentuximab vedotin (Adcetris) include low blood counts, peripheral neuropathy (usually not until the third or fourth cycle of treatment), fatigue, nausea, upper respiratory tract infection, diarrhea, fever, weight loss, mouth sores, constipation, and vomiting. Patients may also experience reactions at the site of the treatment infusion. Hair loss is possible. Rarely, brentuximab vedotin (Adcetris) can be associated with inflammation of the pancreas, and patients with severe abdominal pain or diarrhea should seek medical attention immediately. Polatuzumab vedotin-piiq (Polivy) and loncastuximab tesirine-lpyl (Zynlonta) have similar side effects.

Immune Checkpoint Inhibitors

In patients with lymphoma who are treated with the checkpoint inhibitors nivolumab (Opdivo) or pembrolizumab (Keytruda), the most common side effects include fatigue, upper respiratory tract infection, urinary tract infection, headache, fever, diarrhea, cough, itching, decreased appetite, rash, shortness of breath, muscle, joint and bone pain, constipation, vomiting and nausea.

Immune-mediated adverse reactions can occur in any organ system. The most common immune-mediated adverse reaction is *hypothyroidism* (a condition where the thyroid gland does not create and release thyroid hormone into the blood). Other immune-mediated reactions include *pneumonitis* (infection of the lungs), *colitis* (swelling and/or inflammation of the large intestine), hepatitis, *endocrinopathies* (hormonal diseases), *nephritis* (inflammation of the kidneys) with renal dysfunction, and skin reaction. For patients who receive pembrolizumab (Keytruda), there is an additional risk of solid organ transplant rejection.

Immunomodulators

The most common side effects of the immunomodulatory drug lenalidomide (Revlimid) are decreased red blood cells, white blood cell, and platelet counts. Other common side effects include rash, diarrhea, constipation, muscle cramping, and fatigue. Increased clotting of the blood may occur, and patients are usually advised to take aspirin or another type of blood thinner while taking lenalidomide.

Radioimmunotherapy

The only currently available radioimmunotherapy that is FDA-approved for lymphoma is ibritumomab tiuxetan (Zevalin). The most common side effects are *cytopenias* (low level of blood cells and platelets), fatigue, nasopharyngitis (inflammation of the throat and nasal passages), nausea, abdominal pain, cough, diarrhea and fever, and weakness or loss of energy.

What Side Effects Are Caused by Targeted Therapies?

Many targeted therapies have similar common side effects. These include but are not limited to low blood cell counts, nausea, diarrhea, bleeding, peripheral neuropathy (numbness and pain in the hands and feet), fatigue, *neuralgia* (a type of nerve pain), constipation, vomiting, cough, rash, fever, pain, upper respiratory tract infection, or loss of appetite.

Less commonly, secondary cancers may also arise from the use of targeted therapies. There is also a risk of harm in developing embryos or fetus when using targeted therapies. There are other less common side effects that are specific for each drug or class of targeted therapy.

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

Bruton tyrosine kinase (BTK) inhibitors

Ibrutinib (Imbruvica) and acalabrutinib (Calquence) must be held before and after surgeries or biopsies to prevent significant bleeding complications. Atrial fibrillation (irregular and very rapid heart beat) may occur with ibrutinib (Imbruvica), acalabrutinib (Calquence), zanubrutinib (Brukinsa) and pirtobrutinib (Jaypirca). TLS may occur with ibrutinib (Imbruvica).

Histone deacetylase (HDAC) inhibitors

Patients with rapidly progressing tumors or a large number of tumors who are treated with HDAC inhibitors may also be at risk for TLS. Apart from the common side effects mentioned above, romidepsin (Istodax) may also cause changes in the patients' electrocardiogram (an exam that records the heart's electrical activity), while vorinostat (Zolinza) requires monitoring for high blood sugar and blocked lungs and veins caused by blood clots (*thromboembolism*).

Proteasome inhibitors

Patients treated with bortezomib (Velcade) may experience side effects like TLS, hypotension (low blood pressure), cardiac failure, acute respiratory disease, and acute liver failure.

Phosphatidylinositol-3-kinase (PI3K) inhibitors

Patients receiving idelalisib (Zydelig) can develop severe cutaneous (skin) reactions and elevated liver enzymes. Copanlisib (Aliqopa) may cause low blood sugar, severe cutaneous reactions and high blood pressure. Patients treated with PI3K inhibitors also reported *colitis* (inflammation of the colon) that typically appears later than other events and is serious in most cases (grade 3 or higher).

Tyrosine kinase inhibitors

Crizotinib (Xalkori) may cause cardiac changes, liver failure and severe visual loss.

BCL2 inhibitors

TLS may occur with venetoclax (Venclexta).

Nuclear export inhibitors

Selinexor (Xpovio) may cause low sodium concentrations in the blood (*hyponatremia*) and visual problems like cataracts.

What Side Effects Are Caused by Radiation Therapy?

Radiation therapy itself is painless, but it can cause short-term (immediate) and long-term (occurring over a long period of time) side effects that vary depending on the type of radiation, the dosage, and the area of the body treated. Side effects are usually worse when radiation therapy and chemotherapy are given at the same time. It is important to remember that radiation only affects the area that is treated, much like a flashlight only illuminates the area it shines upon.

Some of the side effects caused by radiation therapy used to treat patients with lymphoma include:

- Dry mouth
- Fatigue
- Loss of appetite and taste
- Nausea
- Skin reactions
- Sterility
- Throat irritation
- Cardiovascular damage
- Secondary cancers

Dry Mouth

Patients who receive radiation therapy to the mouth may experience a temporary decrease in saliva production causing *xerostomia* (dry mouth). Dry mouth may result in difficulty swallowing foods or thick liquids. It can also cause food particles to stick to the teeth and gums.

Because saliva helps prevent cavities, doctors may advise patients to visit the dentist for fluoride treatments before they start radiation therapy to reduce the risk of tooth decay.

Fatigue

The likelihood of patients experiencing fatigue as a result of radiation therapy depends on their disease and their specific radiation plan. Patient tips for coping with fatigue are included on page 186.

Loss of Appetite and Taste

During radiation treatment, patients might lose their appetite for foods they normally enjoy, or their sense of taste may become diminished. Patient tips for coping with these side effects are included on pages 182 and 191.

Nausea

Radiation treatment can cause nausea, especially in patients who receive radiation to the abdomen. Not eating a few hours before radiation therapy may help patients avoid nausea. The doctor may also prescribe an antiemetic medication to be taken before each radiation therapy session. Patient tips for coping with nausea are included on page 193.

Skin Reactions

Radiation therapy can cause redness, itchiness, dry and peeling skin, sores or ulcers, swelling, and puffiness to the affected area. These skin changes usually decrease and disappear over a few weeks after the radiation therapy ends. However, some skin changes, such as darker and blotchy skin, very dry skin, or thicker skin, may last much longer or be permanent. The radiated area can also sunburn more easily than other parts of the body. Patients should avoid tanning beds and protect their skin from sunlight with a wide-brimmed hat, long sleeves, long pants, and sunscreen with an SPF of at least 30.

Patients should speak with their doctor, nurse, or physician assistant if they experience any skin changes. A list of tips to help patients care for their skin during and after radiation therapy is provided below.

PATIENT TIP

Skin Care During and After Radiation Therapy

- Be gentle with your skin; do not rub, scrub, or scratch.
- Use only lotions and other skin products that your doctor prescribes, or your nurse suggests.
- Do not put anything on your skin that is very hot or cold.
- Shower or bathe in lukewarm water and limit your bathing to less than 30 minutes every other day. Use a mild, unscented soap and pat your skin dry after bathing. Be sure not to wash off the ink markings needed for radiation therapy.
- Check with your doctor or nurse before using bubble bath, cornstarch, cream, deodorant, hair removers, makeup, oil, ointment, perfume, powder, and sunscreen.
- Wear soft, loose clothes that allow your skin to breathe.
- Use soft sheets, such as those made with cotton.
- Add moisture (humidity) to the rooms in your home by placing a bowl of water on the radiator or using a properly cleaned and maintained humidifier.
- Do not use tanning beds and protect your skin from the sun every day.
- Do not put adhesive tape or bandages on your skin. Ask your nurse about ways to bandage without tape.
- Ask your doctor or nurse if you may shave the affected area. Shave only with an electric razor, and do not use pre-shave lotion.
- Report any skin changes you notice to your doctor or nurse.

Sterility

Like chemotherapy, radiation may also damage sperm and egg cells, and cause temporary or permanent *sterility* in both men and women. Patients should speak with their doctor about fertility preservation as early as possible before beginning treatment.

Throat Irritation

Radiation therapy to the neck, throat, or chest may cause sore throat, dry mouth, nausea, and/or cough. Patients may have difficulty eating or swallowing, especially toward the end of their treatment regimen. Patients should tell their doctor if swallowing becomes difficult, as there are treatments for the discomfort. Patients should take precautions to avoid becoming dehydrated during treatment (see page 185 for tips on avoiding dehydration). Difficulty swallowing usually goes away a few weeks after treatment is completed. Sometimes a viral infection such as oral herpes or a fungal infection such as thrush can contribute to throat irritation. Patients should notify their doctor if they are experiencing throat irritation.

The tips listed below may help ease throat irritation during radiation therapy.

Easing Throat Irritation During Radiation Therapy

- Eat bland foods that are soft, smooth, and easy to digest, such as pudding, yogurt, and milkshakes.
- Take small bites and swallow each bite completely before taking another one.
- Puree foods in a blender to make them easier to swallow.
- Avoid citrus fruits and citrus juices.
- Ask your doctor whether lidocaine hydrochloride solution (Xylocaine Viscous, a liquid used to relieve the pain and discomfort from a sore throat or mouth) or Magic Mouthwash may be appropriate.

PATIENT TIP

Cardiovascular Damage

Radiation therapy has three major effects on the heart: it damages arteries, most commonly those in the neck (carotid arteries) and the heart (coronary arteries), which can increase the risk of heart attack and stroke; it damages the valves of the heart; and it causes *pericarditis* (inflammation of the membrane that surrounds the heart). Radiation therapy can also damage the conduction system of the heart, which is the muscles and fibers that provide the electrical signals that make the heartbeat regularly. At least every five years, patients who have been treated with radiation therapy to the chest should undergo a complete cardiovascular examination that includes a Doppler ultrasound to examine the carotid arteries, an echocardiogram (ECHO) to measure valve function, and a stress test to assess coronary artery disease. Statin drugs (used to manage cholesterol) are strongly recommended for patients who have received radiation therapy to prevent coronary artery disease.

Secondary Cancers

The risk of developing secondary cancers from radiation therapy depends on the amount of radiation given and the part of the body treated. Newer methods of radiation therapy limit the amount of healthy tissue exposed to radiation, which reduces but does not eliminate the risk of secondary cancers after these treatments. It is imperative that patients protect irradiated skin from direct sun exposure, no matter how long ago the radiation was administered.

What Side Effects Are Caused by CAR T-cell Therapies?

Axicabtagene ciloleucel (Yescarta), tisagenlecleucel (Kymriah), brexucabtagene autoleucel (Tecartus) and lisocabtagene maraleucel (Breyanzi) are the only CAR T-cell therapies approved by FDA to treat lymphoma. Many of the common side effects of these CAR T-cell therapies are similar to those experienced by patients taking other lymphoma therapies, such as fatigue, decreased appetite, chills, pain, diarrhea, *febrile neutropenia* (low levels of white blood cells called neutrophils, along with fever), infection, nausea, cough, vomiting, and constipation. Patients treated with these CAR T-cells therapies may also have prolonged cytopenias. Neurological symptoms may also occur during the first two to three days after receiving the CAR T-cells and include altered mental

state (encephalopathy), headache, tremor, dizziness, speech problems (aphasia), delirium, insomnia, and anxiety. CAR T-cells therapies may also temporarily affect the patients' ability to drive and use heavy equipment or machines after treatment.

Cytokine release syndrome (an intense systemic inflammatory response) is a unique side effect in response to the activation and growth of a patient's CAR T-cells and will be monitored. A medication called tocilizumab (Actemra) was approved by the FDA in 2017 for the treatment of CAR T-cell–induced severe cytokine release syndrome.

More recently, the FDA announced an investigation into several reported cases of secondary T-cell malignancies in patients previously treated with CAR T-cell therapy. Despite the preliminary investigation the FDA determined that the risk of secondary T-cell cancers applies to all currently approved CD19- and B-Cell maturation antigen (BCMA)-directed genetically modified autologous CAR T-cell immunotherapies including, lisocabtagene maraleucel (Breyanzi), axicabtagene ciloleucel (Yescarta), brexucabtagene autoleucel (Tecartus), and tisagenlecleucel (Kymriah).

While there is a potential risk, the development of any type of second cancer after treatment with CAR T-cell therapies is extremely rare and the cause of secondary cancers has not been confirmed in many cases, so it remains unclear whether the secondary T-cell malignancies were caused by CAR T-cell therapy.

In the event of secondary cancers following treatment with CAR T-cell therapy, contact the manufacturer to report the event and ask about the patient testing for the presence of CAR transgene (gene transferred from one organism to another) in the tumor. To report adverse events including T-cell malignancies, contact the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

What Side Effects Are Caused by Stem Cell Transplantation?

The type and frequency of the side effects associated with blood stem cell transplantation are quite different depending on whether the stem cells are autologous (from oneself) or allogeneic (from a donor). Patients treated with high doses of chemotherapy and/or radiation before undergoing a blood stem cell transplant are at increased risk for developing infection, bleeding,

and other side effects as described previously (see the section “What Side Effects Are Caused by Chemotherapy?” on page 181 and the section “What Side Effects Are Caused by Radiation Therapy?” on page 201).

Patients receiving high-dose chemotherapy with autologous stem cell transplantation are followed carefully for the first three to four weeks because of the risks of mouth sores, infection, anemia, and uncontrollable bleeding due to the inability of the blood to clot. Transfusions and antibiotics may be necessary, which are often administered in the hospital.

Additionally, patients undergoing allogeneic stem cell are also at risk of developing *graft-versus-host disease* (GVHD), a serious condition in which the donated stem cells attack the patient’s tissues and organs, resulting in symptoms such as diarrhea, abdominal pain, nausea, and vomiting. GVHD can occur at any time after the transplant, but acute GVHD occurs in the first 100 days after transplant. Drugs can be used to reduce the risk of developing GVHD or to treat the condition once it develops.

When Should a Patient’s Doctor Be Contacted?

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

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

Part 5 — Survivorship and Living with The Side Effects of Treatment

Chapter 20: Managing Life During and After Treatment

This chapter discusses some general issues that patients may encounter in their daily lives during and after treatment for lymphoma.

Survivorship

Following completion of treatment, patients should expect to receive a “survivorship care plan” which is a summary of the cancer type, date of diagnosis, date of ending treatment, all cancer treatments received, and cancer surgery performed. Monitoring for late effects following treatment is an important part of a survivorship care plan. If available, a specialized cancer survivorship clinic can provide a more in-depth evaluation for late effects, monitoring for late effects, and recommendations to reduce risk and improve quality of life.

Coping Strategies

Each person’s experience with cancer is different, and the way an individual copes with the physical and emotional impacts of lymphoma is unique to each patient’s personality and situation. Table 20.1 lists some suggestions for coping with common issues that patients may face.

Table 20.1. Coping Strategies

Build a Strong Support System	<ul style="list-style-type: none">■ Communicate your fears and concerns about your disease by talking to your family, friends, doctors, and counselors.■ Write down your concerns in a journal.■ Find a support group or a one-to-one peer support program such as the LRF’s <i>Lymphoma Support Network</i> or other individuals who are also coping with cancer.
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Get Help for Depression	<ul style="list-style-type: none"> ■ Feeling sad or having a depressed mood from time to time is not unusual in patients living with cancer, but this is not the same as having a psychiatric diagnosis of depression, known as “Major Depressive Disorder.” ■ Watch for signs such as sleeping more or less than usual, a loss of interest in preferred activities, crying, or an inability to concentrate. ■ If these symptoms last more than two weeks, ask for a referral to a psychiatrist, social worker, psychologist, or counselor who can help you cope with your feelings through talk therapy, medications, or both.
Deal With Physical Changes	<ul style="list-style-type: none"> ■ Some patients with lymphoma may feel unattractive because of hair loss and other changes in appearance caused by their treatment. ■ If desired, plan ahead and buy a wig or head covering if hair loss is a possibility. ■ Seek advice from a beautician familiar with the side effects of cancer treatment about makeup if you are concerned about a blotchy complexion. ■ Ask your healthcare team for advice on how to manage other temporary changes in your skin and brittle nails.
Maintain a Healthy Lifestyle	<ul style="list-style-type: none"> ■ Eat a healthy diet that includes fruits, vegetables, proteins, and whole grains. ■ Engage in regular physical exercise, which can help improve mood and reduce anxiety, depression, and fatigue. ■ Get sufficient rest to help combat the stress and fatigue of your disease and its treatment. ■ Quit smoking and reduce alcohol consumption.
Undergo Routine Healthcare and Preventative Care	<ul style="list-style-type: none"> ■ Continue to visit your primary care physician, dentist, dermatologist (skin doctor) and optometrist (eye doctor), and your other regular healthcare providers throughout treatment and afterwards; however, let each one know about your current diagnosis and treatment in case adjustments in your care need to be made. ■ As directed by your healthcare team, continue to receive preventative care, such as vaccines and screenings.
Set Reasonable Goals	<ul style="list-style-type: none"> ■ Having goals for how you want to live your life during and after treatment can help you maintain a sense of purpose. ■ Avoid setting unreasonable goals, such as working full-time if you do not yet have the energy or stamina to do so. ■ Stay as active and involved as you can in work and other activities that interest you.

Maintain a Healthy Lifestyle

Regular physical activity helps keep the cardiovascular system strong and the body muscles flexible. Exercise can also help patients alleviate breathing problems, constipation, and mild depression. Additionally, it may help reduce stress and fatigue. Patients should talk to their doctor before starting an exercise program and consider visiting a physical therapist for advice. The most important point to remember is to avoid overexertion (the use of too much mental and physical effort).

Patients dealing with cancer do not need to perform activities at the same level of intensity that they did before their lymphoma diagnosis, and they should not push themselves to their limit.

Several types of exercise may be particularly helpful, including:

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

A healthy diet is especially important during treatment for lymphoma because it helps patients keep up their strength and energy, tolerate treatment-related side effects, decrease the risk of infections, and heal and recover more quickly. Patients should aim for a diet high in fruits and vegetables, protein (such as poultry, fish, and eggs), and whole grains.

During or after treatments that can lower white blood cell counts, such as chemotherapy and stem cell transplantation, patients may be instructed to follow a *neutropenic diet*, which involves temporarily avoiding raw fruits and vegetables that may increase the risk of infection. The healthcare team can help develop an appropriate eating plan.

Patients should talk to their doctor before taking any dietary supplements, because they may interfere with treatments or have unexpected side effects.

Vaccines

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

Vaccination during chemotherapy should generally be avoided because response to the vaccine may be decreased. If inactivated vaccines (containing dead microbes that cannot cause disease but stimulate the body's immune system) are administered during chemotherapy or stem cell transplant treatment, they should be readministered after immune system function returns to normal. If patients receive a vaccine within 14 days before starting therapies that affect the immune system, they should be revaccinated at least 3 months after the treatment has stopped and immune function has returned to normal. Patients receiving chemotherapy with anti-B-cell antibodies (e.g., rituximab) or stem cell transplant therapy should wait at least 6 months or longer after therapy before receiving inactivated vaccines.

Patients with altered immune system function should not receive live vaccines, and live vaccines should not be administered for at least 3 months after immunosuppressive treatments. Live vaccines can be administered to patients with leukemia, lymphoma, or other malignancies whose disease is in remission, who have restored immune system function, and whose chemotherapy has been discontinued for at least 3 months.

The currently FDA-approved or FDA-authorized coronavirus disease 2019 (COVID-19) vaccines can be safely administered to patients with compromised immune system function. When possible, COVID-19 vaccine doses should be completed at least 2 weeks before starting or resuming immunosuppressive therapies. An additional dose of an mRNA COVID-19 vaccine administered at least 28 days after completion

of an initial 2-dose primary mRNA COVID-19 vaccine series should be considered in patients with moderate to severe immune compromise. Immunocompromised patients are eligible for a third dose including those receiving active treatment for hematologic malignancies, patients who are recipients of CAR T-cell therapy or stem cell transplantation (within 2 years of transplantation or receiving immunosuppressive therapy), and active treatment with chemotherapy classified as severely immunosuppressive.

In addition, the CDC also recommends a booster dose of any of the three available vaccines for patients with cancers of the blood. It is important that lymphoma patients discuss this matter with their healthcare team to determine if and when they should receive a booster dose.

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

Close contacts of patients with lessened immune function, like caregivers and family, should also receive all recommended vaccines, with the exception of smallpox vaccine.

The Importance of Follow-up Care

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

During these follow-up visits, the doctor asks about any medical changes since the last appointment and conducts a physical examination. The doctor may also prescribe blood tests and other laboratory tests, molecular diagnostic testing (laboratory tests that analyze the genetic material or other markers of the disease), or imaging.

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

Be Proactive in Healthcare Decisions

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

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

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

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

Psychological Impact on Survivors

Emotional Effects and Fear of Recurrence

Survivors often report that they entered a very different world once treatment ended. While it may be a time to rejoice and recover from the experience, this “new normal” period often comes with mixed emotions. You may have a hard time trying to return to your routine as it was before you were diagnosed with lymphoma and some things you once did easily may now be challenging, or you may not have the same energy.

It is also very common for survivors to feel anxious about the future. This feeling stem out of the fear that the lymphoma will return (*fear of recurrence*) and can be triggered by simple things like birthdays, a visit to a doctor’s office or an unexpected symptom. You can be proactive and take the following steps to cope with fear of recurrence:

- Be informed about the signs of recurrence for your type of lymphoma.
- Keep track of any questions and symptoms you have and discuss them with your healthcare team.
- Stay up-to-date with your medical appointments and follow your doctor’s recommendations.
- Be patient and allow yourself time to process your feelings.
- Take control of what you can and make a follow-up care plan (see the *When Treatment is Over* fact sheet on LRF’s website at lymphoma.org/publications).

Fear of recurrence can be associated with conditions such as depression and anxiety, which may linger for years. This can manifest in different ways, like trouble sleeping, changes in appetite, lack of interest in activities you previously enjoyed and inability to handle daily chores. Mental health professionals can help you develop skills to reduce stress levels and cope with anxiety and depression. Complementary therapies such as acupuncture, meditation, and massage can also be beneficial in the management of the emotional effects of treatment.

Taking Care of Yourself

As a cancer survivor, it is important that you practice self-care regularly to reset your physical and emotional well-being. Adopting routines of self-care will help you recharge your batteries and stay healthy. Talk with your healthcare team about developing a wellness plan to help you stay physically and emotionally healthy and improve your mood. Consider the following suggestions:

- Stay active with short periods of daily exercise. (30 minutes of power walking, jogging or biking). If not possible, take the stairs instead of the elevator or park farther away than usual.
- Maintain a balanced diet and eat fruits and vegetables.
- Cut down on risk factors. Quit smoking and reduce alcohol intake.
- Try to get 7 hours of sleep per night or take naps when needed.
- Meditation, deep breathing and stretching can help you relax.
- Keeping a journal with thoughts and feelings may help you to let go of worries and fears.

Finding Support

Identify at least one person with whom you feel you can be honest about your feelings. You can open up to friends and family or join a support group for cancer survivors. Having a reliable support network can provide a means to work through your negative emotions and help you cope with physical effects of treatment or deal with aspects of daily life.

The LRF's one-to-one peer support programs - Lymphoma Support Network – connects patients and caregivers with volunteers who have experience with lymphomas, similar treatments, or challenges, for mutual emotional support and encouragement. You may find this useful whether you or a loved one is newly diagnosed, in treatment, or in remission. For more information about this program, please contact the LRF Helpline or visit lymphoma.org/resources/supportservices/lasn.

You can also find assistance online with support-oriented patient organizations such as Cancer Care (call 800-813-4673 or visit cancercare.org/support_groups) and the Cancer Support Community (call (888) 793-9355 or visit cancersupportcommunity.org).

For some individuals, faith and spirituality is the best route to find comfort. Some members of your place of worship may help you cope with your concerns, such as feeling alone, fear of death, searching for meaning, and doubts about faith.

There are many options available, and it is important that you choose the one that is right for you. Follow-up care can also include home care, occupational or vocational therapy, pain management or physical therapy.

Chapter 21: Caring for Someone with Lymphoma

What Is a Caregiver?

A caregiver is someone who is helping a loved one with lymphoma through their treatment. If you are taking care of your partner, a family member or a friend who has lymphoma, you are a caregiver. While it may feel natural, being a caregiver is often demanding and can be a full-time and hard job. Caregiving can mean many things, including helping with daily activities (practical care), overseeing healthcare routines (medical care) and providing emotional support (emotional care).

- **Practical care:** assisting in daily chores, like running errands, cleaning, meal prepping or childcare. You may also be asked to manage financial and insurance matters, keep track of important documents or be a direct contact for any pressing non-medical issues. Some individuals may not want to burden you but would genuinely appreciate what you would do.
- **Medical care:** going to medical appointments, sorting through treatment options, and making sure medications are taken correctly. You may also assist in managing side effects or special diets according to the doctor's instructions.
- **Emotional care:** offering emotional or spiritual support to the person with lymphoma. This includes listening to your loved one and helping them cope with their feelings throughout the course of treatment. The single most important thing to do is to show up and just be present.

Helping Your Loved One

As a caregiver for your loved one diagnosed with lymphoma, the dynamics of your relationship may change. Caregiving often implies a change in roles, like taking care of your parent as an adult, or caring for your spouse or friend who has always been healthy. In this new role, parents may be uncomfortable with receiving help from their adult children, or a patient may only accept help from a spouse. It is very common for caregivers to feel overwhelmed in the beginning, particularly if they lack experience. Many caregivers say that they learn more as they go through their loved one's cancer treatment. There are many ways you can help a loved one with lymphoma, as follows:

- **Be prepared** — Talk with the healthcare team so that you know what to expect throughout the treatment, how to manage symptoms and when to ask for help.
- **Listen** — Each person asks for help in different ways (some require more comfort; others are more action-oriented). It is important that you understand what your loved one wants.
- **Avoid “cheerleading”** — Do not disregard negative feelings (such as sadness, anger, or worry). Be alert to signs of depression (hopelessness, prolonged crying, or persistent inability to enjoy things) and seek expert help from a mental health professional if needed.
- **Organize help** — If an abundance of help is available, find ways to organize and coordinate help amongst those who are willing, so that anyone offering help can be of the greatest value for a specific need at appropriate times.
- **Offer transportation** — This is important for all, including older people with decreased mobility or limited resources. Making sure your loved one gets to the appointment or simply going along for the ride can be very helpful. Patients may not be able to drive after chemotherapy and supportive care medications.
- **Take notes** — If you go into the appointments, write down notes with the doctor's plan, medications, potential side effects, phone numbers and other relevant information. Keep this information in a place that is easy to find in case there are questions (your computer, cell phone or even a spiral notebook).

Long Distance Support

It is possible to support a loved one with lymphoma from afar. This is called long distance caregiving and applies if you are taking care of a loved one who lives an hour or more away. Long distance caregivers can assist with practical issues, which include helping with finances, arranging for in-home medical care and assistance with daily tasks, clarifying insurance coverages and issues with property, and providing emotional support. While this can occur remotely, long distance caregiving can sometimes require in-person visits. Below are simple actions you can take to support a loved one with lymphoma from afar:

- Build a contact network close to your loved one. This includes members of the healthcare team, social workers, or local relatives, friends or neighbors whom you can call during a crisis or just to check in.
- Share a complete list of your contact information (email, home, work, and cell phone numbers) with the healthcare team, local relatives, friends or neighbors. Ask them to update you as frequently as possible.
- Use remote technologies (like Skype, FaceTime, Zoom) that can bring in others to communicate directly with your loved one and provide emotional support
- Explore the local availability of paid or volunteer support, adult day care centers or meal delivery services.
- Plan your visits. Be familiar with the hospital's most recent visitor policy and ask for visitor information packets or lists. Check with the primary caregiver (if there is one) to learn ahead of time what your loved one needs.
- When traveling, check with transportation companies (bus or airlines) for special deals for caregivers. Time your flights or drives so that you have time to rest.

You can also go online to browse for local resources for your loved one. Helpful links include the Family Caregiver Alliance (visit <https://www.caregiver.org/connecting-caregivers/services-by-state/>). The American Red Cross may offer training opportunities on caregiving (visit <https://www.redcross.org/take-a-class>).

Chapter 22: Talking to Children, Teenagers and Siblings

How to Talk to Children and Teenagers?

Explaining cancer to children and teens is difficult, but it is very important that they do not feel left out of what is happening. There are no “right” or “wrong” ways to have this conversation, but you can follow the suggestions below:

- Do not keep it a secret. Children and teens can tell when something is wrong and may think things are worse or even blame themselves.
- Do not make false promises or feed unrealistic expectations. This can raise trust issues with you and other adults, projecting later into adult life.
- Explain that the treatment may cause visible side effects like decreased energy and hair loss.
- Be patient and ready to explain things as many times as needed. Children and teens may have a hard time processing this information, and repeating the same question can be a way for them to ask for reassurance.
- Keep their routines as stable as possible. This can provide reassurance in times of stress.

It is also important to let their teachers know what is going on. They will be alert for any signs of distress and changes in school performance, which may indicate that the child/teen is feeling anxious and overwhelmed. This may also manifest with physical symptoms (like headaches and stomachaches), sleep disturbances or irritability. If the behavioral changes persist, seek help from a qualified mental health professional.

You can also find resources online for teens dealing with a cancer diagnosis in their family (visit cancer.gov/publications/patient-education).

Impact on Siblings

A pediatric lymphoma diagnosis will also affect any siblings. Here are some practical tips to help siblings cope during this demanding time:

- Explain the situation and let them know what to expect during treatment. Keep them up to date and as involved as possible (e.g. include them in hospital visits).
- Set aside some daily time to check in and see how they are doing, even if just for a few minutes. It is important that siblings feel that they are heard.
- Keep their routines as stable as possible (school and extracurricular activities) and have friends and/or neighbors help if they can.
- Be alert for any signs of emotional distress, anxiety or depression, and seek the help of a trained mental health professional if needed.
- You can also find resources online for siblings of children with cancer (visit [cancer.gov/publications/patient-education](https://www.cancer.gov/publications/patient-education)).

Part 6 — Caregivers

Chapter 23: Support During Treatment

Depending on the diagnosis, treatment options could be given intravenously at a hospital or can be taken by mouth. Before starting treatment, the doctor will discuss the risks, benefits, and side effects associated with the different treatment choices. It is important to share questions and concerns with the doctor to decide which option is best. This is also time to clarify any caregiver assistance you may need before, during and after undergoing treatment.

For pediatric patients, speak with the health care team about providing age-appropriate information on treatment to help aid their expectations.

Oral Therapies and Adherence

Today there are many drugs for the treatment of lymphoma that can be taken by mouth, either in liquid or tablet/capsule form. Oral agents can be very effective at suppressing cancer cell growth and at maintaining long-term remission (disappearance of signs and symptoms). Adherence, which refers to a patient's ability to consistently take all medication as prescribed, may be a challenge for some patients.

Caregivers can help their loved ones adhere to oral therapies by using diaries and medication dispensers that record when the pill container was opened. Online reminders and apps for smartphones and devices can also be useful. Lymphoma Research Foundation's (LRF's) award-winning Focus On Lymphoma mobile app provides patients and caregivers with comprehensive content based on their lymphoma subtype and tools to help manage the diagnosis and treatments, including a medication manager and side effects tracker.

CAR T-Cell Therapy

Chimeric antigen receptor (CAR) T-cell therapy requires a significant amount of support from a caregiver, including around-the-clock care and monitoring for side effects. Your loved one should identify suitable primary

and alternative caregivers prior to undergoing CAR T-cell therapy. The healthcare team overseeing the treatment should then help select the person most qualified for the role. Overall, the caregiver for the duration of CAR T-cell therapy should:

- Be at least 18 years of age, in good health, able to provide hands-on care, and available around the clock for a designated time frame.
- Not be hired.
- Understand and recognize symptoms of serious side effects like cytokine release syndrome (flu- like symptoms, fever, low blood pressure, body aches) and neurotoxicity (anxiety, delirium, dizziness, headache, insomnia, difficulty speaking, tremors)
- Be able to measure the patient's oral temperature and identify signs of neurologic impairment.
- Communicate with the health care team when needed.
- Transport or accompany the patient to emergency and scheduled appointments.
- Administer oral and potentially intravenous medications as instructed.
- Prepare meals and keep housing clean.

The chosen caregiver(s) must be aware of housing requirements prior to the start of CAR T-cell therapy. Patients must stay close to the center for at least 4 weeks after the treatment, to be monitored for side effects and treated, if needed. Your loved one's healthcare team will provide necessary guidance throughout all stages of treatment.

Part 6 — Caregivers

Chapter 24: Self-Care

Being a caregiver can be demanding and requires emotional and physical endurance, particularly if you have other responsibilities (such as work or raising children). Caregivers often disregard their own well-being and have a hard time focusing on other matters. Over time, this can lead to “burnout” - a condition marked by irritability, fatigue, sleep disturbances, weight fluctuation, feelings of helplessness or hopelessness, and social isolation. As a caregiver, it is important that you practice self-care regularly to reset your physical and emotional well-being. Adopting routines of self-care throughout the process will help you recharge your batteries and give you the strength you need to carry on. This will make the experience less stressful for you and help you be a better caregiver.

Ways to Take Care of Yourself

Self-care will help you stay physically and emotionally healthy. To achieve that, consider the following suggestions:

Watch your health. Stay up-to-date with your own medical appointments and take any medications as prescribed.

Table 24.1. Tips for Self-Care

Exercise	<ul style="list-style-type: none">■ Stay active with short periods of daily exercise (30 minutes of power walking, jogging, biking)■ Take the stairs instead of the elevator.■ Park farther away than usual.■ Exercise at health facilities or with trainers.
Eat well	<ul style="list-style-type: none">■ Include fruits and vegetables in your meal.■ Maintain a balanced diet
Sleep	<ul style="list-style-type: none">■ Try to get 7 hours of sleep per night.■ Take naps when possible.
Rest	<ul style="list-style-type: none">■ Resting will help you reduce stress.■ Try meditation, deep breathing, and stretching.
Know your limits	<ul style="list-style-type: none">■ It is OK to say no if you do not have time or energy to complete a given task.
Take breaks	<ul style="list-style-type: none">■ Maintain hobbies and keep up with friends.■ Do not neglect your personal life.
Get support	<ul style="list-style-type: none">■ Open up to friends and family.■ Join a support group for caregivers (lymphoma.org/resources/supportservices/lsn).■ Find assistance online with Cancer Care (cancer.org) and Cancer Support Community (cancersupportcommunity.org).
Be alert for signs of burnout	<ul style="list-style-type: none">■ Signs include irritability, fatigue, sleep disturbances, weight fluctuation, feelings of helplessness or hopelessness, and social isolation.■ Seek help from a trained mental health professional if you feel it is too much to handle.

You can also find resources online that address the needs of friends and family members giving care to a person with cancer (visit cancer.gov/publications/patient-education).

Part 6 — Caregivers

Chapter 25: Workplace and Financial Future

Keeping Track of Your Documents

It can be helpful to keep all important documents and paperwork in one place. This will make things easier to find when you need them and will save your valuable time. Important documents that you should keep include:

- Medical and insurance records
- Pensions and social security records
- Bank statements
- Wills
- Power of attorney
- Health care proxy
- Administer oral and potentially intravenous medications as instructed
- Prepare meals and keep housing clean

Knowing Your Rights

Review your loved one's insurance policies to understand what treatments are covered. There are government programs called entitlements that provide aid to people with cancer. Your hospital or community social worker can help you get in touch with the governmental agencies that regulate these aid programs. If you have been working for more than a year in a company with 50 or more employees, you may be eligible for an unpaid leave under the Family and Medical Leave Act (FMLA). Smaller companies may also let you use sick days and vacations for caregiving purposes. Check with the human resources department to find out whether this applies to you.

Finding Financial Resources

If your loved one expects to run into financial difficulties, reaching out to the people involved and working out payment plans early on can be helpful. This applies to hospital bills, creditors, landlords, utilities and

mortgage companies. Resources for cancer patients requiring financial help include:

- Medicine Assistance Tool (call 571-350-8643 or visit medicineassistancetool.org).
- LRF Helpline (call 800-500-9976 or visit <https://lymphoma.org/resources/supportservices/>)
- CancerCare (call 800-813-4673 or visit cancercare.org)
- Patient Advocate Foundation (call 800-532-5274 or visit patientadvocate.org)
- Social Security Administration (call 800-772-1213 or visit ssa.gov)

Questions to Help Your Loved One with Lymphoma

PATIENT TIP

Doctor's Visits

- What documents do I need for the consultations?
- What are the goals of treatment?
- Is there anything we need to do to prepare for treatment?
- How long will the treatment take?
- Can I stay during the treatments?
- Do you have any written information about this treatment?
- What are the side effects of this treatment?
- Are there any ways to help manage side effects?
- How do we know if a side effect is severe enough to call you?
- Are there any other treatment options?
- Are there any clinical trials we should be aware of?
- How should we file insurance claims?
- What is the best way to let you know when we have questions about treatment?

Helping Your Loved One at Home

It can be difficult to know how to open the lines of communication with your loved one. They also may not be ready to talk when you are. It's important to offer emotional support by allowing opportunities for communication and demonstrating a willingness to listen.

While asking your loved one how they feel may provide an opportunity for them to express their emotions, it may not always feel natural. Questions about practical issues such as how their last appointment went or when the next appointment will be could provide a safer context in which to delve further into more emotional topics.

Provide eye contact to demonstrate your warmth and attention. Ask additional questions to invite your loved one to continue to have an opportunity to talk. You could also paraphrase (repeat) what has been said to confirm you understand what your loved one is saying. If it's not the right time for a discussion, let them know you are available to support them when they are ready for a conversation.

ABOUT THE LYMPHOMA RESEARCH FOUNDATION

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

Awareness and Outreach

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

Education Resources and Support Services

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

Professional Education

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

Research

LRF is focused on finding a cure for lymphoma and CLL/SLL through an aggressively funded research program. LRF supports early career investigators through the Clinical Investigator Career Development Awards, Lymphoma Postdoctoral Fellowship Grants and Lymphoma Scientific Research Mentoring Program (LSRMP), and senior investigators through several disease-specific research initiatives. These efforts are led by the Foundation's Scientific Advisory Board (SAB), comprised of 45 world-renowned lymphoma experts. The Foundation has awarded more than \$73 million in funding for lymphoma-specific research.

Contact Information

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

Website: lymphoma.org



LYMPHOMA TOOLS AND RESOURCES AT YOUR FINGERTIPS

Focus on Lymphoma is the first app to provide patients and their caregivers with tailored content based on lymphoma subtype, and actionable tools to better manage diagnosis and treatment.

AVAILABLE FOR FREE
DOWNLOAD



lymphoma.org/focusonlymphoma

LYMPHOMA
RESEARCH • FOUNDATION

LEARN



Explore educational content tailored to your subtype and disease stage and learn at your own pace.

TRACK



A full suite of customized tools helps you track, manage, and organize your lymphoma-related information, all in one convenient place.

CONNECT



Connect with an entire community, including lymphoma patients, survivors, and LRF Helpline staff for individualized support.

Understanding Lymphoma and CLL/SLL

This patient guide is supported through
unrestricted educational grants from:



Contact the Lymphoma Research Foundation

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

Website: lymphoma.org