

Understanding Non-Hodgkin Lymphoma



A Guide for Patients,
Survivors, and
Loved Ones

LYMPHOMA

RESEARCH • FOUNDATION

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

CONTACT THE LRF HELPLINE

Trained staff are available to answer questions and provide support to patients, caregivers and healthcare professionals in any language.

Our support services include:

- Information on lymphoma, treatment options, side effect management and current research findings
- Financial assistance for eligible patients and referrals for additional financial, legal and insurance help
- Clinical trial searches based on patient's diagnosis and treatment history
- Support through LRF's Lymphoma Support Network, a national one-to one volunteer patient peer program

Monday through Friday, Toll-Free (800) 500-9976
or email helpline@lymphoma.org



Understanding Non-Hodgkin Lymphoma

A Guide For Patients, Survivors, and Loved Ones

July 2018

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

Contact the Lymphoma Research Foundation

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

Website: lymphoma.org

This patient guide is supported through unrestricted educational grants from:



Genentech
A Member of the Roche Group

 **Biogen**

© 2018 Lymphoma Research Foundation.

Information contained herein is the property of the Lymphoma Research Foundation (LRF). Any portion may be reprinted or reproduced provided that LRF is acknowledged to be the source and the Foundation's website (lymphoma.org) is included in the citation.

ACKNOWLEDGMENTS

The Lymphoma Research Foundation wishes to acknowledge those individuals listed below who have given generously of their time and expertise. We thank them for their contributions, editorial input, and professional knowledge, which have truly enhanced this publication. The review committee guided the content and development of this publication. Without their dedication and efforts, this publication would not have been possible. We hope those in the lymphoma and chronic lymphocytic leukemia community will now be better informed and have a better understanding of these diagnoses because of the gracious efforts of those involved in the planning and execution of this comprehensive disease guide.

Review Committee

Editorial Board Steering Committee

Editorial Chairman

Morton Coleman, MD, NewYork-Presbyterian Hospital/Weill Cornell Medicine

Medical Review Board

Jorge J. Castillo, MD, Dana-Farber Cancer Institute/Harvard Medical School

Bruce D. Cheson, MD, FACP, FAAAS, FASCO, Lombardi Comprehensive Cancer Center, Georgetown University Hospital

Kieron M. Dunleavy, MD, GW Cancer Center, George Washington University

Arnold S. Freedman, MD, Dana-Farber Cancer Institute

Jonathan W. Friedberg, MD, MMSc, James P. Wilmot Cancer Institute, University of Rochester Medical Center

Leo I. Gordon, MD, FACP, Robert H. Lurie Comprehensive Cancer Center of Northwestern University

Thomas M. Habermann, MD, Mayo Clinic, Rochester

Brad S. Kahl, MD, Washington University Medical School

John P. Leonard, MD, NewYork-Presbyterian Hospital/Weill
Cornell Medicine

John M. Pagel, MD, PhD, Swedish Cancer Institute

Lauren C. Pinter-Brown, MD, FACP, Chao Family Comprehensive
Cancer Center, University of California at Irvine

Steven T. Rosen, MD, City of Hope

Sonali M. Smith, MD, The University of Chicago Medicine

Eduardo M. Sotomayor, MD, GW Cancer Center, George
Washington University

Michael E. Williams, MD, ScM, University of Virginia Cancer
Center

Andrew D. Zelenetz, MD, PhD, Memorial Sloan Kettering Cancer
Center

Lymphoma Research Foundation Reviewers

Izumi Nakano, Associate Director of Patient Services

Peggy Ann Torney, Chief Strategy, Communications and
Engagement Officer

TABLE OF CONTENTS

Abbreviations	4
Introduction	6
Part 1 — Learning the Basics	7
Chapter 1: Understanding the Disease	7
Table 1.1. Main Types of Indolent and Aggressive NHLs (Listed Alphabetically)	16
Chapter 2: Seeking Medical Attention	29
Table 2.1. Signs and Symptoms Commonly Found in Patients With NHL	30
Chapter 3: Receiving a Diagnosis	33
Table 3.1. The Three Main Types of Biopsies	35
Table 3.2. Immunohistochemistry and Flow Cytometry Tests	38
Chapter 4: Work-Up Before Treatment Can Begin	42
Table 4.1 The Eastern Cooperative Oncology Group Performance Status Scale	43
Table 4.2. Types of Imaging Tests	45
Table 4.3. Other Types of Biopsies	46

Part 2 — Treatment of Non-Hodgkin Lymphoma	52
Chapter 5: What to Know Before Starting Treatment	52
Table 5.1. International Prognostic Index.	55
Chapter 6: Treatments for Non-Hodgkin Lymphoma.	66
Table 6.1. Common Chemotherapy Regimens for NHL	69
Table 6.2. Catheters Used to Administer Chemotherapy.	72
Table 6.3. Methods for Delivering Radiation Therapy	88
Table 6.4. Terms Used to Describe Treatment and Its Outcomes	94
Table 6.5. Forms of Complementary Therapy.	97
 Part 3 — Survivorship and Living With the Side Effects of Treatment.	 99
Chapter 7: Common Treatment Side Effects	99
Table 7.1. Five Common Conditions Caused by Decreased Blood Cell Production	102
Chapter 8: Managing Life During and After Treatment	127
Table 8.1. Coping Strategies	127

Part 4 — Hospital Admission 133

Chapter 9: Preparing to Go to the Hospital. 133

**Part 5 — Clinical Trials and Advances
in Treatment** 140

Chapter 10: Overview of Clinical Trials 140

Table 10.1. The Four Phases of Clinical Trials 141

**Chapter 11: Advances in Treatment of Patients With
Non-Hodgkin Lymphoma** 146

About The Lymphoma Research Foundation 150

ABBREVIATIONS

3D-CRT	three-dimensional conformal radiation therapy	CT	computed tomography
ABC	activated B-cell–like	CTCL	cutaneous T-cell lymphoma
ABMS	American Board of Medical Specialties	DHL	double-hit lymphoma
AIDS	acquired immunodeficiency syndrome	DLBCL	diffuse large B-cell lymphoma
AIHA	autoimmune hemolytic anemia	DLCO	diffusing capacity of the lungs for carbon monoxide
AITL	angioimmunoblastic T-cell lymphoma	DNA	deoxyribonucleic acid; genetic material
ALCL	anaplastic large cell lymphoma	DNR	do not resuscitate
ALK	anaplastic lymphoma kinase	EATL	enteropathy-associated T-cell lymphoma
ALL	acute lymphoblastic leukemia	EBV	Epstein-Barr virus
ANC	absolute neutrophil count	ECHO	echocardiogram
ASCO	American Society of Clinical Oncology	ENMZL	extranodal marginal zone lymphoma
ASH	American Society of Hematology	FDA	U.S. Food and Drug Administration
B2M	beta-2 microglobulin	FISH	fluorescence in situ hybridization
BTK	Bruton tyrosine kinase	FL	follicular lymphoma
CAR	chimeric antigen receptor	FNA	fine needle aspiration
CBC	complete blood count	GCB	germinal center B-cell–like
CLL	chronic lymphocytic leukemia	GVHD	graft-versus-host disease
CNS	central nervous system	GVL	graft-versus-lymphoma
CPR	cardiopulmonary resuscitation	HBV	hepatitis B virus
CR	complete remission	HCV	hepatitis C virus
CSF	cerebrospinal fluid	HDAC	histone deacetylase
		HIV	human immunodeficiency virus
		HL	Hodgkin lymphoma

HTLV-1	human T-cell lymphotropic virus type 1	PET	positron emission tomography
IgM	immunoglobulin M	PFT	pulmonary function test
IGRT	image-guided radiation therapy	PI3K	phosphoinositide (or phosphatidylinositol)-3-kinase
IHC	immunohistochemistry	PICC	peripherally inserted central catheter
IMiD	immunomodulatory drug	PMBCL	primary mediastinal B-cell lymphoma
IPI	International Prognostic Index	PML	progressive multifocal leukoencephalopathy
IRB	institutional review board	PR	partial remission
ITP	immune thrombocytopenia	PS	performance status
IV	intravenous	PTCL	peripheral T-cell lymphoma
LDH	lactate dehydrogenase	PTCL-NOS	peripheral T-cell lymphoma, not otherwise specified
LRF	Lymphoma Research Foundation	RNA	ribonucleic acid; genetic material
MALT	mucosa-associated lymphoid tissue	SAB	scientific advisory board
MCL	mantle cell lymphoma	SEER	Surveillance, Epidemiology, and End Results
MMAE	monomethyl auristatin E	SLL	small lymphocytic lymphoma
MR	minor response	SMZL	splenic marginal zone lymphoma
MRI	magnetic resonance imaging	Syk	spleen tyrosine kinase
MUGA	multigated acquisition	TLS	tumor lysis syndrome
MZL	marginal zone lymphoma	TNF	tumor necrosis factor
NCCN	National Comprehensive Cancer Network	TSEBT	total skin electron beam therapy
NCI	National Cancer Institute		
NHL	non-Hodgkin lymphoma		
NIH	National Institutes of Health		
NK	natural killer (cell)		
NSAID	nonsteroidal anti-inflammatory drug		
PCR	polymerase chain reaction		

INTRODUCTION

The purpose of this guide is to educate and support patients with non-Hodgkin lymphoma and their caregivers. It is designed to allow them to familiarize themselves with this disease and to become active participants in their healthcare decisions. Chapters in this guide address different issues faced by patients with non-Hodgkin lymphoma, 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, information is available on the Lymphoma Research Foundation's (LRF's) website at lymphoma.org. The LRF Helpline can also provide additional information and copies of LRF educational and support publications. For Helpline assistance, call (800) 500-9976 or email helpline@lymphoma.org.

Part 1 — Learning the Basics

Chapter 1: Understanding the Disease

Non-Hodgkin lymphoma (NHL) is a type of blood cancer that affects specialized white blood cells called *lymphocytes*. Lymphocytes work together with other cells in the immune system to defend the body against invasion by bacteria, viruses, parasites, and other foreign substances. Lymphocytes travel in the bloodstream and in another network of mostly small vessels called the *lymphatic system*.

Lymphocytes are also found in specialized structures called lymph nodes, in the bone marrow, and in the spleen. Lymph nodes are part of the lymphatic system and typically are the sites in which the body develops an immune response to viruses and bacterial infections.

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

What Is Cancer?

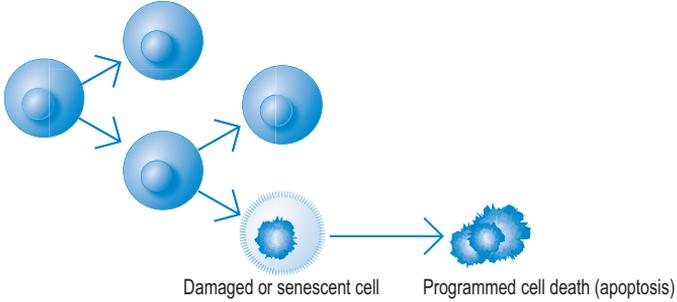
The body is made up of many different types of specialized cells that are organized into tissues and organs that perform the tasks needed to sustain life. To keep the body running smoothly, cells in the body grow, work, and multiply in a very controlled fashion.

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

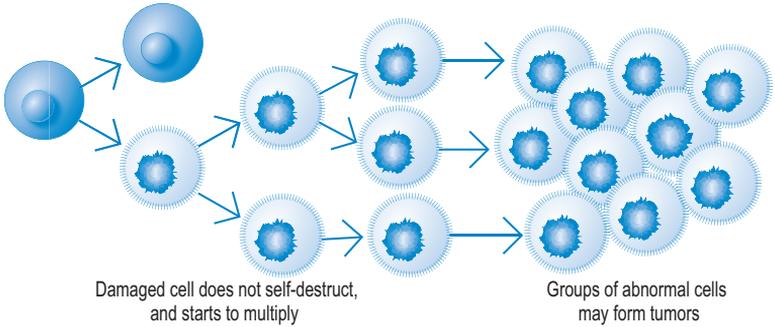
Cancer, or malignancy, is a disease in which abnormal cells gain the ability to multiply uncontrollably. When these cells accumulate, they form a mass called a *tumor* that can interfere with normal organ function.

HOW CANCER FORMS INSIDE THE BODY

Normal cell division



Cancer cell division



Most cancers are named after the organ or cell type of their origin. For almost every normal cell in the body, there is a corresponding cancer. For example:

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

What Are the Different Types of Blood Cells?

There are three main classes of blood cells:

- Red blood cells (or *erythrocytes*) — Red blood cells carry oxygen from the lungs to all the tissues in the body. Red blood cells also remove the carbon dioxide waste produced by cells and bring it to the lungs to be exhaled. A low number of red blood cells is called *anemia*. A person with anemia may feel tired, weak, and/or short of breath.
- 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:
 - Lymphocytes — These are discussed on the following page.
 - Granulocytes — There are three types of granulocytes: neutrophils, basophils, and eosinophils. Neutrophils help fight bacterial infections. A low number of neutrophils in the blood is called *neutropenia*. People with neutropenia are more likely to get infections (mostly bacterial infections) than people with normal numbers of neutrophils. Basophils are cells that take part in inflammatory reactions. Eosinophils also help fight infections—particularly those caused by parasites—and they can become plentiful during allergic reactions.
 - Monocytes — These also play an important role in immunity and are usually the first cells to recover after an episode of neutropenia.

- 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.

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

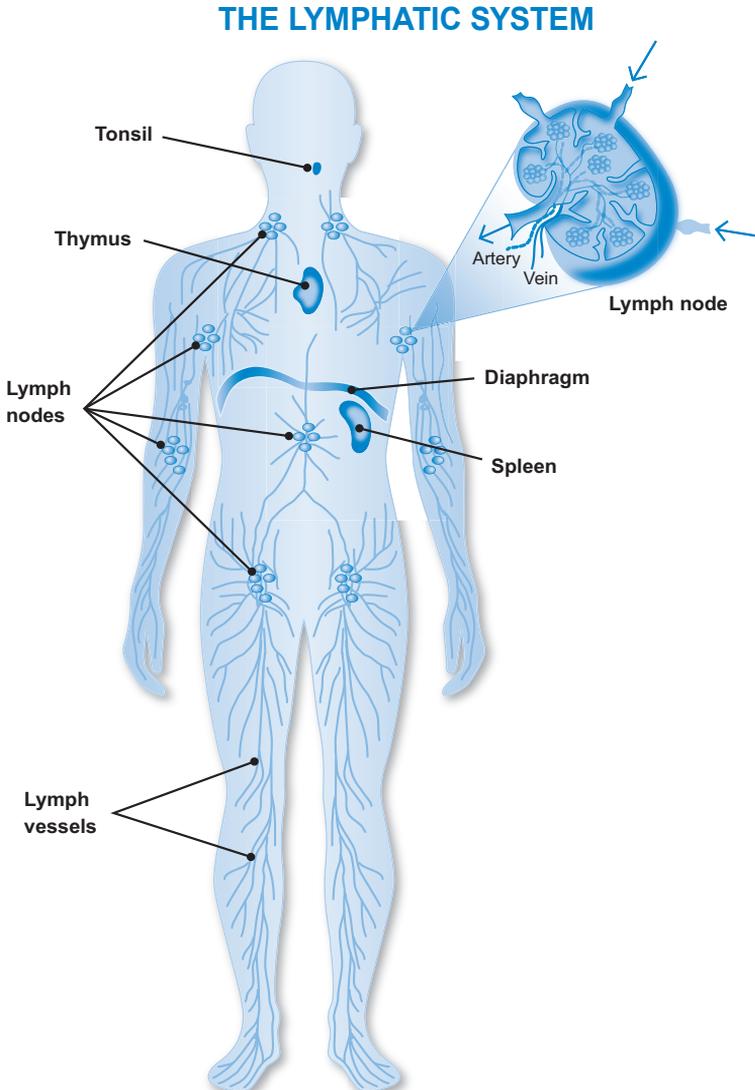
What are Lymphocytes?

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

- B lymphocytes (B cells) — B cells make antibodies 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) — There are many types of T cells. Some help B cells make antibodies, some attack and kill infected cells, and others help control or regulate the way other parts of the immune system fight infections. They are called “T” cells because they develop in the thymus gland, a small organ in the front of the chest.
- Natural killer (NK) cells — NK cells attack and kill cancer cells and virus-infected cells. They also make chemicals called cytokines that help the body get rid of viruses and tumor cells.

What Is the Lymphatic System?

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



Within this huge network of vessels are groups of small, bean-shaped organs called *lymph nodes*, which are also commonly known as “glands.” Lymph nodes filter the lymph fluid, removing bacteria, viruses, and other foreign substances from the body. Hundreds of lymph nodes are 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 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, and basophils.

- **Adaptive** (meaning adapting to external forces or threats) immunity — This type of immunity is provided by the thymus gland, spleen, tonsils, bone marrow, circulatory system, and lymphatic system. B cells and T cells, the two main types of lymphocytes, carry out the adaptive immune response by recognizing and either inactivating or killing specific invading organisms. The adaptive immune system can then “remember” the identity of the invader, so that the next time the body is infected by the same invader, the immune response will develop more quickly and strongly.

What Is Lymphoma?

A *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: non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma (HL). Both of these categories are further subdivided into numerous types, which differ in the way they develop and spread, as well as in the way they are treated. Unlike other cancers, therapy and prognosis are not based solely on the stage at which the disease is diagnosed but rather are determined by the lymphoma type, in addition to a variety of other factors like age and other medical issues.

What Is Non-Hodgkin Lymphoma?

In the United States, NHL (including chronic lymphocytic leukemia and small lymphocytic lymphoma) is the fifth most common type of cancer affecting adults. NHL is not a single disease but rather a large group of several closely related cancers that come from abnormal lymphocytes. The World Health Organization estimates that there are more than 80 types of NHL. While these various types share many common features, certain characteristics set them apart from each other, including:

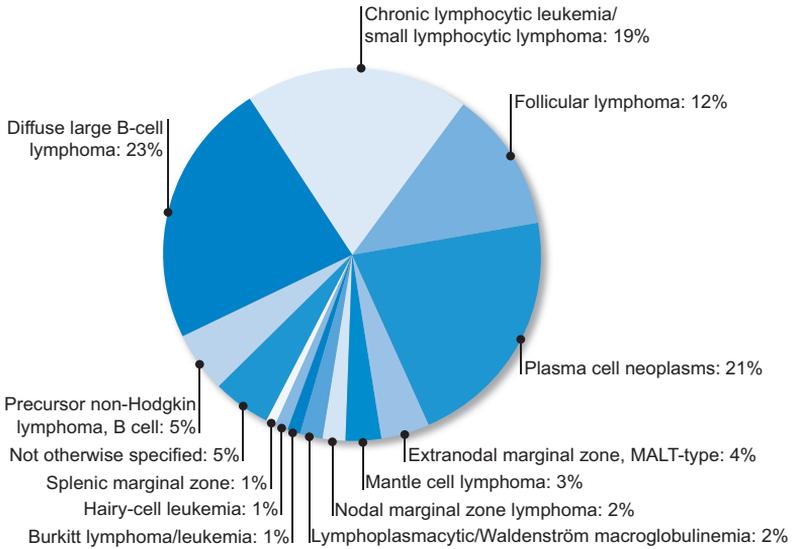
- How they look when examined under a microscope
- Genetic and other molecular characteristics
- How and where they grow in the body

- How their growth and spread affect patients
- How the disease should be treated
- Likely outcome of treatment (curable vs. not curable [but treatable])

NHL is divided into the following two major groups:

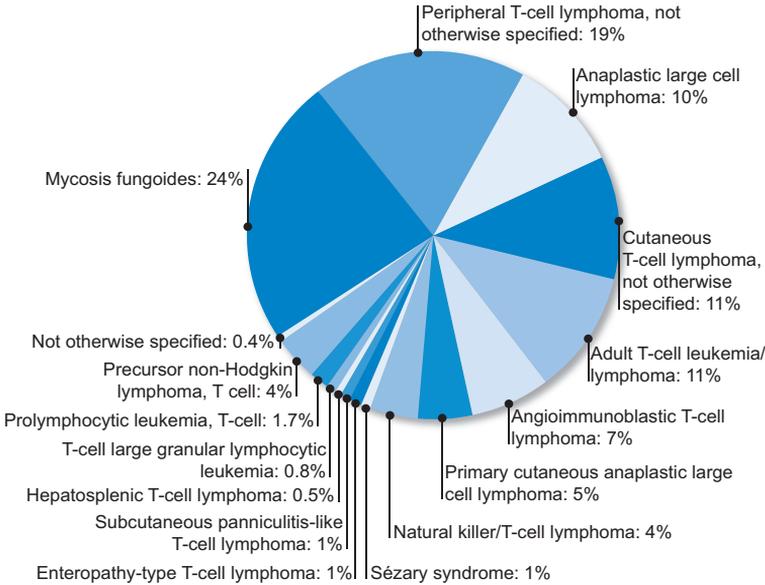
- B-cell lymphomas — These lymphomas develop from abnormal B lymphocytes and are the most common, comprising about 92 percent of all cases of NHL in the United States.
- T/NK-cell lymphomas — These lymphomas develop from abnormal T lymphocytes or NK cells, are less common, and constitute about seven percent of patients with an NHL diagnosis.

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, 2005-2014. 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 Surveillance, Epidemiology, and End Results (SEER) data, 2005-2014. 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 tend to exhibit few symptoms. Indolent lymphomas are generally not curable (similar in some ways to chronic diseases such as diabetes, which is not curable but usually manageable). However, 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, even decades. Over time, some indolent lymphomas may “transform” or develop into aggressive lymphomas.
- **Aggressive** lymphomas grow and spread more quickly than indolent lymphomas. However, aggressive lymphomas can be cured by chemotherapy agents that kill rapidly dividing tumor cells.

**Table 1.1. Main Types of Indolent and Aggressive NHLs
(Listed Alphabetically)**

Indolent NHLs	Aggressive NHLs
Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL)	Anaplastic large cell lymphoma (ALCL)
Follicular lymphoma (FL)	Angioimmunoblastic T-cell lymphoma (AITL)
Lymphoplasmacytic lymphoma/Waldenström macroglobulinemia	Burkitt/Burkitt-like lymphomas
Marginal zone lymphoma (MZL)	Diffuse large B-cell lymphoma (DLBCL)
Mycosis fungoides (subtype of cutaneous T-cell lymphoma)	Lymphoblastic leukemia/lymphoma
	Mantle cell lymphoma (MCL)
	Peripheral T-cell lymphoma (PTCL)
	Sézary syndrome (advanced subtype of cutaneous T-cell lymphoma)

Common Types of Indolent Non-Hodgkin B-Cell and T-Cell Lymphomas

Indolent B-Cell Lymphomas

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

Chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) are a type of lymphoma involving small lymphocytes that can be primarily in the bone marrow and blood (“leukemia”) or primarily 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, about 25 to 50 percent of patients may not experience any

signs or symptoms, so CLL/SLL is often discovered during routine blood tests and/or a physical examination. More than half of CLL/SLL cases occur in people over the age of 70. 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.

For a more detailed description of CLL/SLL, see the *Understanding CLL/SLL: A Guide for Patients, Survivors, and Loved Ones* booklet on the Lymphoma Research Foundation's (LRF's) website at lymphoma.org/publications, or visit lymphoma.org/CLL.

Follicular Lymphoma

Follicular lymphoma (FL) is one of the most common types of NHL in the United States, with over 31,000 people newly diagnosed each year. 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 may eventually transform into a more aggressive form of the disease (for more information on transformation, please see the *Transformed Lymphomas* fact sheet on LRF's website at lymphoma.org/publications).

Follicular lymphoma is graded from one to three depending on the number and pattern of cells called centroblasts seen in biopsy samples. Grades 1 and 2 FL, which have no or only a few centroblasts, are considered to be low grade. About 80 to 90 percent of FLs are grade 1 or 2 at diagnosis. Grade 3 FL can be either grade 3a or 3b. Patients with grade 3b FL are considered to be at high risk for disease progression, and are treated more aggressively. 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 5,300 people newly diagnosed in the United States each year. About 55 percent of cases are characterized by abnormally high levels of a protein called immunoglobulin M (IgM) or paraprotein, which can cause thickening of the blood (*hyperviscosity*); these patients are said to have Waldenström macroglobulinemia.

The disease usually affects older adults and is primarily found in the bone marrow, although the lymph nodes and spleen may sometimes be involved. Symptoms include fatigue, increased bleeding or bruising easily, headache, dizziness, visual changes, abdominal pain, and swollen lymph nodes.

For more information, 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 almost seven percent of all B-cell NHLs. The average age at diagnosis is 60. There are three types of MZL based on location in the body: (1) extranodal MZL (ENMZL; also called mucosa-associated lymphoid tissue [MALT]) occurs outside the lymphatic system; (2) nodal MZL occurs within the lymph nodes; and (3) splenic MZL (SMZL) occurs mostly in the spleen and blood.

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 bacterial pathogen that can cause gastritis and stomach ulcers) may increase the risk of developing ENMZL of the stomach lining.

Different types of infections have also been implicated in other forms of MZL, including *Campylobacter jejuni* (intestinal tract) and *Chlamydia psittaci* (lacrimonal – tear gland of the eye). For this reason, some MZLs can be successfully treated with anti-infective agents. However, the presence of any of these bacterial infections does not necessarily mean that someone has MZL.

Patients with SMZL may have an enlarged spleen. These lymphomas have been associated with hepatitis C virus (HCV) infection, and they may improve 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 men in their 40s, 50s, and 60s. Most forms of CTCL are indolent and involve only skin symptoms, although some forms of CTCL can involve the blood, lymph nodes, and other organs.

Mycosis fungoides is the most common type of CTCL, accounting for approximately one-half of all CTCLs. This type of lymphoma is indolent and usually develops 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)

Anaplastic large cell lymphoma limited to the skin is an uncommon type of indolent CTCL. Sézary syndrome, which is an aggressive form of CTCL, is discussed on page 26.

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

Common Types of Aggressive Non-Hodgkin B-Cell and T-Cell Lymphomas

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.
- Sporadic Burkitt lymphoma occurs throughout the world. The sporadic form seen in the United States accounts for about one percent of all B-cell NHLs in adults, and about five percent of all childhood lymphomas.
- 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 shown to be linked to the development of Burkitt lymphoma. The greatest association between EBV and Burkitt lymphoma is seen with the endemic form.

Burkitt lymphoma may affect the jaw, central nervous system (CNS), bowel, kidneys, ovaries, or other organs. The sporadic and immunodeficiency-related types usually cause a mass to develop in the abdomen. Other symptoms include weight loss, loss of appetite, fatigue, fever, and night sweats. Burkitt lymphoma is potentially curable when treated aggressively.

For more information, 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 23 percent of patients with newly diagnosed NHL. Although it can occur in childhood, the frequency of DLBCL generally increases with age, and most patients are over the age of 60 at diagnosis. The first sign of DLBCL is usually rapid swelling in the neck, underarms, or groin caused by enlarged lymph nodes. Other symptoms include night sweats, chills, unexplained fevers, and weight loss.

DLBCL can develop in the lymph nodes or outside the lymphatic system. It may be localized or spread throughout the body. The three primary subtypes are activated B-cell–like (ABC), germinal center B-cell–like (GCB), and primary mediastinal B-cell (PMBC) lymphoma. Despite being aggressive, DLBCL is curable in many patients. The treatment approach may depend on the DLBCL subtype. For example, the GCB subtype is more likely to respond to the standard chemotherapy regimen than the ABC subtype.

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

Double-Hit Lymphoma

Double-hit lymphoma (DHL) is a type of aggressive B-cell NHL characterized by rearrangements (parts of genes switch places within chromosomes) in the *c-MYC* gene and the *Bcl2* and/or *Bcl6* gene. The appearance of DHL under the microscope often resembles DLBCL but can also have some features of Burkitt lymphoma. Although many cases of DHL arise spontaneously, indolent lymphomas can transform into DHL as well. DHL is usually a very fast-growing type of lymphoma that requires intensive treatment.

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

Mantle Cell Lymphoma

Mantle cell lymphoma (MCL) accounts for about three percent of all patients with B-cell NHLs. This type of lymphoma more frequently affects 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. MCL may follow an indolent course that does not require therapy initially. Most cases, however, behave more aggressively and require treatment as an aggressive lymphoma.

For more information on MCL, please visit LRF's website at lymphoma.org/MCL, and view the *Mantle Cell Lymphoma* fact sheet 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 arises 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. Symptoms include fever, weight loss, night sweats, and superior vena cava syndrome, which is a swelling of the

face and arms and shortness of breath 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.

Aggressive T-Cell Lymphomas

Lymphoblastic Leukemia/Lymphoma

Lymphoblastic leukemia/lymphoma is relatively rare and can originate from both B cells and T cells, but about 85 percent of all cases involve T cells. Although 25 to 30 percent of T-cell lymphoblastic leukemia/lymphoma cases are diagnosed in children, the disease is also common in young adults, and it tends to occur in males more often than females. Lymphoblastic leukemia/lymphoma is aggressive and progresses rapidly, with more than 70 percent of patients presenting with advanced disease at diagnosis. Experts suggest that lymphoblastic leukemia/lymphoma and acute lymphoblastic leukemia (ALL) may be the same disease. 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.

Peripheral T-Cell Lymphoma

Peripheral T-cell lymphoma (PTCL) refers to a group of “mature” T-cell lymphomas that together account for approximately 54 percent of all patients diagnosed with T-cell NHL in the United States. The most common subtypes include PTCL not otherwise specified (PTCL-NOS), cutaneous T-cell lymphoma (CTCL), angioimmunoblastic T-cell lymphoma (AITL), and anaplastic large cell lymphoma (ALCL). PTCLs typically develop in tissues outside of the bone marrow such as the lymph nodes, spleen, gastrointestinal tract, and skin. Most are aggressive lymphomas, with the exception of some forms of CTCL (see page 19). Aggressive PTCL subtypes include AITL, extranodal NK/T-cell lymphoma, PTCL-NOS, enteropathy-type T-cell lymphoma (EATL), and ALCL. 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 rare, accounting for less than one percent of all NHLs and about 10 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). Systemic ALCL can respond well to chemotherapy and may be potentially curable. Cutaneous ALCL is not treated with intensive chemotherapy.

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* responds well to chemotherapy and is generally considered curable. However, *ALK negative* disease may initially respond to chemotherapy, but it tends to *relapse* (disease returns after treatment) and often requires additional therapy such as stem cell transplantation (for more information, see the *Understanding Stem Cell Transplantation* publication on LRF's website at lymphoma.org/publications).

Primary cutaneous ALCL is typically less aggressive than the systemic types. The characteristic features of primary cutaneous ALCL include the appearance of solitary 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 extend beyond the skin to lymph nodes or organs. If this occurs, it is usually treated like systemic ALCL.

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 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/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. 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 19 percent of all T-cell NHLs. It is also the most common subtype of PTCL. PTCL-NOS usually occurs in adults in their 50s and 60s. Although most patients with PTCL-NOS are diagnosed when their disease is still confined 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, aggressive 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.

Why Do Some People Develop NHL?

The reasons why certain people develop NHL are not totally understood. However, scientists have found that people with particular 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 correlation 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 immune disorder (for example, hypogammaglobulinemia or Wiskott-Aldrich syndrome) or infection with human immunodeficiency virus (HIV; the virus that causes AIDS)
- An autoimmune disease (for example, Crohn’s disease, rheumatoid arthritis, systemic lupus erythematosus, or psoriasis)
- Treatment for autoimmune diseases, especially with methotrexate and tumor necrosis factor (TNF)-inhibitor therapy
- Treatment with certain drugs used after organ transplantation
- Infections with certain viruses (for example, Epstein-Barr virus [EBV], human T-cell lymphotropic virus type 1 [HTLV-1], or hepatitis C virus [HCV])
- Infection with *H. pylori*, *Campylobacter jejuni*, or *Chlamydia psittaci*
- Older age (like most cancers, NHL is much more common in adults older than 60, although NHL may develop in children and adults of all ages)
- Male sex (for unknown reasons, NHL is slightly more common in men than in women)

- Exposure to certain chemicals, such as certain 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 from 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 no 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.

Part 1 — Learning the Basics

Chapter 2: Seeking Medical Attention

This chapter explains the signs and symptoms of non-Hodgkin lymphoma (NHL) and discusses how a doctor determines whether a person has the disease.

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

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

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, the 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, 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 may be due to other conditions.

Table 2.1. Signs and Symptoms Commonly Found in Patients With NHL

Sign or Symptom	Possible Reason
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 when the lymphocytes respond to an infection or because of an increased number of abnormal lymphocytes
Swollen, tender abdomen (“belly” or “stomach”)	Enlarged lymph nodes in the abdomen Accumulation of fluid in the abdomen Enlarged liver or spleen
Abdominal pain, nausea, vomiting, or decreased appetite	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
Coughing, trouble breathing, or chest pain or pressure	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>)
Headache, trouble thinking, weakness in extremities (legs or arms), personality changes, double or blurred vision, facial numbness, trouble speaking, or seizures	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
Rash or itchy red or purple lumps or nodules under the skin	Lymphoma of the skin

Table 2.1. Signs and Symptoms Commonly Found in Patients With NHL *(continued)*

Sign or Symptom	Possible Reason
“B symptoms,” including fever for no known reason, unexplained weight loss, or drenching night sweats that soak clothing and sheets	Increased levels of inflammatory chemicals in the blood that are released by lymphoma cells or by the immune system reacting to the lymphoma cells
Severe or frequent infections	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 within a few weeks and/or persistent symptoms should see a doctor to make sure that lymphoma or another serious condition is not present. A good rule of thumb is to seek medical attention if any of the signs or symptoms listed in Table 2.1 last longer than two weeks, or sooner if the symptoms are 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 the Visit?

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

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

If the doctor suspects NHL after reviewing the symptoms reported and the signs discovered during the examination, he or she will order tests to confirm the diagnosis.

These tests should include a complete blood count (CBC) and may also include specific laboratory tests, imaging tests (including scans), lymph node biopsy, and a bone marrow evaluation. Depending on the type and location of the suspected NHL, other tests may be required. However, a diagnosis of NHL cannot be established in most instances without evaluating a sample of the involved tissue. These tests and procedures are discussed in more detail in Chapters 3 and 4.

Part 1 — Learning the Basics

Chapter 3: Receiving a Diagnosis

Doctors need the results of various diagnostic tests to determine accurately whether a patient has non-Hodgkin lymphoma (NHL). This chapter explains the purpose of each test and describes what to expect during and after the test procedures.

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

Questions to Ask Before Having a Diagnostic Procedure

PATIENT TIP

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

Questions to Ask Before Having a Diagnostic Procedure (*continued*)

- 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 be?

How Is NHL Diagnosed?

A tissue biopsy is the test required to establish an initial diagnosis of NHL. After that, one or more of the tests listed below and described in detail on the next few pages may also be used to confirm the NHL diagnosis:

- Bone marrow aspiration and biopsy
- Complete blood count (CBC) with *differential* (a test in which the relative percentages of each type of blood cell are determined)
- Blood smears
- Immunophenotyping by flow cytometry of the lymphocytes in the blood and lymph node
- Cytogenetic or molecular genetic tests

What Is a Biopsy?

A *biopsy* is a procedure in which a piece of tissue from an area of suspected disease is removed from the body and examined under a microscope. The information provided by this tissue sample is crucial to diagnose the disease correctly and to decide on the best course of treatment.

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

Table 3.1. The Three Main Types of Biopsies

Excisional or Incisional Biopsy	<ul style="list-style-type: none">■ This type of biopsy is generally considered the best way to establish an initial diagnosis of lymphoma because it allows the removal of bigger samples than other biopsy procedures. The larger the sample, the more tissue can be examined, which improves the accuracy of the diagnosis and the ability to perform special tests that may direct 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 to numb the area. If the lymph node is in the chest or abdomen, the patient is sedated and the surgeon removes the tissue either <i>laparoscopically</i> (through a scope tube inserted in the body) or by performing more extensive surgery.
Core Needle Biopsy	<ul style="list-style-type: none">■ This procedure is used when the lymph nodes being examined are deep in the chest or abdomen or in other locations that are difficult to reach with an excisional biopsy, or when there are medical reasons for avoiding an excisional or incisional biopsy.■ A large needle is inserted into the lymph node and a small tissue sample is withdrawn using a syringe attached to the needle. This can be done under local anesthesia, and stitches are usually not required.■ Sometimes the material collected may not be adequate for diagnosis, so a subsequent excisional or incisional biopsy may still be necessary.■ Often the core needle biopsy is guided by an imaging test, such as an ultrasound, or computed tomography (CT) scan.

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

Fine Needle Aspirate (FNA) Biopsy	<ul style="list-style-type: none"> ■ This procedure is performed with a very thin needle that is smaller than that used for a core needle biopsy. ■ Because of the small needle size, the sample only contains scattered cells without preserving how the cells are arranged in the lymph node. Therefore, this test cannot provide enough information for a definitive initial diagnosis of NHL. ■ An FNA biopsy is most often used to check for <i>relapse</i> (return of the disease) after treatment.
--	--

After a tissue sample has been removed, it is examined by a *pathologist* (doctor who specializes in the diagnosis of diseases by studying the cells from a patient's body fluids and tissue samples). 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 cancer cells by looking at their shape and size and how they are grouped in the sample.

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. A pathologic diagnosis and accurate classification of specific lymphoma types can sometimes be difficult to make. If the pathologist's interpretation of the biopsy is uncertain, the report should be reviewed by an expert hematopathologist. An accurate diagnosis and subclassification are essential, as subsequent treatment planning and an expectation of the outcome rely on this information.

What Are a Bone Marrow Biopsy and a Bone Marrow Aspiration?

Bone marrow is the spongy, fatty material inside large flat bones (such as the pelvis, vertebrae, and sternum) where blood cells are generated. A *bone marrow biopsy* involves removing a small amount of bone marrow and examining it for the presence of lymphoma cells. A *bone marrow aspiration* is similar to a bone marrow biopsy, except it involves removing only the liquid portion of the marrow using a fine needle. A bone marrow biopsy or aspiration is not typically used for initial diagnosis, but it is commonly used at a later stage to determine if the NHL has spread to the bone marrow. A positive result establishes the presence of advanced (Stage IV) disease. Bone marrow in greater quantity may also be collected for transplantation analysis (see the section “Why Might Another Type of Biopsy Be Needed?” on page 46).

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

In a CBC with differential test, samples of blood are examined to measure the levels of each different type and subtype of blood cells, including:

- The number of red blood cells
- The amount of *hemoglobin* (the oxygen-carrying protein) inside the red blood cells
- The number of total white blood cells, as well as the numbers of each subtype of white blood cells (neutrophils, eosinophils, basophils, lymphocytes, and monocytes)
- The number of platelets

The results of the CBC with differential test assist in the diagnosis of NHL by ruling out other types of blood cancer. The test is often repeated during the course of treatment to help determine how much the chemotherapy has affected the different blood counts and, in some cases, to help gauge how well the treatment is working against the lymphoma.

What Is Immunophenotyping?

Immunophenotyping is a process that can be used to diagnose the specific subtype of NHL. This process distinguishes between different types of cells (for example, normal lymphocytes vs. lymphoma cells) based on the presence of *antigens* (cell markers or proteins) on the cell surface. Antigens are specific to different cell types, just as landmarks are specific to different cities. These antigens are recognized by antibodies that have been chemically modified in the laboratory so that they show color or emit fluorescent light.

Two types of analyses, immunohistochemistry and flow cytometry, may be performed with these antibodies for accurate immunophenotyping (see Table 3.2).

Table 3.2. Immunohistochemistry and Flow Cytometry Tests

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/leukemia 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.
Flow Cytometry	<ul style="list-style-type: none"> ■ Cells from the biopsy sample are placed in a liquid solution and treated with sets of antibodies that recognize antigens found in different types of 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 from the antibodies attached to them. This information is measured and analyzed by a computer and interpreted by a hematopathologist or another specialist.

What Is Cytogenetic Analysis?

Chromosomes contain genes that are made of very long strands of DNA. Normal human cells have 23 pairs of chromosomes. Some lymphoma cells have too many or too few chromosomes, or they may have abnormal chromosomes that have undergone a genetic change. These changes can activate lymphoma cells to multiply.

Cytogenetic analysis involves looking at chromosomes from lymphoma cells under a microscope to check for any abnormalities in number or structure. The results of the cytogenetic analysis often help doctors determine which type and subtype of NHL a patient has; this information can assist in making treatment decisions.

What Are Types of Chromosome Abnormalities?

Chromosome abnormalities can contribute to the development of lymphoma either by damaging or removing genes that regulate lymphocyte growth, or by adding genes that fuel lymphocyte growth. Either of these changes can cause the lymphoma to grow uncontrollably. Some of the most common types of chromosome abnormalities that occur in lymphoma are described below:

- *Translocation*: parts of two different chromosomes break off and switch places with each other
- *Deletion*: part of a chromosome is missing
- *Amplification*: a portion of a chromosome is repeated one or many times, resulting in excessive copies of one or more genes
- *Trisomy*: the cell contains an extra copy of an entire chromosome, so that there are three instead of two

What Is the Purpose of Additional Genetic Tests?

Doctors may order additional genetic tests to confirm the results of cytogenetic tests or to find out more detailed information about the types of chromosomal abnormalities present in the lymphoma cells. The three main types of additional genetic tests used are:

- Fluorescence in situ hybridization (FISH)
- Polymerase chain reaction (PCR)
- DNA/RNA sequencing

Doctors may use some or all of these tests to learn more about the genetics of an individual patient's lymphoma. 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 NHL subtypes based on their genetic profiles, which helps to make decisions about treatments.

It is important for patients to discuss the interpretation of diagnostic tests with their doctor. On the next page is a list of some important considerations when interpreting diagnostic tests.

Cautions About Interpreting Diagnostic Tests

- Biopsies, and in some instances peripheral blood immunophenotyping, are the only definitive tests for NHL.
- The doctor may order cytogenetic/genomic testing that could be used to help determine a patient's next treatment.
- Some test results may be reported as “normal” even though NHL is present.
- Some test results may be reported as “abnormal” even though NHL is not present.
- Other conditions can produce signs and symptoms similar to NHL.
- The interpretation of test results, such as imaging studies and scans, can be lengthy 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.
- If patients wish to look at their written test reports, it is important for them to review the findings carefully with their doctor.

Part 1 — Learning the Basics

Chapter 4: Work-Up Before Treatment Can Begin

After the initial diagnosis of non-Hodgkin lymphoma (NHL), 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 patient's disease *stage*, which is 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 patient'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 NHL is staged.

What Tests Are Used in the Work-Up For NHL?

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

- Physical examination with special attention to the size of the lymph nodes, liver, and spleen
- Determination of general health status (also called *performance status* or *functional status*) to see how well a patient feels and how well he/she 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 NHL that patients may already have), such as diabetes mellitus, coronary artery 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, and weight loss (also called “B symptoms”)
- Complete blood count (CBC) with differential

- Measurement of lactate dehydrogenase (LDH) and beta-2 microglobulin (B2M) levels
- Testing for infection with human immunodeficiency virus (HIV), hepatitis viruses, and other viruses
- Comprehensive metabolic panel
- Computed tomography (CT) and/or positron emission tomography-CT (PET-CT) scans of the neck, chest, abdomen, and pelvis
- Magnetic resonance imaging (MRI) is often used for suspected bone or nervous system involvement
- Excisional, incisional, or core needle biopsy
- Bone marrow aspiration and/or biopsy
- Cytogenetic and genomic testing
- Lumbar puncture and/or MRI brain imaging

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). As shown in Table 4.1, PS is graded on a scale of 0–4, with the lower numbers indicating better health.

Table 4.1. The Eastern Cooperative Oncology Group Performance Status Scale

Grade	Description
0	■ Fully active and able to carry on all pre-disease activities without restriction
1	■ Cannot perform taxing physical activities, but can move around (ambulatory) and carry out light work (such as light house work) 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

What Is the Purpose of the Lactate Dehydrogenase and Beta-2 Microglobulin Test?

High blood levels of the protein lactate dehydrogenase (LDH) are associated with fast-growing lymphomas. However, LDH can also be abnormal due to conditions other than lymphoma (such as growth factor treatment, red blood cell destruction, liver disease, bone marrow disease), so it is important to discuss this with the treatment team. Beta-2 microglobulin (B2M) is another molecule that may indicate a worse prognosis when its blood levels are elevated in NHL patients.

What Is the Purpose of Testing For Hepatitis Virus and HIV?

It is important to determine whether patients with NHL are infected with hepatitis B virus (HBV), hepatitis C virus (HCV), and/or human immunodeficiency virus (HIV), because the presence of these viruses in the body may affect the type of treatments given.

What Is a Comprehensive Metabolic Panel?

A comprehensive metabolic panel measures the levels of certain chemicals in the blood to see whether the NHL is causing any abnormalities in the main organs of the body. The comprehensive metabolic panel usually includes 14 or more specific tests that measure liver and kidney function, electrolytes, acid/base balance, and the levels of blood sugar and other blood proteins.

The results from these tests can help patients and their doctors choose between different treatments. Many of these blood tests may be repeated several times during the course of treatment to see how the treatment and the lymphoma are affecting the patient's body functions.

What Types of Imaging Tests May Be Used?

A doctor will most likely order imaging tests to help identify areas of the body where the lymphoma has spread, and, later on, to determine how well the treatment is working. Most of these tests are painless and require no *anesthetic* (numbing medication). Several types of imaging procedures (described in Table 4.2) may be needed to evaluate the extent of disease.

Table 4.2. Types of Imaging Tests

Chest X-Ray	<ul style="list-style-type: none">■ X-rays use radiation to take pictures of areas inside the body. The amount of radiation used in most diagnostic tests is so small that it poses little risk to the patient.■ Findings from a chest X-ray may indicate whether a tumor is “bulky” (greater than 7–10 centimeters), located in the mediastinum, or measures more than one-third of the diameter of the chest cavity.■ A chest X-ray is the only imaging test conducted while the patient is standing up.
Computed Tomography (CT)	<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 NHL 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 get an intravenous (IV) 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.■ An MRI can provide important information about tissues and organs, particularly the bones and nervous system that is not available from other imaging techniques.■ MRI scans cannot replace CT scans, because they do not provide clear images of lymph nodes as well as CT scans do.

Table 4.2. Types of Imaging Tests (*continued*)

Positron Emission Tomography (PET)	<ul style="list-style-type: none"> ■ A PET scan evaluates NHL activity in all parts of the body. ■ <i>Radioactive fluorodeoxyglucose</i> (a type of sugar) is injected into the body. A positron camera is then used to detect the radioactivity and produce cross-sectional images of the body. This test relies on the fact that cancer cells metabolize sugar faster than normal cells, so that more “uptake” on a PET scan indicates more metabolic activity, suggesting the presence of the malignant cells. ■ While CT scans provide information about the size of a lymph node, PET scans can better indicate whether the lymph node contains active NHL cells. ■ PET scans help distinguish active tumors from scar tissue 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 procedure is slightly modified from that described above.
---	---

Why Might Another Type of Biopsy Be Needed?

Once the NHL 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 4.3).

Table 4.3. Other Types of Biopsies

Bone Marrow Aspiration and/or Biopsy	<ul style="list-style-type: none"> ■ <i>Bone marrow</i> is the soft, spongy material found inside bones. NHLs can spread to the bone marrow or start in the bone marrow. ■ This procedure may be done to determine if the lymphoma has spread to the bone marrow. ■ In bone marrow aspiration, 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. ■ A bone marrow biopsy is often performed immediately after the aspiration. ■ Sometimes light general anesthesia is used for this procedure.
---	--

Table 4.3. Other Types of Biopsies (*continued*)

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 liquid for laboratory analysis.■ The liquid is called <i>pleural fluid</i> when found inside the chest, <i>pericardial fluid</i> when found surrounding the heart, and <i>peritoneal fluid</i> when found inside the abdomen.

Why Is Heart Function Evaluated?

Before beginning some types of lymphoma treatment, the doctor may measure the patient's baseline heart function to make sure that the patient's body can withstand treatment. This is especially important because certain lymphoma treatments can occasionally make heart function worse. Depending on the treatment used, the patient's heart function may be evaluated again during treatment to make sure the heart is tolerating the treatment.

Two tests are used to evaluate heart function: an echocardiogram (ECHO) or a multigated acquisition (MUGA) scan.

An ECHO is an ultrasound of the heart. An instrument called a transducer is placed on the chest and releases high-frequency sound waves that are converted into moving images of the heart. This test

evaluates the function of the cardiac muscle and provides information about the heart valves. An ECHO can be performed while the patient is resting or after exercise.

A MUGA scan creates video images of the *ventricles* (lower chambers of the heart) to measure how well they are pumping blood. During the procedure, a *tracer* (radioactive material) that attaches to red blood cells is injected into the arm. As the tracer moves through the bloodstream, a special camera takes pictures to see how efficiently the heart is pumping the blood.

Why Might Lung Function Be Evaluated?

Some lymphoma treatments can put stress on the lungs. For this reason, the doctor may order pulmonary (lung) function tests (PFTs) before beginning treatment and again during treatment to make sure the patient's lungs are working properly.

Three types of PFTs are typically used. *Spirometry* measures the amount of air a patient breathes in and out. For this test, the patient is fitted with a mouthpiece and a nose clip and is asked to breathe normally. Patients may also be told to inhale and exhale as deeply and/or as rapidly as they can for several seconds.

Plethysmography measures the volume of air in the lungs. For this test, the patient sits or stands in a small booth and breathes into a mouthpiece. The pressure in the booth is measured to determine lung volume.

A third test, called *diffusing capacity of the lungs for carbon monoxide (DLCO)*, measures how well the lungs transfer gas from inhaled air to red blood cells. Patients are asked to inhale air containing a very small amount of carbon monoxide, hold their breath for 10 seconds, and then exhale.

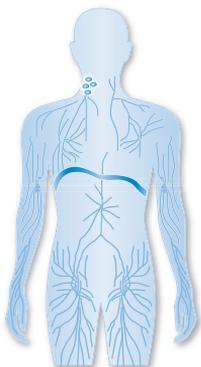
How Is NHL Staged?

Staging is used to describe where the cancer is located and how widely the cancer has spread in patients with NHL. 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.

There are two main divisions of NHL (limited and advanced disease) and four stages designated by the 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 7–10 centimeters [~4 inches] wide). Stages III and IV are considered advanced disease. Although some patients have advanced NHL at the time they are diagnosed, their disease can often be successfully treated and cured. Note that staging of NHL differs from that of solid tumors, such as breast cancer and colon cancer. For solid tumors, only Stage IV cancers have spread through the body, while NHLs of all stages have the potential to circulate through the body due to their location in the lymphatic system.

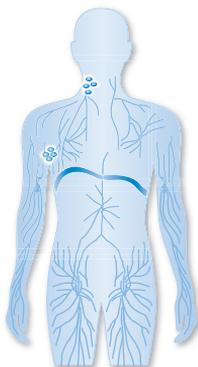
The Ann Arbor staging system has traditionally been used for staging all NHLs other than chronic lymphocytic leukemia (CLL). Although the older staging system is still in use, a modification of the Ann Arbor staging system called the Lugano Classification was proposed in 2014. This system is shown in the figure on the following page.

STAGING OF NHL (LUGANO CLASSIFICATION)



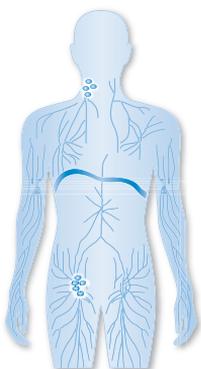
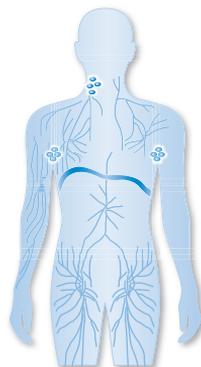
Stage I:

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



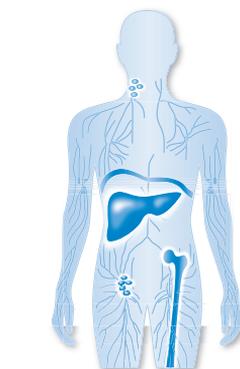
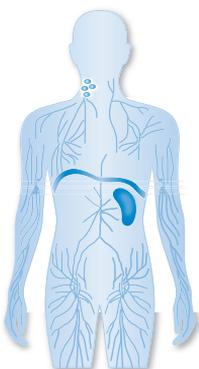
Stage II:

- 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 and organ involvement

The Ann Arbor staging system is used to stage small lymphocytic leukemia (SLL) but not CLL. For CLL, the Rai staging system is commonly used in the United States, while the Binet classification system is more popular in Europe. Because of the differences in staging systems, a patient may have Stage IV SLL (blood and marrow involvement) and Rai Stage 0 CLL. These staging systems are described in greater detail in the Lymphoma Research Foundation's publication *Understanding CLL/SLL: A Guide for Patients, Survivors, and Loved Ones* available at lymphoma.org/publications.

Part 2 — Treatment of Non-Hodgkin Lymphoma

Chapter 5: What to Know Before Starting Treatment

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

PATIENT TIP

First Steps to Take After Receiving a Diagnosis

- Take care of yourself (eat, sleep, rest, and exercise).
- Seek the support of family, friends, and others you trust.
- Learn about the disease and treatment options.
- Find medical care that meets your needs.
- Seek out additional sources of emotional and social support for people with cancer, such as LRF's *Lymphoma Support Network* that connects patients and caregivers with volunteers who have experience with non-Hodgkin lymphoma or chronic lymphocytic leukemia/small lymphocytic leukemia, 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.

Who Plans and Carries Out the Treatment?

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

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

What Is a Prognosis?

Prognosis is the medical term for predicting how a disease will progress and the likelihood for recovery, which is often one of the first questions that patients ask their doctor. A prognosis is usually based on information gathered from hundreds or thousands of other patients who have had the same disease. This statistical information provides doctors with a general idea of what to expect when a patient is diagnosed with a specific type of NHL, and it helps them select which treatments are most likely to work.

Keep in mind that no two patients are alike and that statistics from large groups of people cannot accurately predict what will happen to an individual patient. The doctor most familiar with the patient's situation is in the best position to interpret these statistics and understand how well they apply to a patient's particular situation. Patients should also bear in mind that most published statistics on treatment outcomes do not reflect the benefits of the most recent new therapeutics that might be used in treatment.

What Are Prognostic Factors?

The characteristics that help predict a patient's prognosis are called *prognostic factors*. Favorable or good prognostic factors tend to be associated with better outcomes, while unfavorable or poor prognostic factors tend to be associated with worse outcomes. Some prognostic factors only apply to a particular type of NHL, whereas other factors, like the ones found in the International Prognostic Index, can be applied more generally.

What Is the International Prognostic Index?

The International Prognostic Index (IPI) was first developed for *aggressive* (fast-growing) lymphomas. The IPI is based on five factors represented by the acronym APLES: age, performance status, lactate dehydrogenase (LDH) level, extranodal sites, and stage (as shown in Table 5.1 on the next page). *Performance status* (PS) is a numerical rating of a patients' general health and their ability to carry out normal daily activities (such as getting washed and dressed, going to work, and doing chores). PS is graded on a scale of 0–4, with the lower numbers indicating a better PS.

Table 5.1. International Prognostic Index

Factor	Good Prognostic Factor	Poor Prognostic Factor
Age	60 years or younger	Older than 60 years
Performance Status	Able to function normally	Needs help with daily activities
Lactate Dehydrogenase Level	Normal	Above 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

How to Decide What Treatment Is Best

There are many effective treatment options for patients with NHL. To identify which treatments may work best, doctors consider the following factors:

- Type of NHL
- Stage and location of the lymphoma
- Presence or absence of symptoms
- How rapidly the lymphoma is growing (whether it is an indolent or aggressive lymphoma)
- Levels of lactate dehydrogenase (LDH) or beta-2 microglobulin in the patient's blood
- Cytogenetic/genomic testing results
- A patient's overall health, age, and performance status
- A patient's prognostic factors
- A patient's preferences and goals for treatment
- Whether the treatment is the first the patient has received or the disease has *relapsed* (returned after prior therapy)
- Whether the treatment will impact future treatment options
- Availability of a clinical trial

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 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 NHL 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 at a later point? How are the different treatment choices administered?
- What is a clinical trial? Are clinical trials available that are studying new treatments for my type of NHL? Would a clinical trial be appropriate for me? How would I benefit?
- Do I need more than one type of treatment?
- What is the goal of treatment? What are the expected benefits of each type of treatment?
- How will we know if the treatment is working? What tests will I need to determine if treatment is working, and how often will I need to be tested?
- What are the risks and possible side effects of each treatment? Can these side effects be prevented or controlled?
- What should I do to take care of myself during treatment?

Questions to Ask Before Treatment Begins

(continued)

- Are there any late or long-term side effects I should be aware of?
- Will treatment impact my ability to have children in the future? Is there time for sperm banking/egg harvesting before starting treatment?
- How long will the treatment last?
- What are the chances the treatment will be successful?
- How will the treatment affect my normal activities (for example, work, school, childcare, driving, sexual activity, and exercise)?
- Is there anything my caregiver needs to do to prepare to care for me while I undergo treatment?
- Will I be able to work during treatment? Will I be able to drive or take public transportation during my treatment?
- Should I take care of other medical or dental issues before I start treatment?
- How much will the treatment cost? Will my insurance cover some or all of it? What will my out-of-pocket costs be?

When to Get a Second Opinion

Before starting any type of treatment, a patient may want to consider getting a second opinion, especially if the diagnosis is rare, complicated, or uncertain. The purpose of the second opinion is not to question the doctor's expertise but to make sure the suggested treatment plan is the best choice for the patient's particular case, as well as to evaluate alternative treatment options, including clinical trials.

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 and on the following page.

PATIENT TIP

Part 2

Getting a Second Opinion

- Some 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 NHL is often complex, and some pathologists may have limited experience analyzing NHL cells, so it is valuable to have the pathology results reviewed by an expert hematopathologist with extensive experience in lymphoma.
- To get a second opinion, you will need to provide the consulting doctor with a complete copy of all medical records, pathology samples, images and scans, and reports. When you set up the appointment, ask the office for a list of all the materials you need to bring. It will be useful to keep your own copy of all these records in case you have questions or concerns later on.

Getting a Second Opinion *(continued)*

To identify NHL specialists to contact for a second opinion:

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

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

to feel confident that the providers they select can meet their medical and personal needs. The following questions can be used to help patients select the best medical team.

PATIENT TIP

Questions to Ask to Select the Best Medical Team

- What are the credentials of the doctor, the other members of the medical team, and the hospital or cancer center?
- 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 to certify competency in these specialties?
- How much experience do the doctor and treatment center have in treating patients with NHL in particular?
- How many patients with this type of NHL 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 and diagnostic equipment?
- Is the doctor or clinic affiliated with any major medical center or medical school?
- In case of an emergency, what arrangements are made for medical assistance after hours and on weekends?
- Is my health insurance accepted at this center? Will the treatment center file claims for reimbursement and process the paperwork?
- What kind of patient resources does the clinic or cancer center have for patients with NHL?
- 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.

How to Communicate With the Healthcare Team

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

A good first step for patients is to write down all the questions that come to mind. Before meeting with a doctor, nurse, or physician assistant either for the first time or for follow-up visits, patients should consider organizing their questions into a list to bring to the visit. Since time with doctors, nurses, and physician assistants may be limited, patients should put the two or three most important questions at the top of their list. However, it is also important that a member of the patient's medical team reads all of the questions, because some may be more important than the patient realizes.

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 answers. Patients should ask the doctor, nurse, or physician assistant for permission before recording any conversations.

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

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

Open communication between patients and doctors is paramount. The tips below and on the following page can be used to help patients better communicate with their healthcare team.

Communicating With Your Doctors

At home

- Keep a journal of your symptoms to help you remember the details you want to discuss with your doctor during your next office visit.
- Ask your doctor or nurse 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.

PATIENT TIP

Communicating With Your Doctors (*continued*)

- Ask whether your healthcare team has an online “patient portal.” These portals may provide secure email contact and educational materials, and they often allow patients to check benefits and coverage, schedule non-urgent appointments, and order prescription refills.
- Download the *Focus On Lymphoma* mobile application (app) from LRF to help you plan appointments, manage medications and blood work, document treatment side effects, record doctor visits, and list questions. (lymphoma.org/mobileapp)

At your next doctor’s visit

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

How to Be a Self-Advocate

Being a self-advocate and an active participant in healthcare decisions can be a positive experience and may help patients regain a sense of control that they may have lost following the lymphoma diagnosis. 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.

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

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

Finally, it is important that 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 on the following page offer self-advocacy strategies for patients.

Self-Advocacy

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

Part 2 — Treatment of Non-Hodgkin Lymphoma

Chapter 6: Treatments for Non-Hodgkin Lymphoma

This chapter reviews the most common therapies currently used in the treatment of non-Hodgkin lymphoma (NHL). Keep in mind that new therapies may have been approved by the U.S. Food and Drug Administration (FDA) since this guide was printed. Read Chapter 11 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 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)
 - Immunotherapy, which helps the body's immune system attack lymphoma cells
 - Targeted therapies, which affect special characteristics or internal workings of lymphoma cells
- Radiation therapy, which uses high-energy radiation to kill lymphoma cells
- Stem cell transplantation, usually in combination with high-dose chemotherapy, which involves replacing a 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* (*watchful waiting*) approach, patients' health and disease are monitored through regular checkups and periodic evaluation procedures, such as laboratory and imaging tests, but do not receive any antilymphoma 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.

Doctors recommend active surveillance for select patients with *indolent* (slow-growing) lymphoma who have no significant symptoms or for patients with no significant symptoms from their disease. This approach may be used after the initial diagnosis of NHL or after *relapse* (disease returns after treatment), depending on the situation. Patients are moved from active surveillance to active treatment if they begin to develop lymphoma-related symptoms or if there are signs that the disease is clearly progressing.

Active surveillance is not a treatment option for patients with *aggressive* (fast-growing) NHL. Usually, treatment for these patients should start as soon as possible after diagnosis.

Questions to Ask Before Starting Active Surveillance

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

PATIENT TIP

What Is Chemotherapy?

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

Most patients with NHL are treated with 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 the chemotherapy prescribed. Most patients receive their chemotherapy treatments in an outpatient clinic, hospital outpatient department, or doctor's office, but sometimes patients have to stay overnight in the hospital for their treatment.

Common Chemotherapy Regimens for NHL

For the treatment of some B-cell lymphomas, the standard combination chemotherapy regimen is known as CHOP, which includes the drugs cyclophosphamide (Cytosan, Neosar), doxorubicin/hydroxydaunorubicin (Rubex, Adriamycin PFS), vincristine (Oncovin and others), and prednisone (Deltasone and others). In many cases, doctors add a fifth agent, a *monoclonal antibody* (an engineered molecule that is not considered a chemotherapy) called rituximab (Rituxan), to this combination to create R-CHOP. Sometimes newer regimens are substituted for CHOP. Some of these alternative regimens are shown in Table 6.1. Rituximab is discussed in greater detail on page 75.

For T-cell lymphomas, CHOP is less commonly used as a primary treatment. Instead, a newer class of drugs called histone deacetylase (HDAC) inhibitors (such as belinostat [Beleodaq], romidepsin [Istodax], and vorinostat [Zolinza]) and another drug called pralatrexate (Folotyn) are playing an increasing role in the treatment of T-cell malignancies.

Table 6.1 lists the common chemotherapy regimens used for NHL. This list is subject to change as the FDA approves new lymphoma treatments.

Table 6.1. Common Chemotherapy Regimens For NHL

Drug or Regimen Abbreviation	Generic Name of Drugs (Brand Name)
B	Bendamustine (Treanda, Bendeka)
C	Cyclophosphamide (Cytoxan, Neosar)
Chl	Chlorambucil (Leukeran)
CHOP	Cyclophosphamide Doxorubicin/hydroxydaunorubicin (Rubex, Adriamycin PFS) Vincristine (Oncovin and others) Prednisone (Deltasone and others)
CODOXM-IVAC	Cyclophosphamide Vincristine Liposomal doxorubicin (Doxil) Cytarabine/high-dose Ara-C (Cytosar-U, Tarabine PFS) Methotrexate (Mexate and others) Ifosfamide (Ifex) Etoposide/VP16 (VePesid, Toposar, Etopophos)
CVP (COP)	Cyclophosphamide Vincristine Prednisone
DHAP	Dexamethasone (Decadron and others) Cytarabine/high-dose Ara-C Cisplatin (Platinol, Platinol-AQ)

Table 6.1. Common Chemotherapy Regimens For NHL (*continued*)

Drug or Regimen Abbreviation	Generic Name of Drugs (Brand Name)
DICE	Dexamethasone Ifosfamide Cisplatin Etoposide/VP16
EPOCH	Etoposide/VP16 Prednisone Vincristine Cyclophosphamide Doxorubicin/hydroxydaunorubicin
ESHAP	Etoposide/VP16 Methylprednisolone (Medrol and others) Cytarabine/high-dose Ara-C Cisplatin
FC	Fludarabine (Fludara) Cyclophosphamide
FND	Fludarabine Mitoxantrone (Novantrone) Dexamethasone
GDP	Gemcitabine (Gemzar) Dexamethasone Cisplatin
GemOX	Gemcitabine Oxaliplatin (Eloxatin)
HD MTX and HD Ara-C	High-dose methotrexate Cytarabine/high-dose Ara-C
HyperCVAD/MTX-Ara-C	Cyclophosphamide Vincristine Doxorubicin/hydroxydaunorubicin Dexamethasone Methotrexate Cytarabine/high-dose Ara-C

Table 6.1. Common Chemotherapy Regimens For NHL (continued)

Drug or Regimen Abbreviation	Generic Name of Drugs (Brand Name)
ICE	Ifosfamide Carboplatin (Paraplatin) Etoposide/VP16
MINE	Mesna (Mesnex) Ifosfamide Mitoxantrone Etoposide/VP16
P	Pralatrexate (Folotyn)
SMILE	Methotrexate Leucovorin Ifosfamide Mesna Dexamethasone Etoposide/VP16 Pegaspargase (Oncaspar)

How Is Chemotherapy Given?

Depending on the drug, chemotherapy can be administered *orally* (as a pill or capsule that is swallowed), *subcutaneously* (as an injection just below the skin), *intramuscularly* (as an injection into a muscle), *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 NHL chemotherapy drugs are given by IV. One reason for this is that IVs provide flexibility in dosing, allowing the medication to be given all at once or slowly over many hours or days. Another reason is that many chemotherapy drugs cannot be given orally, either because they cannot be easily absorbed from the stomach into the bloodstream, or because they are too harsh for the stomach lining to tolerate.

To administer IV chemotherapy, a doctor, nurse, or physician assistant will insert an IV catheter, which is a small flexible tube used to deliver medications. 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 chemotherapy over time. Several commonly used types of catheters are described in Table 6.2. Patients and caregivers should discuss with their doctor which catheter, if any, would be best for their particular situation.

Table 6.2. Catheters Used to Administer Chemotherapy

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

Table 6.2. Catheters Used to Administer Chemotherapy

(continued)

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 and attached to a small reservoir (port) that lies under the skin. Nothing is visible on the outside except for a bump on the chest.	Patients do not have to do anything to care for it; a nurse keeps the line open by “flushing” it once a month with a small amount of injected liquid.	Requires surgery to be inserted. Patient must be injected through the skin covering the port with a special needle each time it is used. Can be hard to use to draw blood samples because blood clots often cause clogging. Requires another minor surgical procedure to be removed.

What 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.

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.

Currently used FDA-approved immunotherapies for NHL can be subdivided into five types: monoclonal antibodies, antibody-drug conjugates, radioimmunotherapy, immunomodulatory drugs, and chimeric antigen receptor (CAR) T-cell therapy. For more information, read the sections below about individual treatments and see the *Immunotherapy and Lymphoma* and the *CAR T-cell Therapy for Lymphoma* fact sheets on LRF's website at lymphoma.org/publications.

What Are Monoclonal Antibodies?

Plasma cells are specialized white blood cells 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* (identifying molecule on the surface of certain cells).

Monoclonal antibodies are molecules that have been engineered in a laboratory to behave differently than antibodies found naturally in our bodies. Monoclonal antibodies are specifically designed to recognize and stick to a particular antigen (or protein) on the surface of certain cancer cells. Once injected in the patient, the monoclonal antibodies travel through the blood and attach themselves to the cells that have the antigen they recognize. This can either stop or slow down the growth of the cancer cell, or it can trigger an “alarm” that makes it easier for other cells in the immune system to recognize and destroy the cancer cell.

Before beginning monoclonal antibody therapy, all patients are tested for active hepatitis infection. In addition, to avoid life-threatening infections, patients being treated with monoclonal antibodies should not be vaccinated with live attenuated virus vaccines, such as those for shingles (herpes zoster), yellow fever, and polio (Sabin vaccine), because the monoclonal antibodies can potentially reactivate these viruses.

The monoclonal antibody therapies used in NHL treatment are given to patients as IV infusions or subcutaneously at a doctor's office or clinic. To prevent serious allergic reactions to the infusion/injection, patients are given an oral antihistamine such as diphenhydramine (Benadryl), acetaminophen (Tylenol), and sometimes steroids before the antibody infusion/injection.

Three monoclonal antibodies are used in the treatment of NHL: rituximab (Rituxan), obinutuzumab (Gazyva), and ofatumumab (Arzerra). All of these treatments are directed against CD20, an antigen that is almost universally present on the surface of B cells.

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

Rituximab 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 2018, rituximab is approved by the FDA for treatment of 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 or partial remission, as single-agent maintenance therapy
- Nonprogressing low-grade CD20-positive B-cell NHL as a single agent after first-line CVP chemotherapy
- *Relapsed* (returns after treatment) or *refractory* (does not respond to treatment) low-grade or follicular CD20-positive B-cell NHL as a single agent

- Previously untreated CD20-positive diffuse large B-cell lymphoma (DLBCL) in combination with CHOP or other anthracycline-based chemotherapy regimens
- Previously untreated or treated chronic lymphocytic leukemia (CLL) in combination with FC 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.

A subcutaneous form of rituximab (Rituxan Hycela or “rituximab and hyaluronidase human”) was approved by the FDA in 2017 for use in patients with previously untreated DLBCL, and those with previously untreated and relapsed or refractory follicular lymphoma or CLL. Before patients can receive rituximab and hyaluronidase human (Rituxan Hycela), they must first have at least one full dose of IV rituximab. Dosing of subcutaneous rituximab varies depending on the type of lymphoma being treated.

Obinutuzumab (Gazyva)

In 2013, obinutuzumab was approved by the FDA for the treatment of CLL. As of 2018, obinutuzumab is approved by the FDA for use in the following situations:

- In combination with chlorambucil (Leukeran) for the treatment of patients with previously untreated CLL
- In combination with bendamustine (Treanda, Bendeka) followed by obinutuzumab monotherapy for the treatment of patients with follicular lymphoma that has relapsed after, or is refractory to, a regimen containing rituximab (Rituxan)
- In combination with chemotherapy followed by obinutuzumab 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 follicular lymphoma

Obinutuzumab is also being investigated in other types of NHL.

Obinutuzumab treatment is given as an IV infusion in six 28-day treatment cycles. In patients with CLL, the first dose is given over two days to reduce the risk of a reaction to the infusion of the drug.

Ofatumumab (Arzerra)

In 2009, ofatumumab was approved by the FDA for the treatment of patients with CLL. As of 2017, ofatumumab is approved by the FDA in the following CLL settings:

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

Ofatumumab is given as an IV infusion once weekly over a number of weeks. It may be administered by itself, in combination with chlorambucil (Leukeran), or in combination with fludarabine (Fludara) and cyclophosphamide (Cytoxan, Neosar).

What Are Antibody-Drug Conjugates?

An antibody-drug conjugate is a chemotherapy drug attached to a monoclonal antibody. The only antibody-drug conjugate that is approved for use in NHL is brentuximab vedotin (Adcetris).

Brentuximab Vedotin (Adcetris)

Brentuximab vedotin is a combination of a small toxic drug 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). The MMAE is then released, where it attacks the cellular machinery and causes the cell to stop multiplying and die.

Brentuximab vedotin is approved by the FDA for the treatment of patients with systemic anaplastic large cell lymphoma (sALCL) after failure of at least one previous combination chemotherapy regimen and for patients with primary cutaneous ALCL or CD30-expressing mycosis fungoides who have received prior systemic therapy. It is also approved for use in classical Hodgkin lymphoma. Brentuximab vedotin is given as an IV infusion once every three weeks.

What is 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. An additional benefit of this approach is that the radiation destroys nearby cells in addition to those that have the antigen, giving RIT a “cross-fire” effect. 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 (Y^{90}), and tiuxetan, a molecule that links them together. The ibritumomab component of the drug binds to CD20-positive NHL B cells. Once bound, the radioactive emissions from the Y^{90} damage the cell, triggering its destruction.

^{90}Y ibritumomab tiuxetan was first approved by the FDA in 2002. As of 2017, this agent is approved 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. For more information on radioimmunotherapy, view the *Radioimmunotherapy* fact sheet on LRF's website at lymphoma.org/publications.

What Are Immunomodulatory Drugs?

Immunomodulatory drugs (IMiDs) have many ways of working against tumor cells. They cause tumor cells to die, help keep tumors from getting nutrients from the blood, and stimulate the immune system to encourage the destruction of cancer cells. Only one immunomodulatory drug, lenalidomide (Revlimid), is FDA approved to treat NHL.

Lenalidomide (Revlimid)

Lenalidomide is an IMiD that inhibits the growth and induces the death of some types of malignant blood cells, including mantle cell lymphoma (MCL) cells. For this reason, lenalidomide is FDA approved for the treatment of patients with MCL whose disease has relapsed or progressed after two prior therapies, one of which included bortezomib (Velcade).

Lenalidomide comes as an oral tablet. It is given once a day for three weeks of a four-week cycle. The most common side effects in patients with MCL include low blood cell counts, fatigue, diarrhea, anemia, nausea, cough, fever, rash, shortness of breath, severe itching, constipation, and swollen extremities.

What is CAR T-Cell Therapy?

Chimeric antigen receptor (CAR) T-cell therapy is a type of personalized immunotherapy in which a patient's T cells are enhanced by the addition of an engineered gene. First, the patient's blood is collected, and after the T cells are separated out, the rest of the blood is returned to the patient. The T cells are genetically modified to produce special receptors on their surface called chimeric antigen receptors (CARs), which allow them to recognize and kill malignant cells. While 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. Finally, the patient receives the CAR T-cell therapy via IV infusion. Once in the body, the CAR T cells directly attack the cancer cells. In 2017, the first CAR T-cell therapy, axicabtagene ciloleucel (Yescarta), was approved by the FDA to treat diffuse large B-cell lymphoma (DLBCL), and a second CAR T-cell therapy, tisagenlecleucel (Kymriah), was approved in May 2018 to treat DLBCL. Several other CAR T-cell therapies are being studied.

Axicabtagene Ciloleucel (Yescarta)

Axicabtagene ciloleucel is a CAR T-cell therapy directed to the CD19 antigen which is present on some lymphoma cells. It was approved by the FDA in October 2017 for the treatment of *relapsed* (returns after treatment) or *refractory* (does not respond to treatment) large B-cell lymphoma after two or more lines of *systemic* (throughout the body) therapy, including DLBCL, not otherwise specified; primary mediastinal large B-cell lymphoma; high-grade B-cell lymphoma; and DLBCL arising from follicular lymphoma.

Tisagenlecleucel (Kymriah)

The CAR T-cell therapy tisagenlecleucel is also directed against CD19. It was approved by the FDA in May 2018 for the treatment of relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy including DLBCL, not otherwise specified; high-grade B-cell lymphoma; and DLBCL arising from follicular lymphoma.

For additional information about the CAR T-cell therapy process, please view the *CAR T-cell Therapy for Lymphoma* fact sheet on LRF's website at lymphoma.org/publications.

Many of the common side effects of CAR T-cell therapy are similar to those experienced by patients taking other lymphoma therapies, such as fatigue, decreased appetite, chills, diarrhea, *febrile neutropenia* (low neutrophils [a type of white blood cell] along with fever), infection, nausea, cough, vomiting, and constipation. Patients may also experience *neurological* effects. These symptoms usually occur 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. *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 August 2017 for the treatment of CAR T-cell–induced severe cytokine release syndrome. Patients should talk with their doctor about watching for certain symptoms and side effects.

What Are Targeted Therapies?

A better understanding of the biology and genetics of NHL is helping researchers identify specific molecules in lymphoma cells that may be good targets for new drugs. Most of these recently discovered molecules help control the growth and survival of lymphoma cells. The drugs that target these molecules are broadly called *targeted therapies*. These drugs may kill the cells or slow down or stop their growth. Targeted therapies attack lymphoma cells in a more specific way than chemotherapy drugs.

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

- The histone deacetylase (HDAC) inhibitors belinostat (Beleodaq), romidepsin (Istodax), and vorinostat (Zolinza)
- The proteasome inhibitor bortezomib (Velcade)

- The PI3K inhibitors copanlisib (Aliqopa) and idelalisib (Zydelig)
- The BTK inhibitors acalabrutinib (Calquence) and ibrutinib (Imbruvica)
- The Bcl2 inhibitor venetoclax (Venclexta)

Belinostat (Beleodaq)

Belinostat belongs to a class of drugs called HDAC inhibitors, which influence which genes are active in cancer cells. Belinostat was approved by the FDA in 2014 to treat patients with relapsed or refractory peripheral T-cell lymphoma (PTCL). It is given as an IV infusion on the first five days of a 21-day treatment cycle. The most common side effects are nausea, fatigue, fever, anemia, and vomiting.

Romidepsin (Istodax)

Like belinostat, romidepsin is an HDAC inhibitor. It is approved for the treatment of patients with PTCL who have received at least one prior therapy and for patients with cutaneous T-cell lymphoma (CTCL) who have received at least one prior *systemic* (throughout the body) treatment. Romidepsin is given as an IV injection once a week for the first three weeks of a four-week treatment cycle. The most common side effects are low white blood cell counts, increased infections, bruising or bleeding easily, nausea, fatigue, vomiting, loss of appetite, and changes in heart function.

Vorinostat (Zolinza)

Vorinostat 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 returned after two systemic therapies. Vorinostat is given as a tablet once daily with food. The most common side effects are diarrhea, fatigue, nausea, bruising or bleeding easily, lack of appetite, and a change in the way foods taste.

Bortezomib (Velcade)

Bortezomib 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 is FDA approved for the treatment of mantle cell lymphoma (MCL). It is given by IV twice weekly for two weeks, followed by a 10-day rest period, every three weeks. The most commonly reported side effects of bortezomib include nausea, diarrhea, low blood cell counts, *thrombocytopenia* (low platelets), *neutropenia* (low neutrophils [a type of white blood cell]), *peripheral neuropathy* (numbness and pain in the hands and feet), fatigue, *neuralgia* (a type of nerve pain), anemia, *leukopenia* (low leukocytes [a type of white blood cell]), constipation, vomiting, *lymphopenia* (low lymphocytes [a type of white blood cell]), rash, fever, and *anorexia* (loss of appetite).

Copanlisib (Aliqopa)

Copanlisib is an intravenous (IV) therapy that targets phosphatidylinositol-3-kinase (PI3K)-alpha and PI3K-delta.

Copanlisib was approved in 2017 by the FDA for the treatment of adult patients with follicular lymphoma (FL) who have received at least two prior systemic therapies. It is given once weekly for three weeks, followed by one week off; these four-week cycles are then repeated. The most common side effects are hyperglycemia, hypertension, diarrhea, decreased general strength and energy, *leukopenia* (low leukocytes [a type of white blood cell]), *neutropenia* (low neutrophils [a type of white blood cell]), nausea, lower respiratory tract infection, and *thrombocytopenia* (low platelets).

Idelalisib (Zydelig)

Idelalisib inhibits the signaling protein (PI3K)-delta, blocking the growth and inducing the death of cancerous B cells in some types of NHL. It was first approved by the FDA in 2014, and as of 2017 it is indicated in the following NHL settings:

- In combination with rituximab (Rituxan) for the treatment of patients

with relapsed CLL for whom rituximab alone would be appropriate (because they have received many previous treatments or cannot tolerate chemotherapy)

- For the treatment of patients with relapsed follicular B-cell NHL who have received at least two prior systemic therapies
- For the treatment of patients with relapsed small lymphocytic lymphoma (SLL) who have received at least two prior systemic therapies

Idelalisib may only be used in patients who have received other treatments for NHL; it is not intended to be used as frontline therapy. Idelalisib comes as an oral therapy (pill) that is taken twice daily and must be swallowed whole. Its most commonly reported side effects include diarrhea, liver toxicity, fever, fatigue, nausea, cough, pneumonia, abdominal pain, chills, and rash.

Acalabrutinib (Calquence)

Acalabrutinib inhibits the BTK signaling protein to block the growth and survival of the cancerous B cells in some types of NHL. Acalabrutinib was approved by the FDA in October 2017 for the treatment of adult patients with mantle cell lymphoma (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. The most commonly reported side effects include anemia, *thrombocytopenia* (low platelets), headache, *neutropenia* (low neutrophils [a type of white blood cell]), diarrhea, fatigue, *myalgia* (muscle pain), and bruising.

Ibrutinib (Imbruvica)

Ibrutinib inhibits the signaling protein Bruton tyrosine kinase (BTK) to block the growth and survival of the cancerous B cells in some types of NHL. Ibrutinib was first approved by the FDA in 2013, and as of August 2018, it can be used in the treatment of:

- Patients with mantle cell lymphoma (MCL) who have received at least one prior therapy

- Patients with CLL/SLL with or without 17p deletion
- Patients with Waldenström macroglobulinemia
- Patients with marginal zone lymphoma (MZL) who require systemic therapy and have received at least one prior anti-CD20-based monoclonal antibody therapy
- Patients with chronic graft-versus-host disease (cGVHD) after failure of one or more lines of systemic therapy

Ibrutinib comes in capsules and tablets that must be swallowed whole. It is given once daily. The most commonly reported side effects include *thrombocytopenia* (low platelets), *neutropenia* (low neutrophils [a type of white blood cell]), low blood cell counts, diarrhea, anemia, fatigue, musculoskeletal pain, bruising, nausea, upper respiratory infection, atrial fibrillation, and rash. Due to a risk of bleeding, patients should stop taking ibrutinib three days prior to minor surgery and seven days before major surgery, depending on the type of surgery.

Venetoclax (Venclexta)

Venetoclax targets Bcl2, a protein that plays a major role in cell survival. By inhibiting the activity of Bcl2, venetoclax induces its target cells to die. This agent is approved by the FDA for the treatment of patients with CLL/SLL, with or without a chromosome 17p deletion, who have received at least one prior therapy. Venetoclax comes as an oral tablet given daily. Common side effects include *neutropenia* (low neutrophils [a type of white blood cell]), low blood cell counts, diarrhea, nausea, anemia, upper respiratory tract infection, *thrombocytopenia* (low platelets), and fatigue. Tumor lysis syndrome (TLS) has also been observed in patients receiving venetoclax (see discussion about TLS on page 114).

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 help prevent the lymphoma from returning.

Maintenance therapy typically consists of drugs given at lower doses and longer intervals than those used during initial therapy. Depending on the type of NHL and the drugs used, maintenance therapy may last for weeks, months, or even years. Rituximab (Rituxan, Rituxan Hycela) may be used as maintenance therapy for CD20-positive B-cell NHLs following a good initial response to the drug in patients with high-risk indolent lymphomas, and obinutuzumab (Gazyva) may be used as maintenance therapy following initial treatment with bendamustine (Treanda, Bendeka). Patients may want to use the questions listed below to ask their doctors about maintenance therapy.

For more information, 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?
- What are the benefits and risks?
- 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?
- Will this improve my chances of survival?

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; however, certain drugs can also deliver radioactive molecules directly to tumor cells (see the section “What is Radioimmunotherapy?” on page 78).

A radiation oncologist is in charge of 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 the extent of disease.

To prepare for radiation therapy, the healthcare team marks the patient’s body with *tattoos* (tiny ink dots) to make sure that only the targeted areas receive radiation. On the day of treatment, lead shields 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 the radiation treatment, patients need to carefully protect the radiation site from exposure to sunlight — it is really important to not become sunburned.

Some of the more common types of radiation therapy and delivery methods used for NHL are shown in Table 6.3.

Table 6.3. Methods for Delivering Radiation Therapy

Image-Guided Radiation Therapy (IGRT)/Tomotherapy	<ul style="list-style-type: none"> ■ Repeated imaging scans (such as computed tomography [CT], magnetic resonance imaging [MRI], or positron emission tomography [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, sparing 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 (TSEBT)	<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. ■ Treatment used for patients with cutaneous T-cell lymphoma (CTCL), a type of lymphoma that occurs on the outermost layers of the skin.
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 re-infused back into the patient. ■ This form of therapy has been approved by the FDA for the treatment of CTCL. It may also be effective in the treatment of graft-versus-host disease (GVHD), a common complication following <i>allogeneic</i> (donor) stem cell transplantation.

Patients may wish to use the questions below to ask their doctors about what to expect during and after radiation therapy.

PATIENT TIP

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 and pain medications to maximize relief.

What Is Stem Cell Transplantation?

There are three types of stem cell transplantation that differ based on the source of the stem cells. In an *autologous stem cell transplant*, the patient is his or her own donor. 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 an identical twin.

The primary purpose of stem cell transplantation is to allow patients to receive higher doses of chemotherapy than their bodies could normally withstand. Such high doses of chemotherapy can kill cancer cells effectively, but they can also severely damage or destroy the stem cells that the body uses to create new blood cells. Stem cell transplantation replaces the supply of stem cells killed by the high-dose chemotherapy, allowing the body to recover from such an intense treatment.

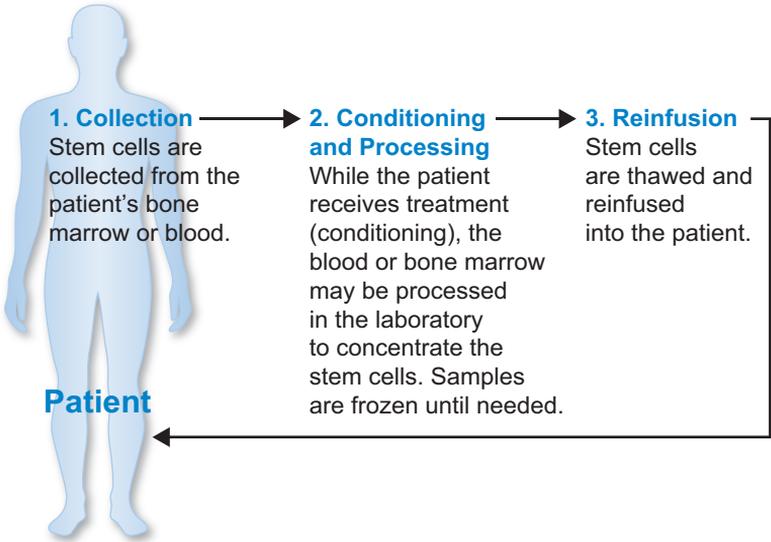
Allogeneic transplantation has a second benefit. Because the transplanted cells come from a donor instead of the patient, the donated cells recognize the patient's lymphoma cells as foreign and attack them, resulting in an immunologic response called the *graft-versus-lymphoma* (GVL) effect. For this reason, allogeneic transplantation generally controls lymphoma better than autologous transplantation. An additional benefit is that the donated cells are not contaminated with the original disease because they come from a different individual. 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 *graft-versus-host disease* (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 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 seen 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 responses to previous therapy. For more information on stem cell transplants, view the *Understanding Stem Cell Transplantation* publication on the Lymphoma Research Foundation's (LRF's) website at lymphoma.org/publications.

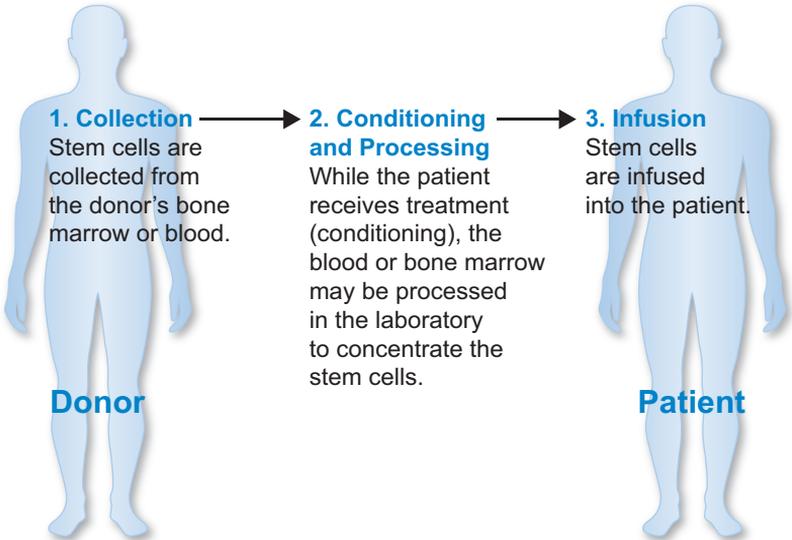
AUTOLOGOUS STEM CELL COLLECTION

A patient's own stem cells



ALLOGENEIC STEM CELL COLLECTION

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



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 Transplantation

- 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 and benefits associated with this procedure?
- What complications may arise as a result of having a transplant?
- 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?
- How do I identify a hospital or transplant center for the transplant?
- How long will I need to be in the hospital?
- How long will I need someone to care for me after the transplant?
- Will my insurance cover this procedure?
- How sick will this treatment make me?
- How will we know if the treatment is working?
- What treatments will be available to me after transplant?
- How and for how long will the treatment affect my normal activities (work, school, childcare, driving, sexual activity, and exercise)?
- What is my chance of making a full recovery?

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

Doctors who treat patients with lymphoma use certain terms to describe a patient's treatment and the anticipated outcomes. Some of these are defined in Table 6.4.

Table 6.4. Terms Used to Describe Treatment and Its Outcomes

Cure	This word is cautiously used 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 the 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. If complete remission is maintained for a long period, it is called a <i>durable remission</i> .
Partial Remission (PR)	This term is used if the 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.
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 NHL 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.

What Is Relapsed or Refractory NHL?

Relapsed NHL means that the disease has returned after responding to treatment, which is sometimes also called a *recurrence*. *Refractory* NHL means that the patient's disease does not respond to a specific treatment or that the response to treatment does not last very long. There are many treatment options for patients with relapsed or refractory NHL. Exactly what type of treatment is optimal 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 already discussed 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.

Patients who do not go into complete remission (CR) following treatment or who do not respond to treatment should not lose hope. Lasting responses to therapy may be achieved after a diagnosis of relapsed or refractory disease. Many patients seek second opinions at any point from diagnosis onward, and 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 most recently approved by the FDA and those being investigated in clinical trials are used specifically for these patients. Lymphoma research continually evolves as doctors and scientists discover new therapies and more effective ways of giving existing treatments. Chapter 11 describes some of the options currently under investigation.

When Should a Clinical Trial Be Considered?

Clinical trials are appropriate for patients to consider at all stages of disease, whether newly diagnosed or at the time of relapse (see the section “Overview of Clinical Trials” on page 140). The purpose of a clinical trial is to safely monitor the effects of a new drug or new combination of drugs on patients over time and to identify more effective therapies for specific diseases. Some trials randomly assign patients to one of two or more treatment arms, each of which receives a different treatment. By participating in a randomized clinical trial, patients may or may not get access to the newest therapies, but at a minimum, they will receive quality standard care in a very carefully controlled and supportive environment.

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

What Are Alternative and Complementary Therapies?

Alternative therapy refers to any treatment used instead of a standard therapy. Alternative therapies are not recognized as effective by the medical profession. **Currently, there are no proven alternative therapies to conventional cancer care for patients with NHL. 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. **Patients and caregivers should talk to the doctor and healthcare team before starting any form of complementary therapy, because a few of these approaches may make their lymphoma treatment less effective.**

Table 6.5 outlines some forms of complementary therapy for cancer, also known as integrative medicine or integrative oncology.

Table 6.5. Forms of Complementary Therapy

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

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

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

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

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

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

Chapter 7: Common Treatment Side Effects

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

Why Does Chemotherapy Cause Side Effects or Toxicities?

Chemotherapy drugs cause side effects because of the nonspecific way these drugs attack lymphoma cells. Most chemotherapy drugs work by killing cells that grow and multiply more quickly 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, and bone marrow, so those cells may also be damaged or killed by chemotherapy. Some chemotherapy drugs can also damage cells in the heart, lungs, or other organs and tissues.

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

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, menopausal symptoms, and neuropathy are examples of long-term effects. In contrast, *late effects* of treatment appear only after treatment has ended—sometimes months, years, or even decades after treatment is completed. Infertility, osteoporosis, heart problems, and secondary cancers are examples of late effects.

What Side Effects Are Caused by Chemotherapy?

The chemotherapy regimens used to treat patients with NHL may cause a number of side effects. Some of these side effects are very common and happen to many or most patients, while others affect a smaller number of patients. Here is an alphabetical list of possible side effects.

- Changes in taste
- Cognitive problems (trouble concentrating, impaired memory; sometimes called “chemo brain”)
- Decreased blood cell production (decreased hemoglobin, white blood cells, neutrophils, or platelets)
- Diarrhea or constipation
- Fatigue
- Hair loss
- Heart damage (cardiotoxicity)
- Increased risk of infections
- Loss of appetite
- Lung toxicity
- Mouth sores
- Nausea or vomiting
- *Peripheral neuropathy* (numbness or tingling in hands and feet)
- Problems with sexual function
- Sterility
- *Tumor lysis syndrome* (a reaction to toxins released by dying cancer cells)

Changes in Taste

Some patients receiving chemotherapy 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. Some patients refer to these side effects as “chemo brain.” Although these side effects can be stressful, they typically disappear over time.

Decreased Blood Cell Production

The bone marrow constantly produces red blood cells, white blood cells, and platelets. Several types of therapies for NHL temporarily interfere with the ability of the bone marrow to produce enough of one or more of these different types of blood cells. This is called *myelosuppression*.

To prevent and monitor myelosuppression, samples of a patient’s blood are tested with a complete blood count (CBC) with differential, which measures the numbers of red blood cells and platelets, as well as all the different subtypes of white blood cells. These tests are usually done before and sometimes during the treatment process. Table 7.1 on the next two pages describes five of the most common conditions involving a decrease in blood cell production.

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

Anemia	<ul style="list-style-type: none"> ■ <i>Anemia</i> is caused by a decrease in the number of red blood cells. ■ 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 can be used to treat severe anemia.
Leukopenia	<ul style="list-style-type: none"> ■ <i>Leukopenia</i> refers to a decrease in the number of leukocytes, or white blood cells. Leukocytes include lymphocytes (B cells and T cells), neutrophils, basophils, eosinophils, and monocytes. ■ Patients with low levels of neutrophils are at increased risk of infections.
Lymphopenia	<ul style="list-style-type: none"> ■ <i>Lymphopenia</i>, also called lymphocytopenia, refers to a decrease in the number of lymphocytes. Lymphocytes produce antibodies and fight bacterial and viral infections. About 20 to 40 percent of white blood cells are lymphocytes. ■ Patients with low levels of lymphocytes are at increased risk of infections.

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

Neutropenia	<ul style="list-style-type: none">■ <i>Neutropenia</i> refers to a decrease in neutrophils, the primary type of white blood cells that fight bacterial infections.■ Patients with low neutrophil counts are at higher risk of serious and even life-threatening infections. Symptoms of infection include fever, chills, and night sweats.■ During chemotherapy doctors regularly monitor the patient's <i>absolute neutrophil count</i> (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 with neutropenia 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 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, so patients taking these drugs might think they are having a heart attack.■ 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).
Thrombocytopenia	<ul style="list-style-type: none">■ <i>Thrombocytopenia</i> refers to a decrease in the number of platelets in the blood. Platelets help start the clotting process when bleeding occurs.■ Patients with low platelet counts may bruise easily; have cuts that bleed more or longer than usual; have nosebleeds or bleeding gums; or bleed from places that have not been injured.■ A platelet transfusion or certain medications may be needed if thrombocytopenia is severe or if the patient develops bleeding.

Diarrhea

Some types of chemotherapy may cause diarrhea. While most patients do not experience severe diarrhea, the most important thing to remember is to stay hydrated. Signs of dehydration include dry mouth or skin, decreased urine, or feeling dizzy or lightheaded after standing up. The doctor should be contacted if the patient has bloody diarrhea or fever with diarrhea. 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).
- 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 NHL. 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 information to plan your activities for the times when you have the most energy.
- Ask for help with housework and other daily activities that are tiring.
- Exercise if your doctor says it is okay to do so, but do not overdo it. Try simple stretching and range-of-motion exercises or a short walk; these activities may energize you without tiring you out. Start slowly and build up to the level that is right for you. Ask your doctor, nurse, or physical therapist to help you create a personalized exercise plan.
- Rest and sleep during therapy are very important, but too much rest may actually decrease your energy levels. An afternoon nap helps some patients feel less tired for the rest of the day, but other patients cannot sleep at night if they nap during the day. If you have trouble sleeping, talk to your healthcare team to find out what you can do to get more rest.
- Be patient. These symptoms usually improve once treatment is completed.

Hair Loss

Certain chemotherapy 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 symptoms of *rhinorrhea* (runny nose). Loss of eyelashes may make eyes more irritated and dry.

While nothing can prevent chemotherapy-induced hair loss altogether, patients may follow the tips below for minimizing and managing chemotherapy-induced 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.

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 NHL treated with potentially cardiotoxic chemotherapy receive these drugs at dosages that are not likely to cause cardiotoxicity. In addition, many patients with diffuse large B-cell lymphoma (DLBCL) are only treated with anthracycline-based chemotherapy during the initial round of treatment. However, because the anthracycline class of drugs can damage the heart, those patients who *relapse* (disease returns after treatment) will usually not receive anthracycline drugs as part of their secondline 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 lifestyle choices (such as smoking and lack of exercise), may increase the chance of developing chemotherapy-related or radiation-related cardiotoxicity.

Careful monitoring by the healthcare team can reduce the chances of patients developing cardiotoxicity. Before deciding to treat patients with a cardiotoxic drug, most doctors order either an echocardiogram (ECHO) or a multigated acquisition (MUGA) scan to measure the patient's cardiac function. These tests ensure that patients are prescribed a safe chemotherapy dosage given their current heart function. Patients with underlying conditions that put them at high risk of cardiotoxicity may also have their heart function monitored more intensively during the course of treatment for NHL. In some instances, agents other than anthracyclines may be chosen for treatment. See Chapter 4 for more information about tests used to evaluate heart function.

Infections

Some NHL treatments can lower a patient's ability to fight infections. Patients with a fever of 100.5°F or greater should call the doctor. Chills or a chilly sensation often precede fever. Patients should ask their provider what to do if they have a sore throat, rash, diarrhea, cough, or redness, swelling, or pain around a wound. The doctor should 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 (caused by herpes zoster, the virus that causes chicken pox). Sometimes, doctors may prescribe medication to prevent shingles from developing during therapy. Other ways to reduce the risk of infections are included below.

PATIENT TIP

Reducing Your Risk of Serious Infection 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).
- Make sure all foods are thoroughly washed and/or cooked; avoid raw foods that may carry germs.
- Do not sleep with pets.

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 medication or by changing eating habits, such as eating several small meals each day and making nutritious food choices. Patients may wish to visit a nutritionist for additional tips. For more information on nutrition, please view the *Nutrition* fact sheet on LRF's website at lymphoma.org/publications.

Mouth Sores

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

The doctor should be informed if a patient develops a sore throat. The doctor may examine the patient's throat and take a swab that is sent to the 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 chemotherapy. Other tips for preventing and caring for mouth sores caused by NHL treatment are listed on the following page.

Preventing and Caring for Mouth Sores

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

Nausea or Vomiting

Some chemotherapy drugs and targeted therapies 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 may prescribe an *antiemetic* (a drug that prevents nausea and vomiting) before chemotherapy. Examples of antiemetics include aprepitant (Emend), ondansetron (Zofran, Zuplenz), granisetron (Kytril and others), metoclopramide (Reglan and others), prochlorperazine (Compazine, Procomp, Compro), dolasetron (Anzemet), and a variety of corticosteroids such as prednisone and dexamethasone. In most cases, these antiemetics are able to partially or completely prevent nausea and vomiting. Tips for controlling or minimizing nausea and vomiting are listed below.

PATIENT TIP

Controlling or Minimizing Nausea and Vomiting

- Before chemotherapy, drink a liquid diet consisting of broth, gelatin, ice pops, and tea. Do not drink milk or have a meal in which the main ingredients are dairy products.
- Do not eat foods that are too hot or too cold, greasy or fatty, or sweet or spicy.
- Eat smaller, more frequent meals instead of fewer, large meals each day.
- Avoid strong or offensive smells. Get plenty of fresh air.
- Take prescribed antiemetics before chemotherapy to prevent nausea.
- If you vomit, make sure to avoid becoming dehydrated (see tips on page 104).
- Finding the best approach is often a process of trial and error. Try different approaches to determine what works best for you.

Peripheral Neuropathy

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

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

Although no medications have been specifically approved by the U.S. Food and Drug Administration (FDA) to treat chemotherapy-induced peripheral neuropathy, there are several different classes of drugs that doctors may prescribe to help alleviate patients' symptoms. These include antiepileptic agents such as pregabalin (Lyrica) and gabapentin (Neurontin, Gralise, Horizant); local anesthetics such as lidocaine patches; opioid pain relievers; and antidepressants that also target pain such as duloxetine (Cymbalta) and amitriptyline (Elavil). Complementary therapy techniques such as acupuncture and massage may also help with neuropathy symptoms (see Table 6.5). Finally, patients should avoid tight-fitting shoes or clothes and exposure to cold, as these may exacerbate neuropathy symptoms in the hands and feet.

Problems With Sexual Function

Psychological factors such as fear about illness, altered body image due to hair loss and depression, combined with physical side effects of treatment on the body and the brain, often cause a drop in sex

drive (*libido*). 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

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

Despite these risks, it is still possible for female patients with NHL to become pregnant and for male patients with NHL to father children during and after cancer treatment. Because chemotherapy and radiation 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 the completion of therapy. The exact duration of this precaution depends in part on the treatment regimen administered. Patients should discuss fertility concerns and pregnancy prevention with their doctor and, if needed, with a fertility specialist.

Tumor Lysis Syndrome (TLS)

Patients who have large, rapidly growing, or multiple tumors may experience *tumor lysis syndrome* (TLS) during treatment for NHL. This condition occurs when an antilymphoma drug triggers the quick death of a large number of lymphoma cells, causing the cells to release toxic substances into the blood that can damage the kidneys and other organs. Specific chemotherapy agents used to treat NHL that may cause TLS include bendamustine (Treanda, Bendeka), cyclophosphamide (Cytoxan, Neosar), doxorubicin (Adriamycin), and fludarabine (Fludara). If not promptly treated, TLS may lead to kidney failure or damage to the heart and nervous system.

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

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).

Can the Chemotherapy Treatment Schedule Be Changed to Reduce Side Effects?

Some treatment-related side effects are unpleasant but tolerable. Other side effects may be more serious, but they can often be anticipated and prevented. Occasionally, side effects may be severe enough that doctors may reduce the dose of chemotherapy or delay one or more treatment cycles until the side effects improve. However, it is important that chemotherapy treatment schedules be maintained to the greatest extent possible, because changing the regimen to reduce short-term side effects can be harmful in the long run. A full course of chemotherapy given on time works best for the treatment of NHL. Research has shown that reducing the dose or delaying chemotherapy cycles can reduce the chance of complete remission and long-term survival for patients with certain types of lymphomas. Patients and their doctors should work together to anticipate and manage short-term side effects, in order to maximize the chances that patients can complete the entire chemotherapy regimen exactly as prescribed.

What Side Effects Are Caused by Steroids?

Corticosteroids (often simply called “steroids”) are commonly given along with chemotherapy. This type of steroid is not the same as androgens and anabolic steroids that can be used to enhance athletic performance. Steroids can serve several purposes in NHL treatment, including helping to treat the lymphoma, reducing inflammation, relieving nausea, and stimulating appetite. However, dexamethasone, prednisone, and other corticosteroid drugs can cause side effects such as *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.

Mood and personality changes from steroids can range from mild to severe. Common reactions include irritability, anger, and depression. Patients should alert their family members and friends that these personality changes may occur during their treatment so that they can watch for changes in the patient's behavior. 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 Monoclonal Antibodies?

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

Infusion/Injection Reactions

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

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

Infections

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

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

What Side Effects Are Caused by Antibody-Drug Conjugates?

An antibody-drug conjugate such as brentuximab vedotin (Adcetris) shares many similarities to standard chemotherapy, including similar side effects. The most common side effects reported in patients treated with brentuximab vedotin include a depressed immune system, low blood counts, peripheral neuropathy (usually not until the third or fourth cycle of treatment), fatigue, nausea, upper respiratory tract infection, diarrhea, fever, rash, cough, and vomiting. Pancreatitis, or inflammation of the pancreas, may also occur. Patients may also experience reactions at the site of the treatment infusion. Hair loss and TLS are also possible.

What Side Effects Are Caused by Radioimmunotherapy?

Ibritumomab tiuxetan (Zevalin) is generally well tolerated, without the hair loss and nausea that often accompany chemotherapy. The most common side effect is a temporary decrease in blood cell counts, which usually occurs approximately four weeks after treatment and returns to near-normal levels by eight weeks after receiving treatment. However, these side effects may last up to several months, which can leave patients susceptible to infections.

Reactions at the site of the treatment infusion are also possible, although rare, and can be severe in some patients. Patients may also experience headache, tiredness, light-headedness, stomach pain, nausea, inflammation of the nose and upper throat, weakness, diarrhea, cough, and mild fever and chills, especially after the first dose. Radiation exposure from treatment with ibritumomab may lead to an increased risk of developing a secondary cancer, specifically myelodysplastic syndrome and/or acute myelogenous leukemia, particularly in those who have been heavily pretreated with prior chemotherapy.

What Side Effects Are Caused by Immunomodulatory Drugs?

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

What Side Effects are Caused by CAR T-cell Therapies?

The most commonly reported side effects in patients receiving CAR T-cell therapies are *cytokine release syndrome* (an intense systemic inflammatory response characterized by fever, low blood pressure, fast heart rate, low oxygen in tissues, decreased blood pumped by the heart, kidney damage, liver damage, and blood clotting problems), fatigue, decreased appetite, chills, diarrhea, low white blood cells (along with fever), infection, nausea, cough, vomiting, constipation, irregular heartbeat, and nervous system effects including brain effects or confusion, headache, tremor, and dizziness. In 2017, tocilizumab (Actemra) was approved for the treatment of CAR T-cell–induced severe or life-threatening cytokine release syndrome.

What Side Effects Are Caused by Targeted Therapies?

The most common side effects observed in patients treated with histone deacetylase (HDAC) inhibitors include nausea, fatigue, fever, anemia, vomiting, loss of appetite, changes in heart function, *thrombocytopenia* (low platelets), and a change in the way foods taste. Doctors may monitor the effects of HDAC inhibitor treatment on the liver and/or heart. Patients with rapidly progressing tumors or a large number of tumors who are treated with HDAC inhibitors may also be at risk for TLS.

The most commonly reported side effects for bortezomib (Velcade) include nausea, diarrhea, low blood cell counts, peripheral neuropathy, fatigue, *neuralgia* (nerve pain), constipation, vomiting, rash, fever, and loss of appetite. TLS is also possible.

Patients who receive idelalisib (Zydelig) may experience diarrhea, bleeding, fever, fatigue, nausea, cough, pneumonia, abdominal pain, chills, and rash.

Patients treated with acalabrutinib (Calquence) most frequently experience low blood counts, headache, diarrhea, fatigue, muscle pain, and bruising.

For ibrutinib (Imbruvica), the most common side effects include diarrhea, anemia, fatigue, musculoskeletal pain, low blood cell counts, bruising, nausea, upper respiratory infection, rash, and liver abnormalities; TLS may rarely occur.

Common side effects of venetoclax (Venclexta) include low blood cell counts, diarrhea, nausea, upper respiratory tract infection, and fatigue. TLS may be observed in patients who receive venetoclax.

What Side Effects Are Caused by Radiation Therapy?

Radiation therapy itself is painless, but it can cause short-term and long-term 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.

Some of the short-term side effects caused by radiation therapy used to treat patients with NHL include:

- Dry mouth
- Fatigue
- Loss of appetite and taste
- Nausea
- Skin reactions
- Throat irritation

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 105.

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.

The loss of appetite and taste are usually short-term problems.

Patients should remember to eat healthy diets, because their bodies need energy and good nutrition to maximize healing. Eating four or five small meals a day may be more comfortable than eating two or three larger meals. Patients should ask their healthcare team for information about how to maintain a healthy diet during treatment.

Nausea

Radiation treatment can cause nausea, especially in patients who receive radiation to the abdomen. Not eating (especially sweet, spicy, or fatty foods) a few hours before radiation therapy may help patients avoid nausea. The doctor may also prescribe an *antiemetic* (antinausea) medication to be taken before each radiation therapy session. Patient tips for coping with nausea are included on page 111.

Skin Reactions

Radiation therapy can cause skin changes to the affected area, such as redness, itchiness, dry and peeling skin, sores or ulcers, swelling, and puffiness. 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 (such as heating pads or ice packs).
- 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 sunbathe or 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.

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 104 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, so that the doctor can take a throat swab to test for these infections and prescribe antiviral or antifungal medications if needed.

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

Easing Throat Irritation During Radiation Therapy

PATIENT TIP

- 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) may be appropriate.

Does Radiation Treatment Make the Body Radioactive?

External-beam radiation does not cause a patient's tissues to become radioactive. However, some types of internal radiation techniques that leave radioactive particles in the body may result in low levels of radiation being emitted from the patient. In some cases, the patient remains in the hospital and shielded from others during short exposures to internal radiation therapy. With permanent internal radiation and systemic radiation treatment, patients are sent home emitting low levels of radiation, especially through bodily fluids. In these cases, patients should temporarily avoid contact with pregnant women and young children. The healthcare team can provide more information to patients, family members, and caregivers about special precautions that should be taken. The radioactivity breaks down over time to the point where no radiation can be measured outside the patient's body.

What Long-Term and Late Side Effects Are Caused by Radiation Therapy?

In addition to the short-term side effects caused by radiation therapy, it can cause long-term and late side effects that may not show up for years or even decades after the initial treatments.

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). 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 (a class of drugs used to manage cholesterol) are 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 such factors as the amount of radiation given and the part of the body treated. All of the currently available information about secondary cancer risk comes from studies that were performed in the past, when higher doses of radiation were used and larger areas of the body were treated with radiation. 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 Stem Cell Transplantation?

Patients treated with high doses of chemotherapy and/or radiation before undergoing a 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 100 and the section “What Side Effects Are Caused by Radiation Therapy?” on page 120).

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.

Patients receiving stem cells from a relative or unrelated donor 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. GVHD can affect the digestive system, resulting in symptoms such as diarrhea, abdominal pain, nausea, and vomiting. GVHD can occur at any time after the transplant. Drugs can be used to reduce the risk of

developing GVHD or to treat the condition once it develops. In 2017, the FDA approved an indication for ibrutinib (Imbruvica) for the treatment of patients with chronic GVHD after failure of one or more lines of systemic therapy.

For more information, view the *Understanding Stem Cell Transplantation* publication on LRF's website at lymphoma.org/publications.

When Should a Patient's Doctor Be Contacted?

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

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

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

Chapter 8: Managing Life During and After Treatment

This chapter discusses some general issues that patients may encounter in their daily lives during and after treatment for non-Hodgkin lymphoma (NHL).

Coping Strategies

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

Table 8.1. Coping Strategies

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

Table 8.1. Coping Strategies (*continued*)

Deal With Physical Changes	<ul style="list-style-type: none"> ■ If desired, plan ahead and buy a wig or head covering if hair loss is a possibility. Some patients with lymphoma may feel unattractive because of hair loss and other changes in appearance caused by their treatment. ■ 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 such as dry 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.
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.

The Importance of Pain Control

Patients may 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 this pain without help. Patients should tell their doctors, nurses, or physician assistants if they have any pain, because the healthcare team can 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 NHL. Patients should ask their healthcare team which options are best to help manage their pain. The tips below may help for managing pain.

PATIENT TIP

Managing Pain

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

Maintain a Healthy Lifestyle

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

Several types of exercise may be particularly helpful, including:

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

Eating a healthy diet is especially important during treatment for NHL 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 eating plan that is appropriate. Patients should talk to their doctor before taking any dietary supplements, such as multivitamins or individual vitamin

supplements, as well as any herbal or “natural” supplements, because they may interfere with treatments or have unexpected side effects.

The Importance of Follow-up Care

At the first visit following the completion of treatment, patients should discuss their follow-up schedule with the doctor. This schedule will be different for each patient depending on his or her lymphoma type and 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, imaging, or other laboratory tests.

Be Proactive in Healthcare Decisions

To stay proactive in healthcare decisions, patients should write out their questions and bring them to their appointments and take notes during their visits. They may also download and start using the LRF *Focus On Lymphoma* app on their mobile devices to learn about and manage NHL. Patients should also obtain and save the following information from their medical team:

- Copies of all medical records (including electronic records) and a written summary of their treatment(s) in case the patient switches doctors or needs to see a physician who is not familiar with the patient’s lymphoma history and treatment
- A list of things to watch for, including signs of disease recurrence and late side effects from treatment

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

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

Part 4 — Hospital Admission

Chapter 9: Preparing to Go to the Hospital

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

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

Most doctors make daily visitation rounds to check on their patients at about the same time each day. The nurse can tell patients when their doctor usually makes rounds. 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 are usually first evaluated by a hospitalist or resident physician. Hospitalists are doctors employed by or consulting for the hospital. Their specialty is typically internal medicine. Patients are also assigned a case manager (usually a nurse) who works with the patient's healthcare team.

What Should Patients Bring With Them to the Hospital?

When being admitted to the hospital, being prepared can ease the process of admission and positively impact patients' care. A brief list of items for patients to take with them is shown on the following 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 pharmaceutical 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 NHL, such as hypertension, epilepsy, or active ulcer
- List of all surgeries (even elective plastic surgeries) regardless of how long ago they occurred
- List of all physicians currently treating you
- Copy of any completed advance directives (for more information see the section on the following page describing advance healthcare directives)
- All insurance cards, a checkbook, a credit card, and a minimal amount of cash

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

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

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

Creating an *advance healthcare directive* (a living will) and appointing a healthcare proxy is important for all adults to consider, not just people with cancer, because accidents and other unforeseen circumstances can happen at any time.

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

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

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

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

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

What Are Patients' Rights?

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

PATIENT TIP

Your Rights As a Patient

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

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

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

What to Look for in the Hospital Informed Consent Document

PATIENT TIP

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

What Do Patients Need to Know at Discharge?

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

PATIENT TIP

Topics for the Case Manager to Address Before Discharge

- Are there any new limitations to what you can do at work or at home? If so, your doctor can provide a note for your employer if needed.
- Will you need physical therapy?
- If you need any new medical equipment, where can it be obtained? Who will order it? Obtain a phone number to ensure you can follow up if there are any problems with equipment delivery.
- Will you need home nursing care or other arrangements?
- 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 if the cost is beyond your capacity to pay?
- What are the side effects of the new medications?
- Will they interact with any medications you are currently taking?
- Are there other instructions from your doctor or the hospital physician?
- With whom should you follow up and when?
- If you are to schedule your own follow-up, whom do you call?

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

Should Patients Provide Feedback on Their Stay?

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

Part 5 — Clinical Trials and Advances in Treatment

Chapter 10: Overview of Clinical Trials

There are numerous clinical trials for patients with non-Hodgkin lymphoma (NHL) now underway in hospitals, cancer centers, and doctors' offices around the country. The government, pharmaceutical and biotechnology companies, universities, and doctor groups often sponsor clinical trials.

What Is a Clinical Trial?

A *clinical trial* is a carefully designed research study that involves 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. Strict rules and oversight procedures make sure that clinical trials are designed and run in a way that protects the rights and safety of the people who volunteer to participate. It can sometimes take years for a clinical trial to be completed and for the results to be compiled and published.

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

As shown in Table 10.1, there are four main types or phases of clinical trials. The first three (Phase I, Phase II, and Phase III) are usually

required before a drug is considered for approval by the FDA. Phase IV trials, sometimes called 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 NHL, and the types of treatments, if any, they have previously received.

Table 10.1. The Four Phases of Clinical Trials

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

Why Is a Placebo Sometimes Used in Phase III Trials?

A *placebo*, or sugar pill, is an inactive ingredient that is used as a comparator in some randomized clinical trials. The placebo is made to look and taste the same as the experimental pill, or to have the same appearance as the experimental intravenous agent, so that patients cannot tell whether they have been randomized to the control group receiving the placebo or the experimental group receiving the new treatment. In some trials, known as double-blind studies, the doctors, nurses, and physician assistants 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.

Should a Patient Participate in a Clinical Trial?

Clinical trials are not a “last resort” for patients. Every drug available today had to be tested in clinical trials before it was approved for general use, and all new and emerging treatments for 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* (disease returns after treatment).

Clinical trials offer both benefits and risks. Patients in clinical trials who are randomized to the experimental group may be able to benefit from a new treatment that is not otherwise available to all patients. However, this new treatment may or may not be more effective than the standard therapy. At the very least, patients who are randomized to the control group will 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 usually a medical doctor. Clinical trials also have a research team that may include nurses, physician assistants, social workers, medical coordinators, and other healthcare professionals. Patients usually continue regular visits with their current healthcare provider, who may work with the research team to ensure that any investigational treatment does not interfere with their current medications or treatments. Clinical trials are carefully supervised by safety monitoring boards, monitoring processes, audits, and other activities to ensure ongoing safety assessments.

What Is Informed Consent in a Clinical Trial?

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

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

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

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

PATIENT TIP

Questions to Ask About a Clinical Trial

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

What Is the Cost of Participating in a Clinical Trial?

Clinical trials are very expensive for the study sponsor. 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.

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

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

Part 5 — Clinical Trials and Advances in Treatment

Chapter 11: Advances in Treatment of Patients With Non-Hodgkin Lymphoma

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 non-Hodgkin lymphoma (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.

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

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

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

For a detailed discussion of currently approved treatment options, please see the "Treatments for Non-Hodgkin Lymphoma" chapter of this guide.

Chemotherapy

Researchers are trying to develop new chemotherapy drugs, improve existing drugs, and find better ways to combine different dosages and sequences of existing drugs. The goal is to develop treatment regimens that are better at eradicating 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 graft-versus-host disease in *allogeneic* (donor) transplants; improving ways to remove all lymphoma cells from stem cell samples used for *autologous* (self) transplants; and developing more effective regimens for reduced-intensity 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. Many monoclonal antibodies are being investigated in clinical trials, including ublituximab (CLL/SLL, DLBCL, FL, MZL, and other B-cell NHLs), MOR00208 (CLL/SLL, DLBCL), and others.

Antibody-Drug Conjugates

Antibody-drug conjugates in development include polatuzumab vedotin (DLBCL, FL, and other NHLs).

Radioimmunotherapy

Betalutin (¹⁷⁷Lu iliotomab satetraxetan) is a radioimmunotherapy that is currently under investigation for the treatment of NHL (DLBCL and other NHLs).

Checkpoint Inhibitors

A newer class of immunotherapies called checkpoint inhibitors has been developed more recently. Two checkpoint inhibitors, nivolumab (Opdivo) and pembrolizumab (Keytruda), which are FDA-approved for the treatment of Hodgkin lymphoma, have shown encouraging results in clinical trials for patients with B-cell NHL. Other checkpoint inhibitors, such as durvalumab (CLL, DLBCL, and other NHLs) and atezolizumab (Tecentriq) (CLL/SLL, DLBCL, FL, and other NHLs), are also under investigation for the treatment of NHL.

Targeted Therapies

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

- Histone deacetylase (HDAC) inhibitors (ALCL, ATLL, Burkitt lymphoma, DLBCL, FL, MCL, peripheral T-cell lymphomas [including cutaneous T-cell lymphoma], other T-cell/NK-cell NHLs)
- Inhibitors of B-cell lymphoma-2 (Bcl2) (Burkitt lymphoma, DLBCL, FL, MCL, MZL, other B-cell NHLs)
- Kinase inhibitors, including:
 - Aurora A kinase inhibitors such as alisertib (MLN8237) (Burkitt lymphoma, DLBCL, FL, MCL, other B-cell NHLs, T-/NK-cell NHLs)
 - Bruton tyrosine kinase (BTK) inhibitors (FL, T-cell NHLs)
 - Phosphoinositide-3-kinase (PI3K) inhibitors (CLL/SLL, FL, MCL, MZL, lymphoplasmacytic lymphoma, Waldenström macroglobulinemia)
 - Spleen tyrosine kinase (Syk) inhibitors (DLBCL and other NHLs)
- Proteasome inhibitors (DLBCL, MCL, T-cell NHLs)

CAR T-Cell Therapy

Chimeric antigen receptor (CAR) T-cell therapies that target the CD19, CD20, CD22, and CD30 antigens are currently being investigated for several types of lymphoma.

Vaccines

Vaccines are commonly used to help protect against viruses and other infections. However, most cancers, including NHL, are not thought to be caused by viruses. In these cases, researchers are focused on developing vaccines to help treat, rather than prevent, lymphomas. The hope is that these vaccines might boost the immune system to recognize and kill lymphoma cells early during the course of the disease.

ABOUT THE LYMPHOMA RESEARCH FOUNDATION

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

Awareness and Outreach

LRF offers numerous advocacy, awareness, and fundraising programs—including the signature *Lymphoma Walk* program and *Team LRF*—which allow members of the lymphoma and CLL/SLL community to become involved with the organization and support the LRF mission. The *LRF Advocacy Program* provides volunteer advocates with the resources necessary to raise attention and support for those public policies most important to the lymphoma and CLL/SLL community. There are currently more than 5,000 LRF advocates in all 50 states and the District of Columbia.

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); Teleconferences; and Videos, Webcasts and Podcasts. All programs and materials are offered free of charge. Learn more at lymphoma.org.

Professional Education

LRF is committed to educating healthcare professionals on the latest developments in lymphoma and CLL/SLL diagnosis and treatment. The Foundation offers a wide range of lymphoma-focused continuing education activities for nurses, physicians, and social workers, including workshops, conference symposia, and webcasts.

Research

LRF is focused on finding a cure for lymphoma and CLL/SLL through an aggressively-funded research program and by supporting the next generation of lymphoma investigators. LRF supports Clinical Investigator Career Development Awards, Lymphoma Fellowships, and several disease-specific research initiatives. These efforts are led by the Foundation's Scientific Advisory Board (SAB), comprised of 45 world-renowned lymphoma experts. The Foundation has funded nearly \$60 million in lymphoma-specific research.

Contact Information

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

Website: lymphoma.org



FOCUS ON LYMPHOMA MOBILE APP

The Lymphoma Research Foundation's mobile app, *Focus on Lymphoma*, is a great tool and resource for lymphoma patients to manage their disease.

Focus on Lymphoma is the first mobile app that provides patients and caregivers comprehensive content

based on their lymphoma subtype and tools to help manage their diagnosis, including a medication manager, doctor sessions tool and side effects tracker.



The *Focus on Lymphoma* mobile app was recently named Best App by PR News and is available for free download for iOS and Android devices in the Apple App Store and Google Play.

For further information on LRF's award winning mobile app or any of our programs and services, call the **LRF Helpline toll free (800) 500-9976**, **email helpline@lymphoma.org** or visit us at **lymphoma.org**.

Understanding Non-Hodgkin Lymphoma

This patient guide is supported through
unrestricted educational grants from:



Genentech
A Member of the Roche Group



Contact the Lymphoma Research Foundation

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

Website: lymphoma.org