Understanding Non-Hodgkin Lymphoma

A Guide for Patients, Survivors, and Loved Ones

September 2015
LYMPHOMA
RESEARCH FOUNDATION

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

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Our support services include:

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- 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
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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

September 2015

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.

National Headquarters
115 Broadway, Suite 1301
New York, NY 10006
(212) 349-2910 phone
(212) 349-2886 fax
Helpline: (800) 500-9976; helpline@lymphoma.org
Website: www.lymphoma.org
Email: LRF@lymphoma.org

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<td>3D-CRT</td>
<td>three-dimensional conformal radiation therapy</td>
</tr>
<tr>
<td>ABMS</td>
<td>American Board of Medical Specialties</td>
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<tr>
<td>ACA</td>
<td>Affordable Care Act</td>
</tr>
<tr>
<td>AIDS</td>
<td>acquired immunodeficiency syndrome</td>
</tr>
<tr>
<td>AIHA</td>
<td>autoimmune hemolytic anemia</td>
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<tr>
<td>AITL</td>
<td>angioimmunoblastic T-cell lymphoma</td>
</tr>
<tr>
<td>ALCL</td>
<td>anaplastic large cell lymphoma</td>
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<tr>
<td>ALK</td>
<td>anaplastic lymphoma kinase</td>
</tr>
<tr>
<td>ALL</td>
<td>acute lymphoblastic leukemia</td>
</tr>
<tr>
<td>ANC</td>
<td>absolute neutrophil count</td>
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<tr>
<td>ASCO</td>
<td>American Society of Clinical Oncology</td>
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<tr>
<td>ASH</td>
<td>American Society of Hematology</td>
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<tr>
<td>ATLL</td>
<td>adult T-cell leukemia/lymphoma</td>
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<tr>
<td>B2M</td>
<td>beta-2 microglobulin</td>
</tr>
<tr>
<td>BTK</td>
<td>Bruton’s tyrosine kinase</td>
</tr>
<tr>
<td>CAR</td>
<td>chimeric antigen receptor</td>
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<tr>
<td>CBC</td>
<td>complete blood count</td>
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<tr>
<td>CLL</td>
<td>chronic lymphocytic leukemia</td>
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<tr>
<td>CNS</td>
<td>central nervous system</td>
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<tr>
<td>CPR</td>
<td>cardiopulmonary resuscitation</td>
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<tr>
<td>CR</td>
<td>complete remission</td>
</tr>
<tr>
<td>CSF</td>
<td>cerebrospinal fluid</td>
</tr>
<tr>
<td>CT</td>
<td>computed tomography</td>
</tr>
<tr>
<td>CTCL</td>
<td>cutaneous T-cell lymphoma</td>
</tr>
<tr>
<td>DLBCL</td>
<td>diffuse large B-cell lymphoma</td>
</tr>
<tr>
<td>DNA</td>
<td>deoxyribonucleic acid; genetic material</td>
</tr>
<tr>
<td>DNR</td>
<td>do not resuscitate</td>
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<tr>
<td>EATL</td>
<td>enteropathy-type T-cell lymphoma</td>
</tr>
<tr>
<td>EBV</td>
<td>Epstein-Barr virus</td>
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<tr>
<td>ECHO</td>
<td>echocardiogram</td>
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<td>ENMZL</td>
<td>extranodal marginal zone lymphoma</td>
</tr>
<tr>
<td>FDA</td>
<td>U.S. Food and Drug Administration</td>
</tr>
<tr>
<td>FISH</td>
<td>fluorescence in situ hybridization</td>
</tr>
<tr>
<td>FL</td>
<td>follicular lymphoma</td>
</tr>
<tr>
<td>FNA</td>
<td>fine needle aspirate</td>
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<tr>
<td>GVHD</td>
<td>graft-versus-host disease</td>
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<tr>
<td>HBV</td>
<td>hepatitis B virus</td>
</tr>
<tr>
<td>HCV</td>
<td>hepatitis C virus</td>
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<tr>
<td>HDAC</td>
<td>histone deacetylase</td>
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<tr>
<td>HIV</td>
<td>human immunodeficiency virus</td>
</tr>
<tr>
<td>HL</td>
<td>Hodgkin lymphoma</td>
</tr>
<tr>
<td>HTLV-1</td>
<td>human T-lymphotropic virus type 1</td>
</tr>
<tr>
<td>IgM</td>
<td>immunoglobulin M</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>------------------------------------------------</td>
</tr>
<tr>
<td>IGRT</td>
<td>image-guided radiation therapy</td>
</tr>
<tr>
<td>IHC</td>
<td>immunohistochemistry</td>
</tr>
<tr>
<td>IMiD</td>
<td>immunomodulatory drug</td>
</tr>
<tr>
<td>IPI</td>
<td>International Prognostic Index</td>
</tr>
<tr>
<td>IRB</td>
<td>institutional review board</td>
</tr>
<tr>
<td>ITP</td>
<td>immune</td>
</tr>
<tr>
<td>IV</td>
<td>intravenous</td>
</tr>
<tr>
<td>LDH</td>
<td>lactate dehydrogenase</td>
</tr>
<tr>
<td>LRF</td>
<td>Lymphoma Research Foundation</td>
</tr>
<tr>
<td>MALT</td>
<td>mucosa-associated lymphoid tissue</td>
</tr>
<tr>
<td>MCL</td>
<td>mantle cell lymphoma</td>
</tr>
<tr>
<td>MMAE</td>
<td>monomethyl auristatin E</td>
</tr>
<tr>
<td>MR</td>
<td>minor response</td>
</tr>
<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
</tr>
<tr>
<td>mTOR</td>
<td>mammalian target of rapamycin</td>
</tr>
<tr>
<td>MUGA</td>
<td>multi-gated acquisition</td>
</tr>
<tr>
<td>MZL</td>
<td>marginal zone B-cell lymphoma</td>
</tr>
<tr>
<td>NCCN</td>
<td>National Comprehensive Cancer Network</td>
</tr>
<tr>
<td>NCI</td>
<td>National Cancer Institute</td>
</tr>
<tr>
<td>NHL</td>
<td>non-Hodgkin lymphoma</td>
</tr>
<tr>
<td>NIH</td>
<td>National Institutes of Health</td>
</tr>
<tr>
<td>NK</td>
<td>natural killer (cell)</td>
</tr>
<tr>
<td>PCR</td>
<td>polymerase chain reaction</td>
</tr>
<tr>
<td>PET</td>
<td>positron emission tomography</td>
</tr>
<tr>
<td>PFT</td>
<td>pulmonary function test</td>
</tr>
<tr>
<td>PI3K</td>
<td>phosphoinositide-3 kinase</td>
</tr>
<tr>
<td>PICC</td>
<td>peripherally inserted central catheter</td>
</tr>
<tr>
<td>PMBCL</td>
<td>primary mediastinal B-cell lymphoma</td>
</tr>
<tr>
<td>PNP</td>
<td>purine nucleoside phosphorylase</td>
</tr>
<tr>
<td>PR</td>
<td>partial remission</td>
</tr>
<tr>
<td>PS</td>
<td>performance status</td>
</tr>
<tr>
<td>PTCL</td>
<td>peripheral T-cell lymphoma</td>
</tr>
<tr>
<td>PTCL-NOS</td>
<td>peripheral T-cell lymphoma, not otherwise specified</td>
</tr>
<tr>
<td>SAB</td>
<td>Scientific Advisory Board</td>
</tr>
<tr>
<td>SALT</td>
<td>skin-associated lymphoid tissue-related</td>
</tr>
<tr>
<td>SEER</td>
<td>Surveillance, Epidemiology, and End Results</td>
</tr>
<tr>
<td>SLL</td>
<td>small lymphocytic lymphoma</td>
</tr>
<tr>
<td>SMZL</td>
<td>splenic marginal zone lymphoma</td>
</tr>
<tr>
<td>Syk</td>
<td>spleen tyrosine kinase</td>
</tr>
<tr>
<td>TLS</td>
<td>tumor lysis syndrome</td>
</tr>
<tr>
<td>TNF</td>
<td>tumor necrosis factor</td>
</tr>
<tr>
<td>TSEBT</td>
<td>total skin electron beam therapy</td>
</tr>
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</table>
INTRODUCTION

The purpose of this booklet is to assist patients with non-Hodgkin lymphoma and their caregivers. It is designed to allow them to become familiar with their illness and to become active participants in their healthcare decisions. Chapters in this book address different issues faced by these patients, including what to expect during diagnosis, work-up, and treatment; how to cope with treatment side effects; and what questions to ask doctors. In addition to this booklet, information is available online at the Lymphoma Research Foundation’s website at www.lymphoma.org.
Understanding Non-Hodgkin Lymphoma

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. Lymph nodes are bean-shaped structures that act as sentinels (ie, soldiers or guards who keep watch) because they are often the first defense against invading organisms, such as viruses and bacterial infections.

This chapter explains these and other terms that will help you understand NHL and how it affects a person’s health. A better understanding of the disease will help patients take a more active role in deciding the course of their treatment.

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 many different tasks needed to function. To keep it running smoothly, there are cells in the body that grow, work, and divide in a very controlled fashion.

All of these cells also have a limited lifespan. Normally, a self-destruct mechanism is triggered when a cell becomes senescent (too old) or when it gets 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, making the cell “immortal” in many ways; this means that the cells that would normally be unable to divide and grow continue to grow indefinitely. Unless the body’s
immune system gets rid of these abnormal cells, they can become cancerous.

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

**HOW CANCER FORMS INSIDE THE BODY**

**Normal cell division**

2. Cells grow and divide.
3. Cells are removed due to programmed cell death (apoptosis).

**Cancer cell division**

1. A damaged or senescent cell does not self-destruct, and starts to multiply.
2. Groups of abnormal cells may form tumors.
Most cancers are named after the organ or cell type of their origin. For every normal cell in the body, there is a corresponding cancer. For example:

- A cancer of pancreas cells is called *pancreatic cancer*.
- A cancer of the lymphocyte is called a *lymphoma* or *lymphatic leukemia* depending on whether the cancer started in the tissue/lymph nodes (lymphoma) or in the bone marrow and circulation (leukemia).

**What Are Red Blood Cells and White Blood Cells?**

Red blood cells carry oxygen from the lungs to all the tissues in the body when you inhale. Red blood cells also bind the carbon dioxide waste produced by cells and bring it to the lungs. In the lungs, the carbon dioxide is released into the air each time you exhale.

White blood cells work as part of the immune system to help the body fight off infections. The main types of white blood cells are lymphocytes, granulocytes, and monocytes. There are also three types of granulocytes (neutrophils, basophils, and eosinophils) and at least three types of lymphocytes (B cells, T cells, and natural killer [NK] cells).

Because red and white blood cells have a limited lifespan, the body needs to constantly replenish its supply of these cells. Red blood cells live for about 120 days; most white blood cells have an even shorter life, ranging from a few hours to a few weeks.

Both red and white blood cells are made by hematopoietic (blood) stem cells, which are specialized cells found in the *bone marrow* (the spongy, fatty material inside large bones, such as the pelvis, vertebrae, and ribs). Healthy bone marrow produces blood stem cells, which are immature (non-specialized) cells that can take on various roles. The blood stem cells in the bone marrow differentiate to produce mature white and red blood cells as well as lymphocytes.
Stem cells differentiate and become mature cells that travel in the blood, such as:

- Red blood cells — These cells carry oxygen and other materials to tissues in the body. A low number of red blood cells causes anemia. A person with anemia may feel tired, weak, and short of breath.

- Neutrophils, basophils, and eosinophils — Neutrophils are a type of white blood cell that helps fight off bacterial infections. A low number of neutrophils is called neutropenia. People with neutropenia are more likely to get infections than people with healthy numbers of neutrophils. Basophils are part of inflammatory reactions, like allergies. Eosinophils also help fight infections and are involved in allergic reactions.
Platelets — These are fragments arising from cells called megakaryocytes that stop bleeding by causing blood to clot. A low number of platelets is called thrombocytopenia. People with thrombocytopenia are more likely to bruise and bleed. They are also more likely to have severe and recurring nosebleeds and bleeding gums.

Once lymphoid stem cells detect pieces of foreign matter (antigens), they increase in size and become lymphoblasts. Lymphoblast cells specialize and divide. Types of lymphocytes include:

- B lymphocytes (B cells)
- T lymphocytes (T cells)
- Natural killer (NK) cells

To learn more about these types of cells, see page 13.

**What Is the Lymphatic System?**

As shown in the picture on the following page, the lymphatic system is a circulatory system that is made up of a spidery network of thin tubes called lymph vessels or lymphatic vessels. Similar to blood vessels, lymphatic vessels branch out into all tissues of the body. While people can clearly see blood vessels, especially at their wrists and on the tops of their hands, most lymph vessels are not visible to the naked eye. However, there is one large vessel of the lymphatic system; it is called the thoracic duct.
Lymphatic vessels carry lymph, a type of liquid that contains lymphocytes to help fight infection. Within this huge network of vessels are groups of small, bean-shaped organs called lymph nodes, which are also commonly known as “glands.” Thousands of lymph nodes are found at locations throughout the body, including the neck, shoulders, underarms, elbows, and groin. Lymphocytes can mostly be found in lymph nodes, where they monitor the lymph for signs of infection in the body. The lymph nodes can change in size, becoming bigger or smaller depending on the number of lymphocytes inside them.

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

If a large number of foreign substances are filtered through a node or series of nodes, swelling may occur and the nodes may become tender to the touch. Most swollen nodes are a reaction to infection or inflammation and are not cancerous.

**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 (which are also found in gamma globulin) to fight infections. They are called “B” cells because they were first discovered in the “Bursa of Fabricius” in birds. Later, similar cells were found in humans.

- **T lymphocytes** (T cells) — There are many types of T cells. Some help B cells make antibodies, some attack and kill infected cells, and some help control the way other parts of the immune system fight infections. They are called “T” cells because they mature and may spend part of their lifespan in the thymus gland, a small organ in the chest.
NK cells — NK (natural killer) cells attack and kill cancer cells and virus-infected cells. They also make chemicals called cytokines, which are substances that can attack viruses and tumor cells.

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 immunity — This type is provided by natural barriers in the body, substances in the blood, and specific types of cells that attack and kill foreign cells that invade the body. Examples of natural barriers include skin, mucous membranes (in the nose, mouth, eyelids, windpipe, lungs, stomach, intestine, and bladder), stomach acid, and the cough reflex. These barriers keep germs and other harmful substances from entering the body. Inflammation (redness and swelling) is also a type of innate immunity. Macrophages, neutrophils, and NK cells are part of the innate immune system.

- Adaptive immunity — This type is provided by the thymus gland, spleen, tonsils, bone marrow, circulatory system, and lymphatic system. These systems work together to make, store, and move specialized cells (such as B cells and T cells) and molecules (such as antibodies) that recognize specific identifying parts (antigens) of invading organisms, ridding the body of viruses, bacteria, or parasites that have these antigens. This process can be tricky because, in order for the immune system to destroy foreign invaders, it has to be able to recognize what is a part of the body ("self" or "auto") and what is not part of the body ("non-self"). Through a complicated process, the body's adaptive immune system "remembers" the identity of the invader, so that the next time the body is infected by the same virus, for example, the immune response will be even stronger. Vaccinations prevent disease by turning on the adaptive immune response before the body is
exposed to the disease, ensuring that it is prepared to recognize and fight the disease.

**What Is Lymphoma?**

A *lymphoma* is a type of cancer that originates from lymphocytes in the lymph nodes. There are two major categories of lymphomas: non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma (HL). Both of these major categories of lymphoma are further subdivided into numerous types, which are different in the way they develop and spread. The particular type of lymphoma a patient has may need its own plan of treatment. Unlike other cancers, therapy and prognosis are not based on the stage at which the disease is diagnosed but rather is determined by the lymphoma subtype.

**What Is Non-Hodgkin Lymphoma?**

In the United States, NHL is the sixth most common type of cancer affecting adults. NHL is not one disease but includes a large group of related cancers that occur in lymphocytes. The World Health Organization estimates that there are at least 60 different 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 affects patients
- How patients should be treated
- Likely outcome with treatment (curable vs. not)
NHL is divided into the following two major groups:

- **B-cell lymphomas** — These lymphomas develop from abnormal B lymphocytes and are the most common, representing about 85 percent of all patients diagnosed with NHL.

- **T/NK-cell lymphomas** — These lymphomas develop from abnormal T lymphocytes or NK cells, are less common, and constitute about 10 to 15 percent of patients with an NHL diagnosis.

### RELATIVE FREQUENCIES OF B-CELL LYMPHOMAS IN THE UNITED STATES

- Chronic lymphocytic leukemia/small lymphocytic lymphoma: 26%
- Follicular lymphoma: 17%
- Lymphoplasmacytic/Waldenström macroglobulinemia: 3%
- Mantle cell lymphoma: 3%
- Nodal marginal zone lymphoma: 3%
- Extranodal marginal zone, MALT-type: 5%
- Hairy-cell leukemia: 1%
- Burkitt lymphoma: 2%
- Not otherwise specified: 6%

Diffuse large B-cell: 32%

MALT, mucosa-associated lymphoid tissue.

Percentages are based on the National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) data, 2002-2011. Some very rare NHL types are not shown in the graph.
Relative Frequencies of T-Cell Lymphomas in the United States

Per centages are based on the National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) data, 2002-2011. Some very rare NHL types are not shown in the graph.

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

- **Indolent** lymphomas (also called *low-grade* lymphomas) usually grow slowly and tend to initially cause few symptoms. While indolent lymphomas are generally not curable (similar in some ways to diabetes, which is not curable but manageable), patients can potentially live a long time with these types of lymphomas because they tend to respond well to treatment and can remain in remission for many years (even decades). Although these lymphomas are slow growing, they tend to be more widespread at diagnosis than aggressive lymphomas. Over time, some indolent lymphomas may “transform” or develop into aggressive lymphomas.
**Aggressive lymphomas** (also called *intermediate-grade* and *high-grade* lymphomas) grow and spread more quickly than indolent lymphomas. These lymphomas are localized in about one-third of cases. Aggressive lymphomas, while potentially life threatening, can be cured because many chemotherapy drugs can kill rapidly dividing tumor cells.

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

<table>
<thead>
<tr>
<th>Indolent NHLs</th>
<th>Aggressive NHLs</th>
</tr>
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<tbody>
<tr>
<td>Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL)</td>
<td>Anaplastic large cell lymphoma (ALCL)</td>
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<tr>
<td>Follicular lymphoma (FL)</td>
<td>Angioimmunoblastic T-cell lymphoma (AITL)</td>
</tr>
<tr>
<td>Lymphoplasmacytic lymphoma/ Waldenström macroglobulinemia</td>
<td>Burkitt/Burkit-like lymphomas</td>
</tr>
<tr>
<td>Marginal zone lymphoma (MZL)</td>
<td>Diffuse large B-cell lymphoma (DLBCL)</td>
</tr>
<tr>
<td>Mycosis fungoides (subtype of cutaneous T-cell lymphoma)</td>
<td>Lymphoblastic leukemia/lymphoma</td>
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</tbody>
</table>

**Pathologists** are doctors who specialize in making a disease diagnosis by looking at tumor tissue under the microscope. They can distinguish among the many different types of NHL by examining biopsy tissue samples as well as blood and bone marrow samples under a microscope and by carrying out various laboratory tests. This information is critically important in deciding how to treat the patient.
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) is the term used when the disease is predominantly presenting in the blood and bone marrow. Small lymphocytic lymphoma (SLL) is the term used when malignant lymphocytes are found mainly in lymph nodes though some ultimate involvement of the bone marrow and peripheral blood is common. However, most cases have both “leukemia” and “lymphoma” components and the disease is most appropriately referred to as CLL/SLL. CLL and SLL represent a clinical continuum of slowly progressive B-cell malignancies involving “small” lymphocytes. More than half of CLL cases occur in people over the age of 70.

About 25 to 50 percent of patients may not experience any symptoms from the disease, which may be discovered during routine blood tests and/or a physical examination. When patients present with signs or symptoms, the most common sign is swollen lymph nodes with symptoms of feeling tired (fatigue), shortness of breath, anemia, bruising easily, and frequent infections.

Over time, CLL may occasionally progress to a more aggressive type of lymphoma (Richter transformation).

Although SLL is staged similarly to other NHLs, the staging system for CLL is different from that applied to other NHLs (see page 55). For a more detailed description of CLL/SLL, visit the Lymphoma Research Foundation’s (LRF’s) “Focus on CLL” website at www.FocusOnCLL.org or request a copy of the LRF publication entitled *Understanding CLL/SLL: A Guide for Patients, Survivors, and Loved Ones* at www.lymphoma.org/publications.
Follicular Lymphoma

Follicular lymphoma (FL) is the second most common type of NHL in the United States. FL accounts for about 15 to 20 percent of all B-cell NHLs. The incidence of FL varies widely around the world. Although it can affect people at any age, most patients diagnosed with FL are adults, with an average age at diagnosis of 60. FL usually appears in lymph nodes spread throughout the body. Often, one of the first signs of FL is a 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.

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 “Focus on Follicular Lymphoma” website at www.FocusOnFL.org.

Lymphoplasmacytic Lymphoma/Waldenström Macroglobulinemia

Waldenström macroglobulinemia (one form of lymphoplasmacytic lymphoma or immunocytoma) is a rare B-cell lymphoma that occurs in one to three percent of people with NHL. There are about 1,500 new cases of Waldenström macroglobulinemia each year. The disease usually affects older adults and is primarily found in the bone marrow, although the lymph nodes and spleen may sometimes be involved. In order for patients to be diagnosed with Waldenström macroglobulinemia, they must have a high level of a protein abnormality called immunoglobulin M (IgM) spike or paraprotein, which can cause increased viscosity (thickening) of the blood. Symptoms include feeling tired (fatigue), increased bleeding or bruising easily, headache, dizziness, visual changes, abdominal pain, and swollen lymph nodes. About 30 to 40 percent of lymphoplasmacytic lymphomas do not have an IgM or other paraprotein. These NHLs are
simply called lymphoplasmacytic lymphomas. For more information, view the *Waldenström Macroglobulinemia* fact sheet on LRF’s website at www.lymphoma.org.

**Marginal Zone Lymphoma**

Marginal zone B-cell lymphomas (MZL) account for approximately nine percent of all NHLs. The average age at diagnosis for this type of lymphoma is 60. These lymphomas include four types: (1) extranodal marginal zone lymphoma (ENMZL) (sometimes referred to as mucosa-associated lymphoid tissue [MALT]), occurring outside the lymph system; (2) nodal, occurring within the lymph nodes; (3) splenic (splenic marginal zone lymphoma [SMZL]), occurring mostly in the spleen and blood; (4) skin-associated lymphoid tissue-related (SALT) B-cell lymphoma is also considered a form of ENMZL.

MZLs (especially ENMZL and SMZL) vary from other types of B-cell NHLs in several ways:

- Many people who develop ENMZL may have a history of inflammation, infection, or autoimmune disorders.

- Chronic inflammation associated with *Helicobacter pylori* (*H. pylori*; a bacterial pathogen that may cause gastritis and stomach ulcers, and 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 track), *Borrelia burgdorferi* (skin-associated lymphoid tissue related, or SALT), *Chlamydia psittaci* (lacrimal gland of the eye), and hepatitis C virus (HCV).
  - Some ENMZLs and SMZLs can sometimes be treated with antibiotics or antivirals.

Patients with SMZL may have an enlarged spleen. These lymphomas have been associated with HCV infection and sometime regress after treatment for the HCV infection. Patients with these lymphomas usually have a good prognosis.
**Indolent T-Cell Lymphomas**

Cutaneous T-cell lymphomas (CTCLs) are a group of lymphomas that originate in the skin. They are usually, but not always, less aggressive than peripheral T-cell lymphoma (PTCL; see page 25). Mycosis fungoides is the most common type of CTCL. Other uncommon indolent CTCL types include anaplastic large cell lymphoma limited to the skin and lymphomatoid papulosis.

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

**Burkitt Lymphoma**

Burkitt lymphoma is a rare, highly aggressive B-cell NHL. There are three main types: endemic, sporadic, and immunodeficiency-related. Endemic Burkitt lymphoma is the most common of the three forms and found in Africa, where it is still the most common childhood cancer. Endemic Burkitt lymphoma is rare outside of Africa. Sporadic Burkitt lymphoma occurs throughout the world. Immunodeficiency-related Burkitt lymphoma can occur in patients who have inherited immune deficiencies or in those who take immunosuppressive medications to prevent rejection after organ transplant, or have acquired immune deficiency syndrome (AIDS). The Epstein-Barr virus (EBV) has been shown to be linked to the development of Burkitt lymphoma, particularly with the endemic form.

The sporadic form seen in the United States and Western Europe accounts for less than one percent of all B-cell NHLs in adults, but it accounts for 30 percent of all childhood lymphomas. By comparison, an endemic form found in equatorial Africa and New Guinea has an incidence about 50 times higher than that seen in the United States.

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. Translocation of a gene known as MYC is characteristic of this type of lymphoma. This lymphoma is a potentially curable malignancy when treated aggressively.

**Diffuse Large B-Cell Lymphoma**

Diffuse large B-cell lymphoma (DLBCL) is the most common type of NHL in the United States and worldwide, accounting for up to one-third of patients with newly diagnosed NHL in the United States. Although it can occur in childhood, the occurrence 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 generalized (spread throughout the body). Despite being an aggressive lymphoma, DLBCL is potentially curable. There are various subtypes including activated B-cell–like, germinal center B-cell–like, and primary mediastinal B-cell lymphoma based on gene-expression profiling. Double- or triple-hit lymphomas are those with alterations, called translocations, in the genes MYC and Bcl2 or/and Bcl6. Intravascular lymphoma is a rare subtype of DLBCL that occurs within blood vessels. The treatment approach will depend on the subtype of DLBCL.

For more information, view the *Diffuse Large B-Cell Lymphoma* fact sheet on LRF’s website at www.lymphoma.org.

**Mantle Cell Lymphoma**

Mantle cell lymphoma (MCL) accounts for approximately three percent of all patients with NHL. This type of lymphoma usually affects men, and the average age of patients at diagnosis is 60. At the time of diagnosis, patients with MCL often have many lymph nodes, one or more organs, and the bone marrow affected by the disease. MCL may
follow an indolent (slow-growing) 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 “Focus on Mantle Cell Lymphoma” website at www.FocusOnMCL.org.

**Primary Mediastinal B-Cell Lymphoma**

Primary mediastinal B-cell lymphoma (PMBCL) is a form of DLBCL that arises from the thymus gland, and is usually limited to the mediastinum (a membranous partition between two body cavities or parts of an organ; often between the lungs). Most patients are 30 to 40 years of age at diagnosis, and the disease is more common in women. Symptoms include superior vena cava syndrome (compression of the vena cava vein that causes swelling of the face and arms associated with shortness of breath), fever, weight loss, and night sweats. PMBCL is distinct from DLBCL based on genetic profiling, and may resemble Hodgkin lymphoma. Patients with PMBCL usually have a better prognosis than those with DLBCL, with most patients being cured.

**Aggressive T-Cell Lymphomas**

**Non-Peripheral T-Cell Lymphoma**

**Lymphoblastic Leukemia/Lymphoma.** Lymphoblastic leukemia/lymphoma is relatively rare and can originate from both B cells and T cells, but it is much more common in T cells (which are affected in about 85 percent of all cases). 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 tends to occur more often in men. 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, feeling tired (fatigue), and bruising easily. The complete remission rate after combination chemotherapy is usually very high.
Peripheral T-Cell Lymphoma

Peripheral T-cell lymphoma (PTCL) refers to a large number of different “mature” T-cell lymphomas that together account for approximately 21 percent of all patients diagnosed with NHL in the United States. The most common subtypes include PTCL, not otherwise specified (PTCL-NOS), angioimmunoblastic T-cell lymphoma (AITL), adult T-cell leukemia/lymphoma (ATLL), and anaplastic large cell lymphoma (ALCL). T-cell lymphomas develop in lymphoid tissues outside of the bone marrow, such as in the lymph nodes, spleen, gastrointestinal tract, and skin. Most are aggressive lymphomas, with the exception of some forms of CTCL (see page 22). Aggressive PTCL subtypes include Sézary syndrome, 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 in this section.

The incidences of PTCL subtypes vary geographically. PTCL-NOS is more common in North America, while AITL is more common in Europe. Anaplastic lymphoma kinase (ALK)-negative ALCL is somewhat more common in Europe, while ALK-positive ALCL is more common in North America. The NK/T-cell lymphomas and ATLL are more common in Asia and seem to be related to infections with EBV and human T-lymphotropic virus type 1 (HTLV-1), respectively. For more information on PTCL, please visit LRF’s “Focus on Peripheral T-Cell Lymphoma” website at www.FocusOnPTCL.org.

Anaplastic Large Cell Lymphoma. Anaplastic large cell lymphoma (ALCL) is rare, accounting for about two percent of all NHLs and about 20 percent of all T-cell lymphomas. Initial symptoms of ALCL can include fever, backache, painless swelling of lymph nodes, loss of appetite, and tiredness. ALCL occurs either systemically (throughout the body) or cutaneously (on the surface of the skin). Systemic ALCL can respond well to chemotherapy and is potentially curable. Cutaneous skin ALCL is not an aggressive disease. It is part of a spectrum of diseases associated with a rare condition called lymphomatoid papulosis.
Patients with systemic ALCL are divided into two groups, depending on whether their cells have an abnormal form of a protein called ALK. The outcome for ALCL depends on whether a patient is *ALK positive* (expresses the protein) or *ALK negative* (does not express the protein). ALK-positive disease tends to occur in patients younger than 40 and is more common in males. ALK-negative disease is more common in adults older than the age of 55, occurs equally in males and females, and is often advanced at diagnosis. ALK-positive disease responds better to chemotherapy, and is generally considered very curable. Although a majority of ALK-negative patients initially respond to chemotherapy, they tend to relapse, often requiring additional therapy and are sometimes treated more aggressively, often with stem cell transplantation. ALCL is also characterized by expression of CD30 antigen on the surface of cancer cells. The expression of CD30 makes the cancer cells susceptible to treatment with brentuximab vedotin (Adcetris), which is indicated for ALCL and HL under certain conditions. For more information, visit LRF’s “Focus on Anaplastic Large Cell Lymphoma” website at www.FocusOnALCL.org.

**Angioimmunoblastic T-Cell Lymphoma.** Angioimmunoblastic T-cell lymphoma (AITL) affects approximately seven percent of all patients with NHL in the United States. Most patients are middle-aged to elderly persons and are diagnosed with advanced stage disease. Symptoms 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 (ie, immune system does not recognize self), the body's immune system destroys its own cells or tissues, such as red blood cells (in the case of AIHA) or platelets (in the case of ITP). Romidepsin (Istodax), indicated to treat certain CTCLs and PTCLs, has produced some durable responses in patients with AITL.

Initially, AITL may be treated with steroids to relieve symptoms, such as joint inflammation/pain and skin rash. Most patients are treated with multiagent chemotherapy and sometimes stem cell transplantation. For more information, view the *Angioimmunoblastic T-Cell Lymphoma* fact sheet on LRF’s website at www.lymphoma.org.
Peripheral T-Cell Lymphoma, Not Otherwise Specified. PTCL-NOS is the most common subtype of PTCL and refers to a group of diseases that do not fit into any of the other PTCL subtypes. PTCL-NOS usually occurs in adults in their 50s and 60s. Although most patients with PTCL-NOS are diagnosed with their disease 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 and tends to relapse (the disease returns after treatment).

Sézary Syndrome. Sézary syndrome is a rare, aggressive form of CTCL that affects both the skin and the peripheral blood. Most cases occur in adults over the age of 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 seen under a microscope and are present in both the skin and the blood.

Why Do Some People Develop NHL?
The characteristics that make a person possibly more susceptible to developing any type of disease are called risk factors.

The reasons why most people develop NHL are not understood. However, scientists have found that people with certain characteristics have a slightly higher risk of developing NHL compared with people who do not have these characteristics.

Having one or more risk factors for NHL does not mean a person will 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 following risk factors 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 the human immunodeficiency virus (HIV; the virus that can cause AIDS)

- An autoimmune disease (for example, Crohn’s disease, rheumatoid arthritis, or psoriasis) or its treatment; in addition, lymphomas may occur following use of tumor necrosis factor (TNF)-inhibitor therapy for rheumatoid arthritis, Crohn’s disease, and other inflammatory diseases

- Treatment with certain drugs used after an organ transplantation

- Infections with certain viruses, such as EBV, HTLV-1, and/or HCV

- Infection with *Helicobacter pylori* (*H. pylori*), *Campylobacter jejuni*, *Borrelia burgdorferi*, *Chlamydia psittaci*, or HCV

- Older age; NHL like most cancers is much more common in adults older than 60, although NHL may develop in children and adults of all ages

- Male gender; for unknown reasons, NHL is slightly more common in men than in women

- Being exposed to certain chemicals, such as certain herbicides and pesticides, and some chemotherapy drugs used to treat other cancers or autoimmune diseases

- Treatment with radiation therapy for some other cancers, including NHL

- Previous treatment for lymphoma

Like other types of cancer, NHL cannot be caused by injury and cannot be caught from someone who has the disease. Children and siblings of patients with NHL have a slightly increased risk of developing this disease compared with the general population. However, there are no clear genetic or hereditary factors to predict this slightly increased risk, and routine screening for NHL is not recommended.
This chapter explains the signs and symptoms of non-Hodgkin lymphoma (NHL) and discusses how a doctor determines whether or not a person has the disease.

A *sign* is anything unusual that doctors or nurses notice when they examine their patients.

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 or nurse. 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 symptoms of the disease. Their doctors might detect the lymphoma during routine blood tests and/or a physical examination. For others, the lymphoma is detected when symptoms occur and the patient goes to the doctor because he or she is worried, uncomfortable, or does not feel well.

As shown in Table 2.1, NHL may cause different symptoms depending on the type of NHL and where it is located in the body. Keep in mind that, because these signs and symptoms are not specific to NHL, they may be due to other conditions.
Table 2.1. Symptoms Commonly Found in Patients With Lymphoma

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Possible Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lumps under the skin on the sides of the neck, above the collar bone,</td>
<td>Lymph nodes, or “glands,” swell when the lymphocytes respond to something wrong like an infection, or because of an increased number of abnormal</td>
</tr>
<tr>
<td>underarms, elbows, or in the groin</td>
<td>lymphocytes</td>
</tr>
<tr>
<td>Swollen, tender abdomen (“belly” or “stomach”)</td>
<td>Enlarged lymph nodes in the abdomen</td>
</tr>
<tr>
<td></td>
<td>Accumulation of liquid in the abdomen (ascites)</td>
</tr>
<tr>
<td></td>
<td>Enlarged spleen</td>
</tr>
<tr>
<td>Abdominal or “stomach” pain, nausea, or vomiting, decreased appetite</td>
<td>Enlarged lymph nodes or an enlarged spleen impinging on normal structures (diaphragm, nerves, spine). This symptom is more common than pain due to</td>
</tr>
<tr>
<td></td>
<td>enlarged spleen impinging on normal structures (diaphragm, nerves, spine). This symptom is</td>
</tr>
<tr>
<td></td>
<td>more common than pain due to intestinal involvement</td>
</tr>
<tr>
<td></td>
<td>Splenic pain</td>
</tr>
<tr>
<td></td>
<td>Lymphoma in the intestine or causing swelling near the intestine, possibly blocking bowel</td>
</tr>
<tr>
<td></td>
<td>movements</td>
</tr>
<tr>
<td></td>
<td>Lymphoma of the stomach or abdomen</td>
</tr>
<tr>
<td>Coughing, trouble breathing, chest pain, or pressure</td>
<td>Lymphoma in the chest, which may press on the windpipe (trachea) or bronchi</td>
</tr>
<tr>
<td>Headache, trouble thinking, weakness in extremity (leg or arm),</td>
<td>Lymphoma of the brain or spinal cord (CNS) or lymphoma originating in other parts of the</td>
</tr>
<tr>
<td>personality changes, double or blurred vision, facial numbness,</td>
<td>body that has spread to the brain and spinal cord or just outside or adjacent to the CNS</td>
</tr>
<tr>
<td>trouble speaking, and sometimes seizures</td>
<td></td>
</tr>
<tr>
<td>Rash or itchy, red or purple lumps or nodules under the skin</td>
<td>Lymphoma of the skin</td>
</tr>
</tbody>
</table>
Table 2.1. Symptoms Commonly Found in Patients With Lymphoma *(continued)*

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Possible Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>“B symptoms” include fever and/or chills for no known reason, unexplained weight loss, and/or drenching night sweats that soak clothing and sheets</td>
<td>Increased levels of inflammatory chemicals in the blood, which are released by lymphoma cells or by the immune system reacting to the lymphoma cells</td>
</tr>
<tr>
<td>Severe or frequent infections</td>
<td>The body is less able to fight infection because of decreased numbers of white blood cells; depending on the type of white blood cell affected, this condition is called leukopenia, neutropenia, or granulocytopenia</td>
</tr>
<tr>
<td></td>
<td>Changes in the immune system due to low gamma globulin</td>
</tr>
</tbody>
</table>

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

**When Should a Patient Seek Medical Attention?**

Anyone who has an enlarged lymph node that does not go away within a few weeks and/or persistent symptoms should see a doctor to make sure that lymphoma or another serious condition is not present. A good rule of thumb is to seek medical attention if any of the symptoms listed in Table 2.1 last longer than two weeks, or sooner if the symptoms are harsh enough to impact a person’s daily life. Most patients with these symptoms do not have lymphoma, as diseases or conditions not related to lymphoma usually cause many of these symptoms.
What Does the Doctor Look For During the Visit?

There are no specific tests that doctors can use to routinely screen patients for NHL.

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

- Ask details about symptoms including duration, frequency, and intensity, in particular about any pain the patient is experiencing
- Measure blood pressure and pulse
- Listen to the heart and lungs
- Check the throat for enlarged tonsils
- Look for any physical signs of infection or any other cancers, especially on the skin
- Check for swollen lymph nodes under the chin, in the neck and tonsil area, above the shoulders, in the underarms, and in the groin
- Examine other parts of the body to see if there is swelling or fluid in the chest and/or abdomen that may be caused by swollen lymph nodes
- Examine the abdomen to see if the liver and/or spleen are enlarged and 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 signs they have uncovered during the examination, he or she will order other tests that can confirm the diagnosis.
These tests should include a complete blood count (CBC) and may also include specific laboratory tests, imaging tests (including scans), and a bone marrow evaluation. Depending on the type and location of the NHL, other tests may be required. However, no diagnosis of NHL can be established without appropriate tumor sampling to establish a pathologic diagnosis. These tests and procedures are discussed in more detail in Chapter 3.
Doctors need the results of various diagnostic tests to accurately determine if a patient has non-Hodgkin lymphoma (NHL). This chapter explains the purpose of these different tests and describes what to expect during and after these procedures.

**How Is NHL Diagnosed?**

To be sure of a diagnosis of NHL or any cancer, a biopsy is required. For NHL, an excisional biopsy to remove an entire lymph node or incisional biopsy to remove a portion of the diseased tissue, is the preferred method for making the diagnosis. Under certain circumstances, particularly if a lymph node is not easily accessible, a core needle biopsy may be performed. A fine needle aspirate is usually insufficient for an initial accurate diagnosis, but may be acceptable in certain situations of recurring lymphoma (see the section “What Is a Biopsy?” on page 36). A pathologist examines a sample from this biopsy under a microscope to see if it contains any lymphoma cells and, if possible, to identify the specific type of lymphoma.

The following tests may be used to confirm the NHL diagnosis:

- Bone marrow biopsy with or without aspiration
- Lymph node biopsy
- Complete blood count (CBC) with differential
- Blood smears
- Immunophenotyping by flow cytometry of the lymphocytes in the blood and lymph node
- Cytogenetics or molecular genetic test
Patients diagnosed with a complicated disease like NHL will be asked to undergo a variety of procedures for the initial diagnosis and work-up before treatment begins, during the course of treatment, and during the follow-up period. Before patients agree to a procedure, they should make sure that they understand the reasons for the procedure and what will be involved. Here is a list of questions patients may want to ask their doctor.

**Questions to Ask Before Having a Diagnostic Procedure**

- Why is this procedure necessary?
- What will the procedure tell us about my condition?
- Can the same information be obtained in another way?
- What is involved in doing this procedure?
- What are the possible risks, complications, and side effects?
- Where will I have the procedure done?
- Will I have to do anything to prepare for the procedure?
- How long will the procedure take? Will I be awake? Will I feel pain?
- How long will it take for me to recover from the procedure?
- Should anyone else be present when I have the procedure?
- Will I need someone to take me home afterward?
- When will I get the results?
- When will we discuss the results?
- Will my insurance cover the procedure?
- What will my out-of-pocket costs be?
- If I will be receiving a dye, are my kidneys healthy enough to handle it?
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 by a pathologist with a number of tests to establish a diagnosis. The information provided by this tissue sample is crucial to correctly diagnose the disease and decide on the best course of treatment.

A pathologist is a doctor who specializes in the diagnosis of diseases by studying the cells from a patient’s body fluids and tissue samples. A hematopathologist is a pathologist who has undergone additional training in the diagnosis of blood diseases by studying lymph nodes, blood, and bone marrow samples, and a lymphoma pathologist specializes in the diagnosis and classification of NHL and Hodgkin lymphoma. These pathologists are trained to recognize different cell types by looking at the shape and size of cells and how they are grouped in tissue samples.

In addition to routine pathology analyses, portions of biopsy samples will be used for other tests to confirm the diagnosis and to more accurately classify the specific subtype of lymphoma. Table 3.1 shows the three main types of biopsies used for the initial diagnosis of patients with lymphoma.
### Table 3.1. The Three Main Types of Biopsies

<table>
<thead>
<tr>
<th>Type of Biopsy</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Excisional or Incisional Biopsy</strong></td>
<td>This type of biopsy is generally considered the best 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 the pathologist can examine, which improves the accuracy of the diagnosis.</td>
</tr>
<tr>
<td></td>
<td>A surgeon cuts through the skin to remove an entire lymph node (excisional biopsy) or a large portion of a lymph node or other tissue (incisional biopsy).</td>
</tr>
<tr>
<td></td>
<td>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 laparoscopically (through a tube inserted in the body) or by performing more extensive surgery.</td>
</tr>
<tr>
<td><strong>Core Needle Biopsy</strong></td>
<td>This procedure is used when the lymph nodes are deep in the chest or abdomen or in other locations that are difficult to reach with excisional biopsy, or when there are medical reasons for avoiding an excisional or incisional biopsy.</td>
</tr>
<tr>
<td></td>
<td>A large needle is inserted into a lymph node suspected to be cancerous and a small tissue sample is withdrawn using a syringe attached to the needle.</td>
</tr>
<tr>
<td></td>
<td>A needle biopsy can be done under local anesthesia and stitches are usually not required.</td>
</tr>
<tr>
<td></td>
<td>Sometimes the material collected may not be adequate for diagnosis and a subsequent excisional or incisional biopsy may be necessary.</td>
</tr>
<tr>
<td></td>
<td>Often the core needle biopsy will be directed by an imaging test, such as an ultrasound, computed tomography (CT) scan, or positron emission tomography (PET) scan.</td>
</tr>
</tbody>
</table>
Table 3.1. The Three Main Types of Biopsies (continued)

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Description</th>
</tr>
</thead>
</table>
| Fine Needle Aspirate (FNA) Biopsy | - As its name implies, this procedure is performed with a very thin needle (smaller than that used for a core needle biopsy).  
- Because of the small needle size, the sample will only contain scattered cells without preserving how the cells are actually arranged in the lymph node. Therefore, this test cannot provide enough information for a precise diagnosis.  
- An FNA biopsy is most often used to check for return of the disease (relapse) and is not adequate for a definitive initial diagnosis. |

After a tissue sample has been removed, it is examined by a pathologist who develops a report. An oncologist (doctor specialized in treating patients with cancer) or hematologist (doctor specialized in treating patients with blood cancers and other blood disorders) then uses this report, along with results of other diagnostic tests, to confirm a diagnosis. A pathologic diagnosis and accurate classification of specific lymphoma types can sometimes be difficult to make. If the pathologist’s interpretation of the biopsy is uncertain, the report should be reviewed by an expert hematopathologist or a pathologist who specializes in lymphoma. 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 bones where blood cells are generated. A bone marrow biopsy involves removing a small amount of bone marrow from inside a bone. The bone marrow is then examined 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 inserted into a bone. A bone marrow biopsy or aspiration is not typically used for initial diagnosis in the vast majority of cases but is commonly used to determine if the NHL has spread to the bone marrow. A positive result establishes the presence of Stage IV...
Understanding Non-Hodgkin Lymphoma

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 53).

**What Is a Complete Blood Count With Differential Test?**

For a CBC with differential test, samples of blood are examined to find out the following:

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

The results from the CBC with differential test will assist the doctor in determining a diagnosis of NHL. The CBC with differential test is often repeated during the course of treatment to help determine how well the treatment is working against the cancer.

**What Is Hematopathology?**

Hematopathology is the study of blood, lymph node, and bone marrow samples to identify disease. Doctors who have undergone special training in this area (hematopathologists) interpret these studies. These specialists identify and classify the cancer cells by looking at their shape and size and how they are grouped in samples from lymph nodes and bone marrow in conjunction with additional tests, such as immunophenotyping, cytogenetic analysis, and/or molecular studies.

**What Is Immunophenotyping?**

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

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

| **Immunohistochemistry (IHC)** | Thin slices of the biopsy sample (or thin layers of fluid) are treated with sets of antibodies that recognize different 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 antibody sticks to the marker.  
  The pathologist identifies and counts the number of cells that are highlighted by color (meaning that they are positive for the marker) with each of the different antibodies.  
  The results from IHC can be used to distinguish between different types of lymphoma, other cancers, or some other diseases. |
| **Flow Cytometry** | Cells from the biopsy sample are placed in a liquid solution and treated with sets of antibodies that recognize different antigens found in different types of lymphoma cells.  
  The cell-antibody mixture is injected into an instrument called a flow cytometer. This machine uses laser beams to sense the different colors the cells emit from the different antibodies attached to them. This information is measured and analyzed by a computer and interpreted by a hematopathologist. |
What Is Cytogenetic Analysis?

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

In cytogenetic analysis, chromosomes from cancer cells are examined under a microscope to check that there are not too few or too many chromosomes, or for the presence of other abnormalities on the chromosomes. It usually takes two to three weeks to obtain results from cytogenetic testing because a sufficient number of cancer cells must be grown in the laboratory to get enough genetic material for the analysis.

The results of the cytogenetic analysis can also help distinguish between different types of NHL or help in making treatment decisions.
What Are Types of Chromosome Abnormalities?

One type of chromosomal abnormality found in some NHL types is called a *translocation*, which occurs when part of a chromosome breaks off from its normal location and becomes attached to another chromosome, as shown in the figure below.

**TRANSLOCATION**

Two different chromosomes exchange portions of their genetic material

Chromosome 14  
Bcl2

Chromosome 18  
Translocation
Another type of chromosomal abnormality is called a *deletion*, which happens when part of a chromosome is missing. This is written, for example, as del(13q), noting there was a deletion in the long arm of chromosome 13 (see figure below).

**DELETION**

A piece of a chromosome is missing

- **Normal Chromosome**
- **Chromosome With a Deletion**

Deleted section of the chromosome
As shown in the image on the right of the figure below, chromosomal amplification occurs when portions of chromosomes are repeated resulting in excessive copies of one or more genes. This finding can lead to abnormal levels of expression of a protein that can influence the growth of a lymphoma.

**AMPLIFICATION**
A piece of the chromosome is duplicated

Another common chromosomal abnormality is called trisomy, which indicates the presence of an extra copy of a chromosome.

This figure on the next page shows the chromosomes as they look during a phase of the cell cycle called metaphase, which occurs just before a cell divides. In metaphase chromosomes, the DNA of the chromosomes is tightly packaged or condensed and two pairs of chromosomes are joined together.
TRISOMY
Metaphase Chromosome Pairs

Trisomy (Three Chromosomes)

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 damage to the genetic information of the lymphoma cells in the patient's body. The main types of additional genetic tests used are shown in Table 3.3.

Table 3.3. Types of Additional Genetic Tests

<table>
<thead>
<tr>
<th>Method</th>
<th>Description</th>
</tr>
</thead>
</table>
| Fluorescence In Situ Hybridization (FISH) | - FISH uses fluorescent chemicals to specifically attach to certain parts of chromosomes to show the presence of translocations and other large abnormalities.  
  - FISH can be performed on blood, lymph node, or bone marrow samples, and test results are usually available within a few days (quicker than cytogenetic testing). |
| Polymerase Chain Reaction (PCR) | - PCR is a test that is used to measure specific genes (i.e., DNA) that cannot be seen under a microscope.  
  - PCR tests can be done on a very small quantity of cells, and it usually takes about one week to get these results. |
| DNA Sequencing                | - Some abnormalities in tumor growth occur because of changes in the sequence of a specific gene or set of genes.  
  - These findings can help define the type of tumor, determine prognosis, or influence treatment choice.  
  - An individual gene may be sequenced or a panel of known critical genes can be sequenced at one time. |
It is important for patients to know that interpreting diagnostic tests should be done between the doctor and his or her patient. Here is a list of some cautions about interpreting diagnostic tests.

**Cautions About Interpreting Diagnostic Tests**

- Biopsies, and in some instances peripheral blood immunophenotyping, are the only definitive tests for NHL.
- Some tests can be reported as “normal” even though NHL may be present.
- Some tests may be reported as “abnormal” even though NHL is not present.
- Other conditions can produce signs and symptoms similar to NHL.
- The interpretation of tests, 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; additional biopsies may be needed to clarify the results.
- Some patients like to review their written reports; when doing so, it is important for the patient to carefully review the findings with their doctor.
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 work-up studies are needed to see if and how much the disease has spread to other parts of the body. Doctors will use these test results to determine the state of advancement, or stage, of a patient’s disease. Other tests will check how the disease has affected a patient’s overall health and major organ functions.

Grade of disease refers to the number of large cells (centroblasts) seen in the high power field of a microscope when lymphoma is being diagnosed. Large cells are more aggressive than small cells. Grade 1 disease corresponds with zero to five centroblasts per field, grade 2 is associated with six to 15 centroblasts per field, and grade 3 is diagnosed when more than 15 centroblasts can be seen per field. Staging of disease is discussed in detail later in this booklet and refers to how far the disease has spread within the body.

Together, all of these tests will provide the information needed to help patients and their doctors decide on the best course of treatment. This chapter will help you understand the reason 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, and many of these tests may also be repeated during the course of treatment.

- Physical examination with special attention to the size of the lymph nodes, liver, and spleen
- A determination of general health status (also called *performance status*) to see how well a patient feels and how well they can carry out their normal daily activities (such as getting washed and dressed, going to work, and doing chores); this topic is discussed further in Chapter 5
- Presence or absence of fever, night sweats, and weight loss (these are also called “B symptoms”)
- Complete blood count (CBC) with differential and platelets
- Comprehensive metabolic panel with lactate dehydrogenase (LDH)
- Testing for signs of infection with hepatitis viruses and other viruses
- Measurement of beta-2 microglobulin (B2M) level
- Computed tomography (CT) scan of the neck, chest, abdomen, and pelvis
- Positron emission tomography-CT (PET-CT) scan; magnetic resonance imaging (MRI) when needed
- Excisional, incisional, or core needle biopsy
- Bone marrow aspiration and/or biopsy
- Lumbar puncture and/or MRI brain imaging

What Is the Purpose of a Complete Blood Count Test?

Doctors will test a patient’s blood to measure the quantity of the different types of cells (red blood cells, white blood cells, and platelets). This information can help determine how advanced the lymphoma is. These blood tests will most likely include a CBC, differential (to measure the relative amounts of different types of white blood cells), and platelets.
What Is the Purpose of the Lactate Dehydrogenase and Beta-2 Microglobulin Test?
Some proteins can be detected in the blood that have been associated with the overall prognosis with therapy. One important “prognostic marker” is the serum lactate dehydrogenase (LDH). Fast-growing lymphoma can cause very high LDH levels in the blood; this level is measured by a simple blood test. Beta-2 microglobulin (B2M) is another important prognostic marker for some lymphomas and is measured by a simple blood test.

What Is the Purpose of Testing For Hepatitis and HIV?
Depending on the type of lymphoma, the blood may also be tested for signs of infection with hepatitis B virus (HBV) or hepatitis C virus (HCV). If a concurrent hepatitis B infection is identified, treatment would be given to reduce the risk of liver injury caused by reactivation of the viral infection. In some cases, patients found to have HCV can have treatment for the disease, which in turn may reduce the lymphoma (especially a form of lymphoma called splenic marginal zone lymphoma [SMZL]). All patients with lymphoma should also be tested for the human immunodeficiency virus (HIV).

What Is the Purpose of Immunoglobulin Testing?
A test for serum immunoglobulins may also be performed to look for the presence of certain immunoglobulins (a type of protein) that can be elevated or depressed in certain types of NHL.
What Is a Comprehensive Metabolic Panel?
A comprehensive metabolic panel measures the amount of different chemicals in the blood that will show if the NHL is affecting any of the main organs in the body. The comprehensive metabolic panel usually includes 14 specific tests that measure liver and kidney function, electrolytes, acid/base balance, and the levels of blood sugar and different blood proteins. Calcium, magnesium, potassium, and sodium are some of the electrolytes found in the body; abnormal levels of electrolytes can make a person sick.

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

What Types of Imaging Tests May Be Used?
A doctor will most likely order imaging tests to help find areas of the body where there may be cancer, to learn how far the cancer has spread, and to determine how well the treatment is working later on. Most of these tests are painless and require no anesthetic. Several types of imaging procedures described in Table 4.1 may be needed to thoroughly evaluate the extent of disease.
### Table 4.1. Types of Imaging Tests

<table>
<thead>
<tr>
<th>Computed Tomography (CT) Scan</th>
<th>Magnetic Resonance Imaging (MRI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
<td>Like a CT scan, an MRI takes images from different angles around the body, but an MRI does not use radiation (X-rays) like a CT scan; instead, it uses magnets and radiofrequency waves.</td>
</tr>
<tr>
<td>Patients with NHL often have CT scans of the neck, chest, abdomen, and pelvis to find out how many lymph nodes are involved, how large they are, and whether internal organs are affected by the disease.</td>
<td>An MRI can provide important information about tissues and organs, particularly the nervous system, which is not available from other imaging techniques.</td>
</tr>
<tr>
<td>The amount of radiation exposure during a CT scan varies depending on the area scanned. Most CT scans are of little risk to the patient. 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 abnormal areas that may be present in the body.</td>
<td>Because this testing technique works well to obtain clear images of the bones, brain, and spinal cord, an MRI may be ordered if a doctor wants to see whether the lymphoma has spread to these areas.</td>
</tr>
<tr>
<td>MRI scans cannot replace CT scans because they do not image lymph nodes as well as CT scans do.</td>
<td></td>
</tr>
</tbody>
</table>

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Table 4.1. Types of Imaging Tests (continued)

<table>
<thead>
<tr>
<th>Positron Emission Tomography (PET) Scan</th>
<th>Reasons for PET scans:</th>
</tr>
</thead>
<tbody>
<tr>
<td>A PET scan evaluates NHL activity in all parts of the body.</td>
<td>A PET scan evaluates NHL activity in all parts of the body.</td>
</tr>
<tr>
<td>Radioactive fluorodeoxyglucose (a type of sugar) is injected into the body. A positron camera is then used to detect the radioactivity and produce cross-sectional images of the body.</td>
<td>Radioactive fluorodeoxyglucose (a type of sugar) is injected into the body. A positron camera is then used to detect the radioactivity and produce cross-sectional images of the body.</td>
</tr>
<tr>
<td>PET scans help distinguish active tumors from scar tissue and may be used to assess a patient’s response to treatment.</td>
<td>PET scans help distinguish active tumors from scar tissue and may be used to assess a patient’s response to treatment.</td>
</tr>
<tr>
<td>While CT scans show the size of a lymph node, PET scans show if the lymph node is active (still has disease). PET scans rely on the fact that tumor cells metabolize sugar faster than normal cells, resulting in more “uptake” on the scan image. PET scans are therefore considered to be “functional imaging tests.” PET and CT scans are now combined into one test (PET-CT).</td>
<td>While CT scans show the size of a lymph node, PET scans show if the lymph node is active (still has disease). PET scans rely on the fact that tumor cells metabolize sugar faster than normal cells, resulting in more “uptake” on the scan image. PET scans are therefore considered to be “functional imaging tests.” PET and CT scans are now combined into one test (PET-CT).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Chest X-Ray</th>
<th>Reasons for Chest X-rays:</th>
</tr>
</thead>
<tbody>
<tr>
<td>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.</td>
<td>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.</td>
</tr>
<tr>
<td>Findings on a chest X-ray may indicate whether the disease is “bulky” (tumor greater than 10 centimeters) or more than one-third of the diameter of the chest wall.</td>
<td>Findings on a chest X-ray may indicate whether the disease is “bulky” (tumor greater than 10 centimeters) or more than one-third of the diameter of the chest wall.</td>
</tr>
</tbody>
</table>

Why Might Another Type of Biopsy Be Needed?
Once the diagnosis is made, the doctor may order other types of biopsies for additional pathology studies and other tests to see if and how the disease has spread to other parts of the body (see Table 4.2).
### Table 4.2. Other Types of Biopsies

<table>
<thead>
<tr>
<th><strong>Bone Marrow Aspiration and Biopsy</strong></th>
<th><strong>Lumbar Puncture (Spinal Tap)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone marrow is the soft, spongy material found inside our bones. NHLs can spread to the bone marrow or start in the bone marrow.</td>
<td></td>
</tr>
<tr>
<td>This procedure may be done to determine if the lymphoma has spread to the bone marrow.</td>
<td></td>
</tr>
<tr>
<td>For the aspiration part of this procedure, the doctor cleans and numbs the skin over the hip, inserts a thin, hollow needle into the bone, and removes a small amount of liquid from the bone marrow.</td>
<td></td>
</tr>
<tr>
<td>For the biopsy part of this procedure, a sample of the bone is withdrawn intact for pathologic analysis.</td>
<td></td>
</tr>
<tr>
<td>Sometimes, light general anesthesia is used for this procedure.</td>
<td></td>
</tr>
<tr>
<td>骨髓穿刺和活检</td>
<td></td>
</tr>
<tr>
<td>这种程序可以用于确定淋巴瘤是否扩散到骨髓。</td>
<td></td>
</tr>
<tr>
<td>对于穿刺部分的程序，医生会在臀部皮肤清洗和麻醉后，插入一根细的空心针，从骨髓中取出少量液体。</td>
<td></td>
</tr>
<tr>
<td>对于活检部分的程序，从骨中取出一块完整的样本用于病理分析。</td>
<td></td>
</tr>
<tr>
<td>有时，轻度局部麻醉用于这种程序。</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Pleural or Peritoneal Fluid Sampling</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>This procedure is used to determine if the lymphoma has spread to the lining of the chest and the abdomen, where it can cause liquid to accumulate.</td>
</tr>
<tr>
<td>The doctor will order this test only for patients with certain types of lymphoma or those who have symptoms suggesting that the disease has reached the brain.</td>
</tr>
<tr>
<td>The doctor inserts a thin needle into the lower back after the area has been numbed with a local anesthetic. A small needle is used to remove a sample of fluid that will be sent to a laboratory for analysis.</td>
</tr>
<tr>
<td>The liquid is called <em>pleural fluid</em> when found inside the chest and <em>peritoneal fluid</em> when found inside the abdomen.</td>
</tr>
<tr>
<td>胸或腹腔液采样</td>
</tr>
<tr>
<td>这种程序用于确定淋巴瘤是否扩散到胸腔和腹腔的内膜，这些内膜可能引起液体积聚。</td>
</tr>
<tr>
<td>医生只会为某些类型的淋巴瘤患者或有疾病已扩散至大脑症状的患者进行此项测试。</td>
</tr>
<tr>
<td>医生在麻醉局部区域后，将细针插入下背部，用小针头抽取样本并送实验室分析。</td>
</tr>
<tr>
<td>胸腔内的液体称为<em>pleural fluid</em>，腹腔内的液体称为<em>peritoneal fluid</em>。</td>
</tr>
</tbody>
</table>
Why Evaluate Heart Function?
Some treatments, like doxorubicin (Adriamycin), can impact heart function. However, it is important for the doctor to establish baseline heart function for a number of treatments in lymphoma to make sure that the patient’s body can withstand treatment.

Heart function is typically evaluated by one of two tests. A **MUGA** (multi-gated acquisition) scan is an imaging test that looks at how well the heart muscle is working. MUGA scans may be done when patients are resting or exercising, depending on what their doctor wants to assess.

Alternatively, the doctor may order a two-dimensional echocardiogram (ECHO). This test can also evaluate the function of the cardiac muscle and may be done while the patient is resting or after exercise. It has the additional benefit of providing information about the heart valves.

Why Might a Lung Function Test Be Needed?
Lung function tests are done to make sure that the body can withstand treatment with certain lymphoma drugs that may stress a patient’s lung function (for example, bleomycin and cyclophosphamide). A doctor may order breathing tests (pulmonary functions tests [PFTs]) before beginning treatment and at other times during treatment to make sure that a patient’s lungs are still working properly.

How Is NHL Staged?
Staging is used to describe how widely the cancer has spread in patients with NHL. The Ann Arbor staging system has been used for staging NHLs other than CLL. Although the older staging system is still in use, a modification of the Ann Arbor staging system—the Lugano Classification—was proposed in 2014, which is shown in the following figure. There are two main classifications (limited and advanced disease) and four stages of lymphoma designated by the Roman numerals I through IV. Stages I and II are considered limited disease, although Stage II can be considered advanced in some cases. Stages III and IV are considered advanced disease.
Staging is not to be confused with grade. These are not the same. Grade is the number of large cells seen under the microscope.

STAGING OF NHL (Lugano Classification)

Stage I:
• Single lymph node or group of adjacent nodes

Stage II:
• Two or more groups of lymph nodes on the same side of the diaphragm

Stage III:
• Lymph nodes on both sides of the diaphragm
• Lymph nodes above the diaphragm with spleen involvement

Stage IV:
• Widespread disease in lymph nodes and organ involvement
Stage II disease that is also called *bulky*, meaning that the patient has a tumor greater than 10 centimeters (4 inches) wide depending on the type of NHL, can sometimes be considered advanced disease.

The newer staging system is similar to the previous Ann Arbor staging system, except that the “A” and “B” designations are no longer used except for the staging of Hodgkin lymphoma (HL).

Doctors use the stage of disease, test results, and/or other factors to help decide the best time to begin treatment and what treatments are likely to be the most effective for each patient.

Being diagnosed with advanced NHL is common in most patients. Keep in mind that these advanced stages can be successfully treated.

The Ann Arbor staging system is used to stage SLL but not CLL. Rather, the Rai staging system is commonly used in the United States to stage CLL, and 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 patient booklet *Understanding CLL/SLL: A Guide for Patients, Survivors, and Loved Ones*. 
Part 2 — Treatment of Non-Hodgkin Lymphoma

Chapter 5: What to Know Before Starting Treatment

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

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 and rely on.
- Learn about the disease and treatment options.
- Find medical care that meets your needs.
- Find emotional and social support.
- Understand 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).
Who Will Plan and Carry Out the Treatment?
Treatment is usually overseen by a medical oncologist or hematologist who specializes in cancer and/or blood diseases, respectively. Depending on the patient’s healthcare needs, the doctor may refer him or her to work with specialists, such as a surgical oncologist and a radiation oncologist. The doctor may suggest a second opinion at a cancer center with particular expertise in that type of lymphoma or for participation in a clinical trial.

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

What Is a Prognosis?
*Prognosis* is the medical term that doctors use for predicting how the disease will progress and the likelihood for recovery, which is often one of the first 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 also gives guidance on the kinds of treatments that have been most successful in treating that NHL type.

While doctors and scientists have learned a lot about NHL, it is not always possible to predict which specific treatments are most likely to work in an individual patient.

*Keep in mind that no two patients are alike and that statistics from large groups of people cannot accurately predict what will happen to a specific individual patient.* The doctor most familiar with the patient’s situation is in the best position to help interpret these statistics and understand if and how they may apply to a patient’s
particular situation. Also be aware that most published statistics on treatment outcomes do not reflect the benefits of the most recent new therapeutics.

**What Are Prognostic Factors?**
The characteristics that help predict a patient’s prognosis are called *prognostic factors*. Favorable prognostic factors tend to be associated with a better outcome, while adverse prognostic factors tend to be associated with a worse outcome. Some prognostic factors only apply to a particular type of lymphoma, whereas other factors, like the ones found in the International Prognostic Index, can be applied more generally.

Keep in mind that prognostic factors are generated by studying the outcomes of large groups of patients. **No two patients are alike. It is impossible to accurately predict what will happen to a specific patient. Patients should talk with their doctor to understand if and how prognostic factors might apply to their specific situation.**

**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 (APLES): age, performance status (see next page), lactate dehydrogenase (serum), extra-nodal progression, and stage of disease.

**Table 5.1. International Prognostic Index**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Good Prognostic Factor</th>
<th>Poor Prognostic Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>60 years or younger</td>
<td>Older than 60 years</td>
</tr>
<tr>
<td>Stage</td>
<td>I or II</td>
<td>III or IV</td>
</tr>
<tr>
<td>Location of the lymphoma</td>
<td>Only in lymph nodes or in only one area outside of the lymph nodes</td>
<td>In two or more organs outside of lymph nodes</td>
</tr>
<tr>
<td>Performance status</td>
<td>Able to function normally</td>
<td>Needs help with daily activities</td>
</tr>
<tr>
<td>Serum lactate dehydrogenase</td>
<td>Normal</td>
<td>Above normal</td>
</tr>
</tbody>
</table>
Based on the success of the IPI, new prognostic indexes have been developed for follicular lymphoma (FL; FLIPI) and mantle cell lymphomas (MIPI).

What Is Performance Status?

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

Table 5.2 The Eastern Cooperative Oncology Group PS Scale

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Fully active; able to carry on all pre-disease activities without restriction.</td>
</tr>
<tr>
<td>1</td>
<td>Cannot perform taxing physical activities, but can move around (ambulatory) and carry out light work (such as light house work) or do things that can be done while sitting (such as office work).</td>
</tr>
<tr>
<td>2</td>
<td>Can move around and take care of oneself, but unable to do any work. Up and about for more than half of awake hours.</td>
</tr>
<tr>
<td>3</td>
<td>Can only partially take care of oneself. Confined to bed or chair for more than half of awake hours.</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled. Cannot take care of oneself. Completely confined to bed or chair.</td>
</tr>
</tbody>
</table>

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:

- The type of NHL
- The stage and location of the lymphoma (see page 56)
- The presence or absence of lymphoma symptoms
- How rapidly the lymphoma is growing (whether it is an indolent or aggressive lymphoma)
- Levels of lactate dehydrogenase (LDH) in the patient’s blood; higher levels of LDH or beta-2 microglobulin suggest the lymphoma may be in a more advanced stage or an aggressive type. (Patients with normal levels of these proteins may have better outcomes than those with higher levels.)
- A patient’s overall health, age, and performance status
- A patient’s prognostic factors (see page 60)
- A patient’s preferences and goals for treatment
- Whether the treatment is the first the patient has received or if the disease has returned after prior therapy (relapsed)
- Availability of a clinical trial

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

**Questions to Ask Before Treatment Begins**
- What is my exact diagnosis? May I have a copy of the report from the pathologist?
- What is the stage of my disease? Where is the disease located?
- What are my prognostic factors?
- What are my treatment choices? Which do you recommend for me? Why?
Questions to Ask Before Treatment Begins
(continued)

- What is a clinical trial? Are clinical trials available that are studying new treatments? Would a clinical trial be appropriate for me? How would I benefit?

- 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? How often will I need to be tested?

- What are the risks and possible side effects of each treatment? Can these side effects be prevented or controlled?

- What should I do to take care of myself during treatment?

- Are there any late or long-term side effects I should be aware of? Will treatment impact my ability to have children?

- 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 while I undergo treatment?

- Will I be able to drive or take public transportation after my treatment?

- Should I take care of other medical or dental issues before I start treatment?

- Do I need radiation?

- Will I be able to work during treatment?

- How often will I need a checkup?

- How much will the treatment cost? Will my insurance cover it?
When to Get a Second Opinion

Before starting any type of treatment, a patient may consider getting a second opinion—especially if some characteristics of the diagnosis are complicated or uncertain. The purpose of the second opinion is not to question the doctor’s expertise but to make sure the suggested treatment plan is reasonable and optimal for the patient’s particular case and evaluate alternative treatment including clinical trials (see Part 5, Chapter 10 for more information).

Most doctors will be supportive and helpful if patients tell them they would like to get a second opinion. Patients should ask the doctor if it would be okay to briefly delay the start of treatment to provide the time needed to get a second opinion. Keep in mind that some insurance programs require second opinions; others may provide coverage if a patient or doctor requests it.

It is also potentially valuable for patients to get a second opinion regarding the pathology. The pathology of NHL is often complex and some pathologists may have limited experience in the specialized form of pathology called hematopathology. It is advisable to have the pathology reviewed by an expert hematopathologist with extensive experience in lymphoma.

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

Getting a Second Opinion

- Some hematologists/oncologists/lymphoma specialists associated with medical schools or cancer centers may provide a consultation and be willing to work together with a local oncologist to provide possible treatment and follow-up care.
- As part of the second opinion, another pathologist must review the tissue and blood samples to confirm the diagnosis. Locate a pathology group with experience diagnosing patients with lymphoma.
Getting a Second Opinion (continued)

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

To identify lymphoma specialists to contact for a second opinion:

- Ask your current doctors, family members, other patients, friends, and coworkers.

- Contact the patient referral service at your local hospital and at the nearest hospital associated with a medical school; many hospitals have online directories that can be searched to find a specialist in your area.

- Visit the Lymphoma Research Foundation (LRF) website at www.lymphoma.org or contact LRF directly by phone (800-500-9976) or email (helpline@lymphoma.org).

- 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 an interest in lymphoma.

- Visit the National Cancer Institute (NCI) web page at http://www.cancer.gov/researchandfunding/extramural/cancercenters/find-a-cancer-center to identify the nearest NCI-designated cancer center, or call (800-4-CANCER or 800-422-6237) to find out about their lymphoma specialists.

- 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 will probably make a referral to a specialist—likely 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, and most physicians who treat all of these diseases are certified in one or the other or both.

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

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 cancer in general, and NHL in particular?
- How many patients with this type of NHL are being treated here now?
- Does the doctor and/or center participate in clinical trials?
Patients enrolled in a managed care program may have limited choices. However, patients have the right to choose another healthcare team if they are not entirely satisfied with their first consultation visit. It is important that patients are comfortable with their healthcare team. They should talk with other patients and caregivers about their experiences and ask them if they would recommend their doctor and healthcare team. Also, patients and caregivers who are not satisfied with their healthcare team should 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. Open communication with the healthcare team can help patients and caregivers better learn about what the prescribed treatment regimen is, how it works, what tests are involved, and what side effects and complications may be associated with it.

Questions to Ask to Select the Best Medical Team

- 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?
- What arrangements are made for medical assistance after hours and on weekends, in case of an emergency?
- 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 you coordinate my cancer care with my other doctors?
A good first step for patients is to write down all questions that come to mind. Before meeting with a doctor or nurse, for the first time or for follow-up visits, patients should consider organizing questions into a list to bring to the visit. Since time with doctors or nurses 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 he or she may see some that are more important than the patient realizes.

Patients should consider having a family member or close friend accompany them to the doctor’s office or clinic 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 to record the answers. Patients should ask the doctor or nurse for permission before recording any conversations.

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

Although family members are often very concerned about their loved one and want information concerning his or her care, confidentiality rules prohibit doctors from giving out information to anyone without the patient’s expressed permission. For efficiency, designate one family member as the family contact. The patient must remember to specifically tell the doctor the identity of the primary family contact. Most importantly, it is essential for patients to have the names and addresses of the physicians involved in their care so that the oncologist or hematologist will be able to communicate with them regularly.

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

At home

- Keep a journal of your symptoms to help you remember the details you want to discuss with your doctor during your next office visit.
- Ask your doctor or nurse which symptoms need to be communicated immediately to them and which can wait for your next visit.
- Make a list of questions you want to ask your doctor. However, if the questions are urgent, do not wait for the next visit; call the doctor’s office to discuss your concerns.
- Review patient portals for contacting your healthcare team. They may provide secure email contact, educational materials, allow patients to check benefits and coverage, schedule non-urgent appointments, and order prescription refills.
- Download the free *Focus on Lymphoma* mobile application (app) from LRF to help you plan appointments, keep track of medications and blood work, and document treatment side effects (www.FocusOnLymphoma.org).

At your next doctor’s visit

- Bring your symptom journal and list of questions to discuss with your doctor or nurse.
- Ask a family member or friend to come with you to provide emotional support and take notes.
- Do not be afraid to ask questions if you do not understand something. Your doctor will want to know if you are uncertain or confused and will be happy to address your concerns.
- Inquire about whom should be contacted for specific questions or weekend support and how you can reach them.
- Inquire whether members of your healthcare team communicate electronically (by email, patient portals, etc.). Please note that there could be privacy issues.
Communicating With Your Doctors (continued)

- Make sure you understand the next steps in your care before you leave the doctor’s office.
- Request written information that you can take home to help you.

How to Be a Self-Advocate

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

It is important 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 there is a feeling the team is not a good match, patients should ask for a referral to a different healthcare team.

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

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

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

**Self-Advocacy**

- Do not be afraid to ask your doctors or nurses questions about your care.
- Learn more about NHL by asking your doctor for information and visiting reliable websites, such as LRF at www.lymphoma.org.
- Take advantage of counseling, support groups, nutritional counseling, fitness classes, expressive arts, and other services offered at your doctor’s office, cancer center, or hospital.
- Consider joining the Lymphoma Support Network, a nationwide buddy program that matches patients and caregivers with people who have had similar experiences. For information about the program, call (800) 500-9976 or email support@lymphoma.org.
In this chapter, you will learn about the most common therapies currently used in the treatment of patients with 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 booklet went to print. Read Chapter 11 to learn more about new treatments under investigation.

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

There are also small but important differences in the cancer cells found in different patients diagnosed with the same type of cancer. Because of these differences, a treatment that may work very well in one patient may not have the same positive effect in another.
What Types of Treatments Are Used in Patients With NHL?

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

- Watchful waiting (no treatment given) in which the patient is closely monitored to see if/when treatment should be started
- Drug therapy, which includes one or more of the following types of drugs:
  - Chemotherapy, which affects general cell growth and proliferation
  - Monoclonal antibodies, which can specifically attack lymphoma cells
  - Targeted or biologic therapies, which affect special characteristics or internal workings of lymphoma cells
  - Immunomodulatory drugs, which interact with the immune system to encourage the destruction of lymphoma cells
- Radiation therapy, which uses high-energy radiation to kill lymphoma cells
- Stem cell transplantation

These types of therapies are described in detail throughout this chapter.
What Is Watchful Waiting?

With the *watchful waiting* approach, patients do not receive any anti-lymphoma treatments, but their health and disease are monitored through regular checkup visits and follow-up evaluation procedures, such as laboratory and imaging tests. 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 watchful waiting for select patients with *indolent* (slow-growing) lymphoma or patients with no significant symptoms from their disease. This approach may be started after the initial diagnosis or after *relapse* (disease returns after treatment), depending on the situation. Active treatment is started if the patient begins to develop lymphoma-related symptoms or if there are signs that the disease is progressing.

Watchful waiting is not a treatment option for patients with *aggressive* (fast-growing) NHL or Hodgkin lymphoma. Usually, treatment for these patients should start as soon as possible after diagnosis.

**Questions to Ask Before Starting Watchful Waiting**

- What happens if I choose watchful waiting and then change my mind?
- Will the disease be harder to treat later?
- How often will I have checkups?
- Between checkups, what symptoms and other problems should I report?
What Is Chemotherapy?
Chemotherapy drugs work against general characteristics of cancer cells, such as their tendency to grow and multiply very quickly. Depending on the drug, patients may have to swallow a pill or receive a liquid infused directly into a vein (intravenous infusion or IV). Sometimes, chemotherapy drugs have to be injected in the space around the spinal cord using a lumbar puncture.

During chemotherapy, patients receive the drug(s) at certain intervals, such as once every 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. These chemotherapy drugs are given in a specific order (schedule) during certain days of each treatment cycle—this is called a treatment regimen. The purpose of combining drugs is to increase how effectively they damage or kill cancer cells.

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

Common Chemotherapy Regimens For NHL
The mainstay combination chemotherapy regimen has been and continues to be CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), usually combined with rituximab (Rituxan; R-CHOP), when B-cell lymphomas are treated. More recently other regimens have been substituted for CHOP, some of which are shown in Table 6.1.
While CHOP is a less consistent mainstay for T-cell lymphomas, histone deacetylase (HDAC) inhibitors (belinostat, romidepsin, vorinostat) and pralatrexate are playing an increasing role in T-cell disease.

Many regimens can also include the monoclonal antibody rituximab (abbreviated by the letter “R”), which is usually shown at the beginning or end of the regimen abbreviation (such as R-CHOP). Further discussion of rituximab is located on page 83. Table 6.1 lists the common chemotherapy regimens given for NHL. This list is subject to change as new approvals are made by the FDA.

Table 6.1. Common Chemotherapy Regimens For NHL

<table>
<thead>
<tr>
<th>Drug or Regimen Abbreviation</th>
<th>Generic Name of Drugs (Brand Name)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>Bendamustine (Treanda)</td>
</tr>
<tr>
<td>C</td>
<td>Cyclophosphamide (Clafen, Cytoxan, Neosar)</td>
</tr>
<tr>
<td>Chl</td>
<td>Chlorambucil (Leukeran)</td>
</tr>
<tr>
<td>Cisplatin + RT + VIPD</td>
<td>Cisplatin (Platinol, Platinol-AQ)</td>
</tr>
<tr>
<td></td>
<td>Radiation therapy</td>
</tr>
<tr>
<td></td>
<td>VP16 (Etoposide)</td>
</tr>
<tr>
<td></td>
<td>Ifosfamide (Ifex)</td>
</tr>
<tr>
<td></td>
<td>Dexamethasone (Decadron, Dexasone)</td>
</tr>
<tr>
<td>CVP (COP)</td>
<td>Cyclophosphamide (Clafen, Cytoxan, Neosar)</td>
</tr>
<tr>
<td></td>
<td>Vincristine (Oncovin, Vincasar PFS)</td>
</tr>
<tr>
<td></td>
<td>Prednisone (Deltasone)</td>
</tr>
<tr>
<td>CHOP</td>
<td>Cyclophosphamide (Clafen, Cytoxan, Neosar)</td>
</tr>
<tr>
<td></td>
<td>Doxorubicin/hydroxydaunorubicin (Adriamycin, Rubex)</td>
</tr>
<tr>
<td></td>
<td>Vincristine (Oncovin, Vincasar PFS)</td>
</tr>
<tr>
<td></td>
<td>Prednisone (Deltasone)</td>
</tr>
</tbody>
</table>
Table 6.1. Common Chemotherapy Regimens For NHL (continued)

<table>
<thead>
<tr>
<th>Drug or Regimen Abbreviation</th>
<th>Generic Name of Drugs (Brand Name)</th>
</tr>
</thead>
</table>
| CODOXM-IVAC                 | Cyclophosphamide (Clafen, Cytoxan, Neosar)  
                               | Vincristine (Oncovin, Vincasar PFS)  
                               | Doxorubicin (Doxil)  
                               | Cytarabine (Cytosar-U, Tarabine PFS)  
                               | Methotrexate (Otrexup, Rheumatrex, Trexall)  
                               | Ifosfamide (Ifex)  
                               | VP16 (Etoposide) |
| DHAP                        | Dexamethasone (Decadron, Dexasone)  
                               | Cytarabine (Cytosar-U, Tarabine PFS)  
                               | Cisplatin (Platinol, Platinol-AQ) |
| DICE                        | Dexamethasone (Decadron, Dexasone)  
                               | Infusional ifosfamide (Ifex)  
                               | Cisplatin (Platinol, Platinol-AQ)  
                               | Infusional etoposide (Etopophos, Toposar, Vepesid) |
| DRC                         | Dexamethasone (Decadron, Dexasone)  
                               | Rituximab (Rituxan)  
                               | Cyclophosphamide (Clafen, Cytoxan, Neosar) |
| EPOCH                       | Infusional etoposide (Etopophos, Toposar, Vepesid)  
                               | Prednisone (Deltasone)  
                               | Infusional vincristine (Oncovin, Vincasar PFS)  
                               | Cyclophosphamide (Clafen, Cytoxan, Neosar)  
                               | Infusional doxorubicin/hydroxydaunorubicin (Adriamycin, Rubex) |
| ESHAP                       | Etoposide (Etopophos, Toposar, Vepesid)  
                               | Methylprednisolone (Solu-Medrol)  
                               | Cisplatin (Platinol, Platinol-AQ)  
                               | Cytarabine (Cytosar-U, Tarabine PFS) |
| FC                          | Fludarabine (Fludara)  
                               | Cyclophosphamide (Clafen, Cytoxan, Neosar) |
Table 6.1. Common Chemotherapy Regimens For NHL *(continued)*

<table>
<thead>
<tr>
<th>Drug or Regimen Abbreviation</th>
<th>Generic Name of Drugs (Brand Name)</th>
</tr>
</thead>
</table>
| GDP                          | Gemcitabine (Gemzar)  
    Dexamethasone (Decadron, Dexasone)  
    Cisplatin (Platinol, Platinol-AQ)                                                      |
| GemOX                        | Gemcitabine (Gemzar)  
    Oxaliplatin (Eloxatin)                                                                 |
| HyperCVAD/MTX-Ara-C          | Cyclophosphamide (Clafen, Cytoxan, Neosar)  
    Vincristine (Oncovin, Vincasar PFS)  
    Doxorubicin/hydroxydaunorubicin (Adriamycin, Rubex)  
    Dexamethasone (Decadron, Dexasone)  
    Methotrexate (Otrexup, Rheumatrex, Trexall)  
    Cytarabine (Cytosar-U, Tarabine PFS)                                                  |
| ICE                          | Ifosfamide (Ifex)  
    Carboplatin (Paraplatin)  
    Etoposide (Etopophos, Toposar, Vepesid)                                                |
| HD MTX and HD Ara-C          | High-dose methotrexate (Otrexup, Rheumatrex, Trexall)  
    High-dose Ara-C                                                                     |
| MINE                         | Mesna (Mesnex)  
    Ifosfamide (Ifex)  
    Mitoxantrone (Novantrone)  
    Etoposide (Etopophos, Toposar, Vepesid)                                               |
| P                            | Pralatrexate (Folotyn)                                                                             |
| SMILE                        | Methotrexate (Otrexup, Rheumatrex, Trexall)  
    Leucovorin  
    Ifosfamide (Ifex)  
    Mesna (Mesnex)  
    Dexamethasone (Decadron, Dexasone)  
    Etoposide (Etopophos, Toposar, Vepesid)  
    pegasparaginase (Oncaspar)                                                            |
How Is Chemotherapy Given?

Depending on the regimen, patients will be given chemotherapy in a pill form, as an injection, or as an IV drip through a vein. To make it easier to give and receive multiple cycles of chemotherapy by IV, the doctor may insert an IV catheter that will stay in place for a few weeks or for the duration of the chemotherapy treatment. There are several types of catheters, which are described in Table 6.2. Patients and caregivers should discuss with the doctor which catheter, if any, would be best for their particular situation.

<table>
<thead>
<tr>
<th>Type of Catheter</th>
<th>Description</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral Venous Catheter</td>
<td>A needle is used to insert a small, flexible tube (the catheter or cannula) into a vein in the hand or arm. Drugs and other fluids are given through the various types of attachments.</td>
<td>No need for surgical insertion.</td>
<td>Sterile dressing needs to be kept clean and dry and replaced daily; the line needs to be injected periodically with a blood thinner (heparin) to prevent blockage. To minimize the risk of infections, the catheter needs to be replaced at least every three days or sooner if it becomes blocked. Cannot be used to draw blood for blood tests.</td>
</tr>
<tr>
<td>Hickman and Broviac</td>
<td>Consists of one to three tubes surgically inserted through the subclavian vein (the vein that runs underneath the collar bone) in the chest wall into a vein. Six to 12 inches of tubing remain outside the skin.</td>
<td>It makes it easy to draw blood and give drugs using standard needles and without having to pierce the skin.</td>
<td>Requires proper care to reduce the risk of infection and blockage. The tubes on the outside of the body make it more obvious that a catheter is in place. Patients need training and instructions to learn how to clean and take care of the external tubes.</td>
</tr>
</tbody>
</table>
Table 6.2. Catheters Used to Administer Chemotherapy
(continued)

<table>
<thead>
<tr>
<th>Type of Catheter</th>
<th>Description</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infusaport or Portacath</td>
<td>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.</td>
<td>Patients do not have to do anything to care for it; a nurse keeps the line open by “flushing” once a month with a small amount of injected liquid.</td>
<td>The patient must be injected through the skin with a special needle each time it needs to be used. Sometimes it is hard to use it to draw blood samples because of clogging (due to a blood clot). If an infection occurs, the catheter may need to be removed through a minor surgical procedure.</td>
</tr>
<tr>
<td>Peripherally Inserted Central Catheter (PICC line)</td>
<td>A thin, soft plastic tube is inserted in a large vein in the arm.</td>
<td>A good option for patients who only need to have many short infusions or continuous infusions given in a hospital or at home with a portable pump.</td>
<td>This is more temporary than the other types of catheters.</td>
</tr>
</tbody>
</table>

Why Is It Important to Adhere to the Chemotherapy Treatment Schedule?

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

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

What Other Types of Drugs Are Used to Treat Patients With NHL?
In addition to chemotherapy and radiation therapy, there are many types of other drugs used to treat NHL. These include monoclonal antibodies, radioimmunotherapy, immunoconjugates, proteasome inhibitors, histone deacetylase (HDAC) inhibitors, and immunomodulatory drugs. Most of these drugs have been developed relatively recently. The FDA may have approved other types of drugs since the time this booklet was printed.

What Are Monoclonal Antibodies?
As part of our immune system, specialized white blood cells, which are the most mature kind of B cells (plasma cells), make proteins called antibodies. Antibodies help fight infection by recognizing and sticking to anything the body considers “foreign.” Each antibody our body makes is naturally designed to recognize one specific type of identifying molecule (antigen).

Monoclonal antibodies are molecules engineered in the laboratory that are designed to recognize and stick to a specific part of a particular molecule (called an antigen) on, for example, the surface of cancer cells. When a monoclonal antibody attaches itself to a cancer cell, it can stop or slow down its growth or it can make it easier for the immune system to recognize and destroy it. Once injected in the patient, the monoclonal antibodies travel through the blood and stick to the cells that have the antigen they recognize. Most of these will be NHL cells. Once they stick, the antibodies trigger an alarm that draws cells from the immune system to help destroy and kill the cancer cells.

Monoclonal antibody therapies are given to patients as IV infusions during visits at the doctor’s office or clinic. To prevent serious allergic reactions, patients are given oral antihistamines, acetaminophen (Tylenol), and sometimes steroids before the antibody infusion. All
patients should be tested for active hepatitis infection. To avoid life-threatening infections, patients being treated with monoclonal antibodies should not be vaccinated with live attenuated virus vaccines, such as those for shingles (herpes zoster), yellow fever, and the Sabin vaccine for polio. The sections that follow provide additional information about each of these monoclonal antibodies.

**Common Monoclonal Antibodies For NHL**
The monoclonal antibody rituximab is approved by the FDA to treat patients with many types of NHL. The monoclonal antibodies obinutuzumab (Gazyva) and ofatumumab (Arzerra) are approved by the FDA to treat chronic lymphocytic leukemia (CLL).

**Table 6.3. Common Monoclonal Antibodies For NHL**

<table>
<thead>
<tr>
<th>Generic Name of Monoclonal Antibodies (Brand Name)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obinutuzumab (Gazyva)</td>
</tr>
<tr>
<td>Ofatumumab (Arzerra)</td>
</tr>
<tr>
<td>Rituximab (Rituxan)</td>
</tr>
</tbody>
</table>

**Obinutuzumab (Gazyva)**
In 2013, obinutuzumab, a CD20 targeted type 2 (second-generation) antibody, was approved by the FDA for the treatment of patients with previously untreated CLL when given together with the oral chemotherapy drug chlorambucil. Obinutuzumab is also being investigated in other types of NHL.

Obinutuzumab treatment is given as an IV infusion. It is dosed during 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 that has not responded to previous therapy with the chemotherapy drug fludarabine and the monoclonal antibody alemtuzumab. Ofatumumab, a CD20 targeted antibody, is usually used as monotherapy (alone, not in combination with other drugs) for patients with relapsed or refractory (disease does not respond to treatment) CLL. In 2014, ofatumumab was approved for the treatment of newly diagnosed patients with CLL in combination with chlorambucil for whom fludarabine-based therapy is not considered appropriate. Ofatumumab is also being investigated in other types of NHL.

Ofatumumab is given as an IV infusion. In previously untreated CLL patients, ofatumumab is administered in combination with chlorambucil in 28-day cycles for a minimum of three cycles until best response or a maximum of 12 cycles. In refractory CLL, the recommended ofatumumab regimen is 12 doses.

Rituximab (Rituxan)
Rituximab is the most commonly used antibody for NHL. The target is CD20, which is expressed almost universally on B-cell lymphomas. Prolonged use of rituximab can cause a drop in gamma globulins. In 1997, rituximab became the first monoclonal antibody approved by the FDA for the treatment of patients with cancer—specifically for patients with relapsed or refractory low-grade or follicular B-cell NHL and subsequently in combination therapy (chemoimmunotherapy or immunochemotherapy) in newly diagnosed patients with diffuse large B-cell lymphoma (DLBCL) in 2006 and follicular lymphoma (FL) in 2011. As of 2015, rituximab is approved by the FDA for the treatment of patients with:

- NHL
- CLL
- Other indications including treatment for rheumatoid arthritis as well as Wegener granulomatosis, and microscopic polyangiitis
Rituximab is used in B-cell lymphomas as monotherapy (alone, not in combination with other drugs for four weekly doses) or in various combinations with chemotherapy drugs or other monoclonal antibodies (see Table 6.1 on page 76). Rituximab treatment 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.

What Are Other Antibody-Based Therapies?
In radioimmunotherapy, a radioactive particle (radioisotope) is attached to a monoclonal antibody to deliver small amounts of radiation therapy directly to the cells that the monoclonal antibody recognizes, limiting the exposure of healthy cells to radiation. When a patient is treated with radioimmunotherapy, the doctor will talk with them about any necessary safety precautions.

While there are differences in scheduling, doses, and side effects, patients are treated with radioimmunotherapy for two weeks, but usually have to undergo monitoring of blood counts for up to six weeks during and after treatment. For more information on radioimmunotherapy, view the Radioimmunotherapy fact sheet on LRF’s website at www.lymphoma.org.

Ibritumomab Tiuxetan (Zevalin)
Similar to rituximab, ibritumomab tiuxetan targets CD20-expressing B cells. It consists of the monoclonal antibody ibritumomab linked to tiuxetan, a specialized molecule (called a chelator) that is bound to a radioactive isotope called yttrium-90 ($^{90}$Y). The ibritumomab component of the drug specifically binds to NHL B cells that express CD20. Once bound, the radioactive emissions from $^{90}$Y damage the cell, triggering its destruction.
Ibritumomab tiuxetan first received approval by the FDA in 2002. It is approved to treat patients with the following types of diseases:

- Relapsed/refractory, low-grade or follicular B-cell NHL
- Newly diagnosed follicular NHL in patients who have achieved partial or complete responses to first-line (initial) chemotherapy

Ibritumomab tiuxetan is given through an IV injection in combination with two rituximab treatments.

**Brentuximab Vedotin (Adcetris)**

Brentuximab vedotin is an immunoconjugate, which is a combination of a monoclonal antibody against CD30 (brentuximab) attached to the small toxic drug called monomethyl auristatin E (MMAE; vedotin). The monoclonal antibody part of this drug attaches itself to lymphoma cells that express CD30, causing them to transport the drug to the inside of the cells. Once inside cells, the MMAE drug is separated from the antibody molecule. The MMAE attacks and breaks up an internal support skeleton (called the *microtubule network*) of the cells, causing them to stop dividing and die.

Brentuximab vedotin is approved by the FDA for the treatment of patients with:

- Classical Hodgkin lymphoma (HL) after failure of autologous stem cell transplantation (SCT) or after failure of at least two previous combination chemotherapy regimens in patients who are not candidates for autologous SCT
- Classical HL after autologous SCT as consolidation treatment in patients who are at high risk of disease relapse or progression
- Systemic anaplastic large cell lymphoma after failure of at least one previous combination chemotherapy regimen

Brentuximab vedotin is given as an IV infusion once every three weeks.
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, novel, or biologic therapies. These drugs may kill the lymphoma cells or slow down or stop their growth. Targeted therapies attack cancer cells in a more specific way than chemotherapy drugs.

Table 6.4. Common Targeted or Novel Therapies for NHL

<table>
<thead>
<tr>
<th>Generic Name of Targeted Therapy (Brand Name)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belinostat (Beleodaq)</td>
</tr>
<tr>
<td>Bortezomib (Velcade)</td>
</tr>
<tr>
<td>Ibrutinib (Imbruvica)</td>
</tr>
<tr>
<td>Idelalisib (Zydelig)</td>
</tr>
<tr>
<td>Lenalidomide (Revlimid)</td>
</tr>
<tr>
<td>Romidepsin (Istodax)</td>
</tr>
<tr>
<td>Vorinostat (Zolinza)</td>
</tr>
</tbody>
</table>

Belinostat (Beleodaq)
Belinostat is an HDAC inhibitor. Histones are proteins that are needed to help regulate DNA and play a role in the expression of genes. Inhibiting HDAC prevents some of the actions of histones and causes cells to stop growing and die. 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, feeling tired (fatigue), fever, anemia, and vomiting.
**Bortezomib (Velcade)**

Bortezomib is a proteasome inhibitor—a class of drugs that inhibit the ability of cells to properly dispose of proteins. Proteasome inhibition causes an abnormal build-up of proteins in a cancerous cell, resulting in cell death. Bortezomib was the first proteasome inhibitor developed, and it was first approved in 2003 for the treatment of multiple myeloma. Bortezomib was subsequently approved in 2006 for the treatment of relapsed mantle cell lymphoma (MCL; a type of NHL) and in 2014 for previously untreated MCL. Bortezomib is being studied for other NHL types as well. Its most commonly reported side effects include nausea, diarrhea, thrombocytopenia, neutropenia, peripheral neuropathy, fatigue, neuralgia, anemia, leukopenia, constipation, vomiting, lymphopenia, rash, pyrexia, and anorexia.

**Ibrutinib (Imbruvica)**

Ibrutinib inhibits a type of signaling molecule called a tyrosine kinase. Tyrosine kinases are specialized proteins called enzymes found in the cells. The main job of tyrosine kinases in B cells is to send signals from the B cell receptor on the cell surface to the cell’s control center (its nucleus). These signals help both healthy and cancer cells grow and survive. Cancer cells are more dependent on this signaling system and thus more sensitive to the medication. Ibrutinib interferes with growth and survival of NHL cells and blocks (inhibits) the signals from Bruton’s tyrosine kinase (BTK), a tyrosine kinase that is especially important for B cells. By inhibiting the signal from BTK, ibrutinib can help stop or slow down the growth of NHL cells. Certain drugs may interfere with ibrutinib’s function. Patients should check with their pharmacist to make sure they are not taking any drugs that would interact with ibrutinib.

Ibrutinib comes in capsules that must be swallowed whole with a large glass of water at the same time once a day, every day. Patients should not open, break, or chew the capsules. During the course of treatment with ibrutinib, patients should not eat or drink grapefruit products or Seville oranges as these products may interact with ibrutinib. Certain drugs may interfere with ibrutinib function. Patients should check with their pharmacist. Its most commonly reported side effects include...
effects include thrombocytopenia, neutropenia, diarrhea, anemia, fatigue, musculoskeletal pain, bruising, nausea, upper respiratory infection, and rash.

In 2013, ibrutinib was approved by the FDA for the treatment of patients with MCL who had received at least one prior therapy. In 2014, ibrutinib was approved by the FDA to be used as monotherapy for the treatment of patients with previously treated CLL or CLL with a 17p deletion. In 2015, ibrutinib was approved for the treatment of patients with Waldenström macroglobulinemia.

**Idelalisib (Zydelig)**

Idelalisib is a type of signaling inhibiting drug; it is a small molecule that blocks (inhibits) the signals from the B-cell receptor through phosphoinositide 3-kinase (PI3K)-delta. The main job of PI3K-delta is to transmit signals that help B cells grow, move, divide, and survive. By inhibiting the signal from PI3K-delta, idelalisib helps stop or slow down the growth of NHL cells. In laboratory studies, idelalisib has also been shown to kill NHL cells.

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

Idelalisib was approved by the FDA in 2014 to be used in combination with rituximab for the treatment of patients with CLL that has returned (relapsed) and to be used as monotherapy for the treatment of patients with SLL or relapsed follicular B-cell NHL (follicular lymphoma) who have relapsed after at least two prior therapies. Certain drugs may interfere with idelalisib function. Patients should check with their pharmacist. Its most commonly reported side effects include diarrhea, pyrexia, fatigue, nausea, cough, pneumonia, abdominal pain, chills, and rash.
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 on an electrocardiogram.

Vorinostat (Zolinza)
Vorinostat is an HDAC inhibitor approved for treatment of patients with CTCL whose disease has gotten worse or 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.

What Are Immunomodulatory Agents?
Immunomodulatory agents are drugs that interact with the immune system to encourage the destruction of cancer cells. There are three main immunomodulatory drugs, but only one of these, lenalidomide (Revlimid), is FDA approved to treat NHL—specifically for patients with MCL that has relapsed or is refractory to two prior therapies, one of which included the proteasome inhibitor bortezomib.

Lenalidomide (Revlimid)
Lenalidomide is an immunomodulatory drug (IMiD). It binds to a protein called cereblon and alters the breakdown of key regulators of immune cell function ikaros (IKZF-1) and aiolos (IKZF-3). The impact of the IMiDs are numerous and include improving the effectiveness of antibodies (such as rituximab), improving T-cell immune function, and altering the tumor microenvironment.

Lenalidomide comes as an oral tablet at a number of dosage
strengths. It can be prescribed as a single agent or in combination with other drugs.

Lenalidomide was initially approved by the FDA for treatment of multiple myeloma. Later, it was approved for the treatment of myelodysplastic syndromes and mantle cell lymphoma (MCL). It has been evaluated in the treatment of multiple NHLs and has had a significantly positive impact in activated B-cell DLBCL, FL, CLL/SLL, and marginal zone lymphoma.

Lenalidomide is given by mouth (orally) once a day for three weeks of a four-week cycle. The most common side effects in patients with MCL include low neutrophils (neutropenia), bruising or bleeding easily (thrombocytopenia), feeling tired (fatigue), diarrhea, anemia, nausea, cough, fever, rash, shortness of breath (dyspnea), severe itching (pruritus), constipation, swollen extremities (peripheral edema), and low leukocytes (leukopenia).

Thalidomide (Thalomid) and pomalidomide (Pomalyst) are two other immunomodulatory agents. Both thalidomide and pomalidomide are approved for the treatment of multiple myeloma and are being studied in some types of NHL but are not yet FDA approved for NHL.

**What Is Maintenance Therapy?**

Maintenance therapy refers to the ongoing treatment of patients whose disease has responded well to first-line (initial) treatment. The purpose of maintenance therapy is to help prevent the cancer from returning and to help keep a more aggressive cancer that has stopped growing from beginning to grow again and spread to other parts of the body.

Maintenance therapy typically consists of drugs given at lower doses and longer intervals than when given during initial therapy. Depending on the type of NHL and the drugs used, maintenance therapy may last for weeks, months, or even years. Rituximab is commonly used as maintenance therapy for CD20-positive B-cell NHLs following an initial response to rituximab containing regimens (immunochemotherapy) in
high-risk indolent lymphoma patients. Patients can use the questions below to ask their doctors about maintenance therapy.

**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?
- Would I jeopardize the possibility of other therapies?
- How often and for how long will I receive this treatment?
- Does my insurance cover this treatment?
- Is this better for me than watchful waiting (checking for recurrence, with no treatment)?
- Will this improve my 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 used to describe *external beam radiotherapy*, in which radiation is delivered using an external radiation beam; however, certain drugs can also deliver radioactive molecules directly to tumor cells (see the section “What Are Other Antibody-Based Therapies?” on page 84).

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

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

Some of the more common types of radiation therapy and delivery methods used for NHL are shown in Table 6.5.

**Table 6.5. Methods For Delivering Radiation Therapy**

<table>
<thead>
<tr>
<th>Method</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Three-Dimensional Conformal Radiation Therapy (3D-CRT)</td>
<td>One of the most common types of external beam radiation, this form of radiation therapy uses very sophisticated computer software and advanced machines to deliver radiation to a very precisely shaped targeted area of the body.</td>
</tr>
<tr>
<td>Electron Beam Radiation</td>
<td>In electron beam radiation, a machine is used to send electrons, or negatively charged particles, directly to the area where the lymphoma is found and, potentially, to nearby lymph nodes.</td>
</tr>
<tr>
<td>Image-Guided Radiation Therapy (IGRT)/Tomotherapy</td>
<td>This technique uses repeated imaging scans (such as computed tomography [CT], magnetic resonance imaging [MRI], or positron emission tomography [PET]) during treatment.</td>
</tr>
<tr>
<td></td>
<td>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.</td>
</tr>
</tbody>
</table>
Table 6.5. Methods For Delivering Radiation Therapy *(continued)*

<table>
<thead>
<tr>
<th>Method</th>
<th>Description</th>
</tr>
</thead>
</table>
| Photopheresis or Extracorporeal Photochemotherapy | - Doctors remove a fraction of the patient's blood and treat it with a chemical that makes lymphocytes more likely to die when exposed to ultraviolet A light.  
- The blood is exposed to this ultraviolet light 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 allogeneic (donor) stem cell transplantation. |
| Proton Therapy                  | - This form of external beam radiation uses a type of charged particle called a proton beam.  
- In NHL patients with tumors near the heart, lungs, or esophagus, it is hard to treat the tumor with regular radiotherapy without damaging these organs in the process.  
- Proton therapy may reduce radiation exposure to normal-surrounding tissues and allow higher doses to be delivered to the tumor. |
| Total Skin Electron Beam Therapy (TSEBT) | - This therapy is often used for the treatment of patients with CTCL, which is a form of lymphoma that occurs on the outermost layers of the skin.  
- TSEBT directs radiation to the entire surface of the body; however, because the radiation is weak, it only penetrates the outer layers of the skin. The deeper layers of skin and other tissues are not exposed to radiation. |

Patients can use the questions on the following page to ask their doctors about what happens before they start radiation therapy.
Questions to Ask Before Starting Radiation Therapy

- What is the goal of my radiation therapy?
- How will the radiation be given?
- When will treatment begin? When will it end?
- 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 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 (for example, work, school, childcare, driving, sexual activity, and exercise)?

What Is Palliative Radiation?
Radiation may be given in order 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 cancer 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 different types of stem cell transplantation, depending on who donates the stem cells. In an *autologous stem cell transplant*, the patient is his or her own donor. In an *allogeneic stem cell transplant*, the donor is another person who is genetically similar to the patient;
Understanding Non-Hodgkin Lymphoma

this person is typically a brother or sister. If the donor is an identical twin, the transplant is called syngeneic. A donor can, however, be an unrelated person or stem cells can come from umbilical cord blood.

The purpose of autologous or full-intensity (“myeloablative”) allogeneic stem cell transplantation is to allow patients to receive high-dose chemotherapy. Such high doses effectively kill cancer cells but can also severely damage the bone marrow as a side effect, destroying the body’s source of blood cells responsible for fighting infection, preventing bleeding, and carrying oxygen. Stem cell transplantation re-populates the stem cells responsible for making these blood cells. The major difference between autologous and allogeneic transplantation is that in autologous transplantation, the main benefit is the high-dose chemotherapy or radiation. In addition to the high-dose chemotherapy or radiation, in allogeneic transplantation the cells from the donor recognize the lymphoma as foreign (graft vs. lymphoma) and attack the lymphoma, resulting in an immunologic treatment. In general, control of the lymphoma is better with allogeneic transplantation, but the toxicity and risk of complications is higher because the donor immune cells can attack the normal organs of the host, recognizing them as foreign, resulting in graft-versus-host disease (GVHD). The decision about which treatment to use is complex and should involve a detailed discussion with the patient’s doctor and a referral to a major cancer center.

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. In deciding if transplantation is a good option, doctors will consider the patient’s health status, age, medical history, cancer stage, and responses to previous therapy. For more information, view the Transplant in Lymphoma fact sheet on the Lymphoma Research Foundation’s (LRF’s) website at www.lymphoma.org.
AUTOLOGOUS STEM CELL COLLECTION
A patient’s own stem cells

1. Collection
Stem cells are collected from the patient's bone marrow or blood.

2. Processing
Blood or bone marrow may be processed in the laboratory to purify and concentrate the stem cells. Samples are frozen until needed.

3. Reinfusion
Stem cells are thawed and reinfused into the patient.

ALLOGENEIC STEM CELL COLLECTION
Stem cells from a donor who is genetically similar to the patient

1. Collection
Stem cells are collected from the donor's bone marrow or blood.

2. Processing
Blood or bone marrow may be processed in the laboratory to purify and concentrate the stem cells.

3. Infusion
Stem cells are infused into the patient.
Reduced-intensity transplantation (also called non-myeloablative or mini-allogeneic stem cell transplantation) uses lower doses of chemotherapy and/or radiation prior to allogeneic transplantation. This option is available only for allogeneic transplantation and cannot be used for autologous transplantation. This approach takes advantage of the GVHD effect, in which the transplanted cells (the “graft”) 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, although they still have increased risks of serious side effects as compared with autologous stem cell transplantation due to the potential for GVHD, in which donor immune cells attack the normal organs of the patient (host).

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

**Questions to Ask Before Deciding to Undergo Stem Cell Transplantation**

- What type of transplantation is most appropriate for me?
- Why do you think this is a good idea?
- Why do you recommend this particular type of transplantation?
- What are the risks versus benefits associated with this procedure?
- Would I jeopardize the possibility of other therapies?
- If I need a donor, how will I find one?
- How long will I need to be in the hospital?
- Once I’m back home, will I need special care?
- Will I need someone to care for me immediately after the transplant?
- Will my insurance cover this procedure?
- What type of special care will I receive?
What Terms Do Doctors Use to Describe Treatment and Its Outcomes?

Doctors use several terms to describe a patient’s treatment and the anticipated outcomes. Table 6.6 highlights these terms.

Table 6.6. Terms Used to Describe Treatment and Its Outcomes

<table>
<thead>
<tr>
<th>Terms</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Remission (CR)</td>
<td>This term is used when all signs of the lymphoma have disappeared after treatment. This finding does not mean the lymphoma is completely cured; it means the symptoms have disappeared and the lymphoma cannot be detected using current tests. If this response is maintained for a long period, it is called a durable remission.</td>
</tr>
<tr>
<td>Cure</td>
<td>This word is cautiously used by doctors when there are no signs of the lymphoma reappearing after many years of continuous CR. The term is most often applied to DLBCL or HL.</td>
</tr>
<tr>
<td>Disease Progression</td>
<td>This term means the disease has worsened or the tumor has grown during therapy or observation. Other terms used to describe disease progression are relapse, treatment resistance, or resistant disease.</td>
</tr>
</tbody>
</table>
Table 6.6. Terms Used to Describe Treatment and Its Outcomes

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor Response (MR) or Improvement</td>
<td>This term is used if the tumor has shrunk following therapy but is still more than one-half of its original size.</td>
</tr>
<tr>
<td>Partial Remission (PR)</td>
<td>This term is used if the lymphoma has responded to treatment and shrunk to less than one-half of its original size.</td>
</tr>
<tr>
<td>Primary Therapy</td>
<td>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 pathologic characteristics of the disease, including the factors described previously in this booklet. Also called initial therapy or front-line therapy.</td>
</tr>
<tr>
<td>Refractory Disease</td>
<td>This term is used to describe when the lymphoma does not respond to treatment (meaning that the cancer cells continue to grow) or when the response to treatment does not last very long.</td>
</tr>
<tr>
<td>Relapse</td>
<td>This term refers to disease that reappears or grows again after a period of remission.</td>
</tr>
<tr>
<td>Stable Disease</td>
<td>This term means the disease has not gotten worse or better following therapy (the tumor has not grown or shrunk) but has stayed about the same.</td>
</tr>
</tbody>
</table>

**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 type of lymphoma, the patient’s age and overall health, extent and location of disease, type of previous therapies received, and length of response to previous therapies.

Many combination chemotherapies already discussed can be effective in patients with relapsed or refractory NHL, as well as targeted
therapies, such as ibrutinib and idelalisib. Rituximab may be used in combination with targeted agents and with many chemotherapy regimens. The radioimmunotherapy drug ibritumomab tiuxetan is also used in patients with relapsed indolent disease. Many treatment centers will 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. Sequential transplantations are possible if the disease does not fully respond.

Patients who do not go into complete remission (CR) following treatment or who do not respond to treatment should not lose hope. Lasting responses to therapy may be achieved after a diagnosis of relapsed or refractory disease. Many patients seek second opinions at any point from diagnosis onward and often choose to do so if their disease relapses or is considered refractory. Clinical trials are a good option for patients at all stages of disease.

Many of the novel therapeutic agents most recently approved by the FDA and those being investigated in clinical trials are used specifically for patients with relapsed or refractory disease. Lymphoma research continually evolves as doctors and scientists discover new therapies and more effective ways of giving existing treatments. Chapter 11 describes some of the options currently under investigation.

**When Should a Clinical Trial Be Considered?**

Clinical trials are appropriate for patients at all stages of disease, whether newly diagnosed or at the time of relapse (see the section “Overview of Clinical Trials” on page 142). 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. By participating in a randomized clinical trial, patients may or may not get access to the newest therapies but will, at a minimum, receive quality care and the standard treatment in a very carefully controlled and supportive environment.
If patients are interested in participating in a clinical trial, they should ask their doctor if there is an appropriate trial for them and what the potential risks and benefits may be. For more information about clinical trials, please refer to LRF’s “Clinical Trial Information Service” available at www.lymphoma.org/clinicaltrials_forpatients.

**What Are Alternative and Complementary Medicine (CAM) Therapies?**

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

*Complementary therapy* may be used 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 some of these practices may make their cancer treatment less effective.

Table 6.7 outlines some forms of complementary therapy, also known as integrative medicine or integrative oncology.

**Table 6.7. Forms of Complementary Therapy**

<table>
<thead>
<tr>
<th><strong>Acupuncture</strong></th>
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</thead>
<tbody>
<tr>
<td>▪ Acupuncture may relieve pain, nausea, fatigue, hot flashes, and <em>neuropathy</em> (numbness or tingling in the hands and feet) associated with chemotherapy and may help decrease mild depression.</td>
</tr>
<tr>
<td>▪ Using ultra-thin needles applied to specific points on the body, acupuncture is safe and painless. Needles should only be used once and disposed of after use.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Chiropractic and Massage Therapy</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ Chiropractic and massage therapies are the most commonly used modalities, and can help relieve side effects and stress.</td>
</tr>
</tbody>
</table>
Table 6.7. Forms of Complementary Therapy (continued)

| Herbal Therapy | ▪ Ask your doctor before using herbal therapies. Some herbal therapies may interfere with other medications, particularly St. John's wort. |
| Mind/Body Therapies | ▪ Examples of mind/body therapies include meditation, guided imagery, self-hypnosis, Tai Chi, and yoga.  
  - Meditation, guided imagery, and self-hypnosis can help manage stress.  
  - Yoga and Tai Chi have been shown to minimize stress and improve balance and flexibility. |
| Nutrition | ▪ Patients undergoing lymphoma treatment should eat a healthy, well-balanced diet that contains five to seven servings of fruits and vegetables a day, fish or poultry, and whole grains. |
| Touch Therapies | ▪ Examples of touch therapies include massage, reflexology (foot massage), and Reiki.  
  - These techniques apply therapeutic pressure to the body to help restore a sense of harmony, relaxation, and well-being.  
  - Studies suggest that massage may lessen pain. |

**Drug Costs: What to Do if Insurance Will Not Pay**

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

Patients in need of financial assistance should talk with their doctor and social worker about available options and how to enroll in an appropriate program. Before undergoing a medical procedure, patients should check with the insurance carrier to ensure 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, the patient should contact their state’s insurance agency. For more information on financial aid, please view the *Resources for Financial Assistance* fact sheet on LRF’s website at www.lymphoma.org. You may also call LRF’s Helpline at (800) 500-9976 or email helpline@lymphoma.org.
Patients with non-Hodgkin lymphoma (NHL) may experience various side effects or toxicities caused by their cancer treatment. All treatments (including chemotherapy, biologic/targeted therapies, and radiation therapy), can cause side effects. Fortunately, medications and lifestyle changes can effectively prevent or lessen the severities of most side effects. Patients should ask their healthcare team about possible treatment side effects and how to prevent and manage them; and tell their doctor or nurse if they experience any side effects. This chapter explains the causes of these side effects, the types of side effects caused by different treatments, and steps to take to minimize these side effects.

**Why Does Chemotherapy Cause Side Effects or Toxicities?**

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

The type and severity of side effects caused by chemotherapy vary widely depending on the types of drugs that are given and an individual patient’s response. 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 several years. Fatigue, menopausal symptoms, and cardiovascular problems are examples of long-term effects.

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

The combination of the chemotherapy drug doxorubicin (Adriamycin) and radiation, especially when the radiation is directed to the chest area, can lead to late effects to the heart. This may cause a decrease in cardiac function and accelerated atherosclerosis in which plaque builds up on the inside of the arteries.

What Side Effects Are Caused by Chemotherapy?

Side effects vary depending on the type of chemotherapy. Additionally, these adverse effects can be caused by factors other than chemotherapy.

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

- Cardiotoxicity
- Changes in taste
- Cognitive problems (trouble concentrating, impaired memory)
- Decreased blood cell production leading to anemia; increased risk of infection (due to decreased white blood cells); or bleeding (due to decrease in platelets)
- Diarrhea or constipation
- Fatigue
- Hair loss
- Increased chance of infections
- Loss of appetite
- Lung toxicity
- Mouth sores
- Nausea or vomiting
- Peripheral neuropathy (numbness or tingling in fingers or toes)
- Problems with sexual function
- Sterility
- Tumor lysis syndrome (TLS; abnormalities in electrolytes in the blood from rapid death of lymphoma cells)

_Cardiotoxicity_

_Cardiotoxicity_ refers to damage to cells in the heart or heart muscle. Long-term use of certain chemotherapy drugs can cause heart damage in some patients. Doxorubicin is an example of a drug that is possibly cardiotoxic.

In general, most patients with NHL treated with potentially cardiotoxic chemotherapy receive these drugs at dose levels and numbers of cycles where cardiac toxicity is usually not a problem. For example, many patients with diffuse large B-cell lymphoma only need to be treated with chemotherapy once; therefore, their risk for developing chemotherapy-related cardiovascular disease is small.

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

Careful monitoring by the healthcare team can reduce the chances of patients developing cardiotoxicity. Before deciding to treat patients with a cardiotoxic drug, most doctors will have the patient undergo either an echocardiogram or a multi-gated acquisition (MUGA) scan to
measure their cardiac function. This test will ensure that patients are prescribed a safe chemotherapy dose given their current heart function and that they are monitored more intensively if needed.

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

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

*Decreased Blood Cell Production*
The bone marrow constantly produces red blood cells, white blood cells, and platelets. Some types of chemotherapy and immunotherapy 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 control myelosuppression, samples of a patient’s blood are tested for complete blood count (CBC), which measures the numbers of white blood cells, red blood cells, and platelets, and the differential, which measures the numbers of the different types of white blood cells. These tests are usually done before and sometimes during each chemotherapy cycle. Table 7.1 describes the four main conditions caused by a decrease in blood cell production.
### Table 7.1. The Four Main Conditions Caused by Decreased Blood Cell Production

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anemia</strong></td>
<td>This condition is caused by a decrease in the number of red blood cells. Normal levels of red blood cells are 4.7 to 6.1 million per microliter for men and 4.2 to 5.4 million per microliter for women. Many chemotherapy drugs cause mild or moderate anemia. Anemia can make people feel tired and short of breath, especially when it is severe. Although seldom needed, anemia can be treated with drugs or red blood cell transfusions.</td>
</tr>
<tr>
<td><strong>Lymphopenia</strong></td>
<td>Lymphopenia, also called lymphocytopenia, refers to a decrease in the number of lymphocytes. Lymphocytes produce antibodies and fight bacterial and viral infections. Usually, of all white blood cells, about 20 to 40 percent are lymphocytes. Patients with low levels of lymphocytes are at risk of latent infections. For example, if the patient had chicken pox as a child, he or she could get shingles if he or she has low levels of lymphocytes.</td>
</tr>
</tbody>
</table>
Table 7.1. The Four Main Conditions Caused by Decreased Blood Cell Production (continued)

<table>
<thead>
<tr>
<th>Neutropenia</th>
<th>Thrombocytopenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia refers to a decrease in neutrophils—the primary type of white blood cells that fight bacterial infections.</td>
<td>Thrombocytopenia refers to a decrease in the number of platelets in the blood; platelets help start the clotting process when bleeding occurs. Normal platelet count levels are 150,000 to 450,000 per microliter.</td>
</tr>
<tr>
<td>Patients with low neutrophil counts are at risk of serious and even life-threatening infections. Symptoms of infection include fever, chills, and night sweats.</td>
<td>Patients with low platelet counts may bruise easily; have cuts that bleed for too long or too much; have nosebleeds or bleeding gums; or may bleed from places that have not been injured.</td>
</tr>
<tr>
<td>A normal white blood cell count ranges from 4,000 to 10,000 cells per microliter. Doctors regularly monitor the absolute neutrophil count (ANC), the number of neutrophils in the peripheral blood. Because patients with an ANC below 500 are at high risk for infections, their doctors may decrease the chemotherapy dosage or delay the next treatment in order to keep the ANC above 500.</td>
<td></td>
</tr>
<tr>
<td>Some patients require treatment with antibiotics and hospitalization to prevent or treat infections.</td>
<td></td>
</tr>
<tr>
<td>To avoid a patient missing a dose of chemotherapy, doctors sometimes prescribe drugs like filgrastim (Neupogen and Granix) and pegfilgrastim (Neulasta) to reduce the duration and severity of neutropenia. These drugs can sometimes cause bone pain, which is usually temporary.</td>
<td></td>
</tr>
</tbody>
</table>
Diarrhea

Some types of chemotherapy may cause diarrhea. While most patients do not experience severe diarrhea, the most important thing to remember is to avoid dehydration, which is a loss of body fluids. The doctor should be contacted if the patient has bloody diarrhea or fever with diarrhea. Patients may follow the tips below that outline how to avoid dehydration from diarrhea or vomiting.

Avoiding Dehydration From Diarrhea or Vomiting

- Drink plenty of liquids (8 glasses a day), such as water or electrolyte replacement drinks like Gatorade, Pedialyte, and Powerade. Sometimes it helps to drink small amounts very frequently rather than too much at once. Soup, especially broth, is a rich source of nutrients.

- Look for the following signs of dehydration: dry mouth or skin, decreased urine, or feeling dizzy or lightheaded when you stand up.

- Do not drink or eat dairy products because they can worsen diarrhea.

- Do not eat high-fiber and other hard-to-digest foods because they can worsen diarrhea.

- Eat plenty of bananas and other high-potassium foods (check with your doctor or dietitian to make sure these foods will not interfere with your chemotherapy or other medications you are taking).

- Take the medicines that your doctor recommends to control diarrhea or vomiting (call your doctor if symptoms persist).
Fatigue

Fatigue is a common side effect of many types of chemotherapy. Fatigue should decrease after patients have completed their lymphoma treatment, but it could take weeks or months until they return to their normal energy levels. Patients may use the tips below to help them cope with fatigue.

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.

- Exercise if your doctor says it is okay to do so, but do not overdo it. Try simple stretching and range-of-motion exercises or a short walk; these activities may energize you without tiring you out. Start slowly and build up to the level that is right for you. Ask your doctor, nurse, or physical therapist to help you create a personalized exercise plan.

- Rest and sleep during therapy are very important, but do not rest more than you need because it may decrease your energy levels. An afternoon nap helps many patients feel less tired for the rest of the day. Other patients cannot sleep at night if they nap during the day. If you have trouble sleeping, talk to your healthcare team to find out why and what you can do about it.

- Be patient. These symptoms usually improve once treatment is completed.
Hair Loss

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

If hair loss occurs, it often starts two to six weeks after the first chemotherapy treatment. Remember that hair loss caused by chemotherapy is usually temporary. Hair will probably grow back after the end of chemotherapy treatments. When the hair first grows back, it may have a slightly different texture or color than it had before treatment. Over time, the texture and color often return to normal. Loss of hair in the nose and nasal passages may lead to symptoms of *rhinorrhea* (runny nose). Patients may follow the tips below for managing chemotherapy-induced hair loss.

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**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.
- Many patients choose to use a wig, scarf, turban, soft cotton hat, or head wrap. Some health insurance companies cover the cost of wigs if you have a doctor’s prescription. Check your policy to see if it covers this cost.
- Use a hat or scarf to protect your scalp when you are out in the sun and to help keep you warm when you are indoors.
Infections
Some kinds of treatments can lower a patient's ability to fight infections. Patients are sometimes at increased risk for viral infections, particularly shingles (herpes zoster), and sometimes the doctor will prescribe medication to prevent a shingles outbreak during therapy. Many of these side effects are temporary, but some could last for an extended period.

Patients with a fever of 100.5°F or greater should call the doctor. Chills or a chilly sensation often precede fever. They should ask the doctor what to do if they have a sore throat, rash, diarrhea, cough, or redness, swelling, or pain around a wound. The doctor should be contacted if the patient experiences any painful local rash with or without blisters.

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

Reducing Your Risk of Serious Infection During Chemotherapy

- Check with your doctor to make sure your vaccinations are up to date before starting treatment.
- Wash your hands diligently and regularly.
- Avoid crowds.
- Make sure all foods are thoroughly washed and/or cooked; avoid raw foods that may carry germs, as your body is more sensitive to them.
- Do not sleep with pets.
Loss of appetite is sometimes a symptom of the lymphoma or may be a side effect of chemotherapy. Patients may eat less than normal, not feel hungry, or feel full after eating only a small amount of food. Ongoing loss of appetite can lead to weight loss and poor nutrition, which can become serious. Side effects from chemotherapy, such as nausea and vomiting, mouth sores or pain, fatigue, depression, or dry mouth and difficulty swallowing, can all contribute to a patient’s loss of appetite. The patient’s healthcare team should be notified about lack of appetite to determine the underlying cause. Loss of appetite can sometimes be treated with other drugs or by changing eating habits, such as eating several small meals each day and making nutritious food choices. For more information on nutrition, please view the Nutrition fact sheet on the Lymphoma Research Foundation’s (LRF’s) website at www.lymphoma.org.

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. The doctor should be informed if the patient develops a sore throat. The doctor will examine the patient’s throat and may take a swab that will be sent to the laboratory to check for infection. Several medications are available to treat different types of infections. To help decrease chances of infection, patients should have a complete dental checkup and cleaning before starting chemotherapy. Tips for preventing and caring for mouth sores caused by treatment are listed on the following page.
Preventing and Caring for Mouth Sores

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

Nausea or Vomiting
Some chemotherapy drugs can cause nausea or vomiting, which typically occurs on the day chemotherapy is administered but may also occur one or two days later. The doctor may prescribe a drug that prevents nausea and vomiting (*antiemetic*) before chemotherapy. Examples of antiemetics include: aprepitant (Emend), ondansetron (Zofran), granisetron (Kytril), metoclopramide (Reglan), prochlorperazine (Compazine), dolasetron (Anzemet), and a variety of corticosteroids, such as prednisone (Deltasone) or dexamethasone (Decadron). 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 on the following page.
Controlling or Minimizing Nausea and Vomiting

- Before chemotherapy, drink a liquid diet, such as broth, consommé, or water. Do not drink milk or have a meal 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 and more frequent meals instead of fewer large meals each day.
- Avoid strong or offensive smells. Get plenty of fresh air.
- Take prescribed antiemetics before chemotherapy to prevent nausea.
- If you vomit, make sure to avoid becoming dehydrated.
- Finding the best approach is often a process of trial and error. Try different approaches to determine what works best for you.

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

Problems With Sexual Function
Psychological factors, such as fear about illness, altered body image due to hair loss and depression, and the physical side effects of treatment 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, recommend seeing a
specialist, or prescribe medications to restore erectile function in men or hormone therapy to alleviate vaginal dryness and other menopausal symptoms in women.

Sterility

Since chemotherapy and radiation may damage sperm and egg cells, these 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 specific dose, the number of therapies given, and the patient’s age at the time of treatment. There are options available to help preserve fertility including possible protection of the ovaries, cryopreservation of sperm cells and egg cells, or in vitro-fertilized embryos. Patients should speak with their doctor about fertility preservation before beginning treatment. For more information and resources about sterility, visit LRF’s web page on “Fertility” available at www.lymphoma.org/fertility.

Patients receiving chemotherapy and/or radiation should always use birth control methods because these drugs may harm the fetus or cause birth defects.

Tumor Lysis Syndrome

Patients who have rapidly growing tumors or those who have developed many tumors may experience tumor lysis syndrome (TLS). TLS occurs when an anti-lymphoma drug triggers the quick death of a large number of lymphoma cells, making them break apart and spill their contents into the blood. The spilled cellular material floating in the blood can damage kidneys and other organs. If not properly treated, TLS may lead to kidney failure and damage to the heart and nervous system.

To prevent TLS, patients may receive extra fluids and medications such as allopurinol (Zyloprim). If TLS develops, it can be treated with medications such as rasburicase (Elitek).
Other Possible Side Effects

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

What Side Effects Are Caused by Steroids?

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

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

What Side Effects Are Caused by Monoclonal Antibody Therapies?

The monoclonal antibodies used to treat patients with NHL may cause side effects, such as low blood cell counts and infusion reactions, which are usually mild but can sometimes be severe. Other rare, but potentially very serious, side effects include infections and TLS.
**Infusion Reactions**

When infusion reactions occur, they are typically during or within 24 hours after the infusion and are most likely to happen after the first infusion. Symptoms of infusion reactions include dizziness, fainting, headache, feeling warm or flushed, fever or chills, hives, itching, shortness of breath, changes in heart rate and blood pressure, pain in the back or abdomen, and swelling of the face, tongue, or throat.

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

**Infections**

Reactivation of hepatitis B virus (HBV) infection is a rare but very serious side effect of obinutuzumab (Gazyva), ofatumumab (Arzerra), and rituximab (Rituxan) therapy. Reactivation of hepatitis B may also occur with steroid or chemotherapy treatment. People may not know they have HBV because a healthy immune system can force the virus to hide without causing noticeable symptoms. Treatment with the CD20-directed monoclonal antibodies can effect immune system changes that enable reactivation of HBV. If unchecked, this reinitiation of HBV infection can cause acute liver failure. To prevent HBV from reinitiating, patients are screened for HBV infection before treatment. Patients who have the virus are closely monitored during and after treatment and may be given antiviral treatment to control hepatitis B infection. Patients should be mindful of signs of an active HBV infection, such as increasing fatigue and yellowing of the skin or eyes. Very rare cases of a serious CNS infection called JC virus infection (progressive multifocal leukoencephalopathy) can occur with any of the monoclonal antibodies.
Serious, sometimes deadly, infections have been reported in patients treated with alemtuzumab (Campath). Because of this risk, patients are treated with anti-infection medications against bacterial pneumonia and herpes virus before the start of treatment with alemtuzumab.

**What Side Effects Are Caused by Histone Deacetylase Inhibitors?**

The common histone deacetylase (HDAC) inhibitor therapies belinostat (Beleodaq), romidepsin (Istodax), and vorinostat (Zolinza) can cause diarrhea, thrombocytopenia (low platelet counts) with an increased risk of bleeding, nausea, loss of appetite, weight loss, muscle aches, high blood sugar, and fatigue. Tests may be done to monitor the effects of treatment on the liver and/or heart. Patients with rapidly progressing tumors or a large number of tumors may also be at risk for TLS.

**What Side Effects Are Caused by Signaling Inhibitors?**

*Ibrutinib (Imbruvica)*

The most common side effects caused by ibrutinib are decreased platelets and neutrophils, anemia, diarrhea, upper respiratory tract infections/inflammation, feeling unusually tired or weak, muscle and bone pain, swelling of the hands, feet, ankles, and lower legs, nausea, bruising, difficulty breathing, constipation, rash, stomach pain, vomiting, sinus infection, and decreased appetite. Serious side effects include bleeding problems, hypertension, atrial fibrillation (a disorder of the heart rhythm), infections, kidney problems, and secondary cancers (such as skin cancer). In patients who have history of atrial fibrillation or are at risk for atrial fibrillation (ie, patients with diabetes or hypertension), ibrutinib has been associated with an increased risk. New drugs may have unforeseen cardiac toxicities.
Patients receiving ibrutinib should notify their doctor if they are considering any surgical procedure or if they have undergone any emergency procedure because ibrutinib treatment will have to be stopped for a short period of time before and after these procedures because of an increased risk of bleeding.

**Idelalisib (Zydelig)**

Idelalisib is well tolerated by most patients. The most common side effects associated with idelalisib therapy are diarrhea, fever, fatigue, nausea, cough, pneumonia, abdominal pain, chills, and rash. Rarer but serious side effects include severe skin reactions, life-threatening allergic reaction (anaphylaxis), and low neutrophil count (neutropenia). Very serious and potentially life-threatening side effects, such as liver problems, colitis with severe diarrhea, pneumonitis with lung or breathing problems, and tears in the intestinal wall (perforation) have also occurred in patients receiving idelalisib.

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

- Any symptoms of liver problems (yellow skin, dark or brown urine, pain in the upper-right side of the stomach, bleeding, or bruising more easily than normal)
- An increase in the number of bowel movements to six or more per day
- A new or worsening cough, shortness of breath, difficulty breathing, or wheezing
- A new or worsening pain in the stomach area, chills, fever, nausea, or vomiting
What Side Effects Are Caused by Lenalidomide (Revlimid)?
The most common side effects of lenalidomide are decreased red
cell, white blood cell, and platelet counts. Other common side
effects include diarrhea, rash, constipation, muscle cramping, and
feeling tired. Increased clotting of the blood may also occur and
patients may be advised to take aspirin or a blood thinner while taking
lenalidomide.

What Side Effects Are Caused by Radiation Therapy?
Radiation therapy itself is painless, but it can cause short-term and
long-term side effects, which vary depending on the type of radiation,
the radiation dose used, and the area of the body treated. Side effects
are usually worse when radiation therapy and chemotherapy are given
at the same time. It is important to remember that radiation only affects
the area that is treated much like a flashlight only illuminates the area
it shines upon.

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

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

The potential short- and long-term side effects of radiation therapy are
shown in the box on the following page.
Examples of Potential Short-Term Side Effects of Radiation Therapy

- Nausea, vomiting, and diarrhea due to radiation to the stomach area.
- A dry, sore throat, mouth sores, and trouble swallowing due to radiation to the chest and neck.
- Hair loss and red, dry, and tender skin may occur due to radiation to any area of the body.
- Decreased levels of red and white blood cells may occur due to radiation to the pelvis, legs, and torso (the large areas of your body that contain most of your blood-producing bone marrow).
- Fatigue, which may progressively worsen during the later weeks of the treatment cycle, may be due to radiation to any part of the body.

Examples of Potential Long-Term Side Effects of Radiation Therapy

- Development of new cancers may occur in the parts of the body treated with radiation.
- Cardiovascular damage to the coronary arteries, the cardiac muscle, or the heart valves, which can increase the risk of heart attack and stroke due to radiation to the chest.
- Lung damage and problems breathing due to radiation to the chest.
- Thyroid cancer or thyroid problems (such as fatigue and weight change) later in life due to radiation to the neck.
- Headaches, memory loss, personality changes, and trouble concentrating due to radiation to the brain.
- Neck muscle weakness (“neck drop”) causing difficulty lifting the head, and neck pain or discomfort due to radiation to the neck.
**Cardiovascular Damage**
Radiation therapy can cause damage to the arteries, most commonly those in the neck (carotid arteries) and in the heart (coronary arteries), which could increase the risk of heart attack and stroke. Patients treated with radiation should receive regular evaluations to check for heart damage. Statin drugs are frequently used to prevent coronary artery disease.

**Dry Mouth**
Patients who receive radiation therapy to the mouth may experience a temporary decrease in saliva production, or dry mouth (*xerostomia*). Dry mouth may result in difficulty swallowing foods or thick liquids. Dry mouth 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.

**Fatigue**
The likelihood that patients will experience fatigue depends on their disease and their specific radiation plan. Patient tips for coping with fatigue are included on page 110.

**Loss of Appetite and Taste**
During radiation treatment, patients might lose their appetite for foods they normally enjoy. The loss of appetite and taste are usually short-term problems. Patients should remember to eat healthy because their body needs energy and good nutrition to heal. 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 on 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 the patient avoid nausea. The doctor may prescribe an anti-nausea (*antiemetic*) medication to be taken before each radiation therapy session. Patient tips for coping with nausea are included on page 115.

Secondary Cancers
The risk of developing secondary cancers from radiation therapy depends on such factors as the amount of radiation given (the dose) and the part of the body treated (the field). All the information currently available is from studies 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, but risk of secondary cancers after these treatments is unknown. It is imperative that all patients protect irradiated skin from direct sun exposure, even if the radiation was administered in past years.

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. Some skin changes may last much longer or be permanent. These changes include darker and blotchy skin, very dry skin, or thicker skin. The radiated area will sunburn more easily than other parts of the body. Patients should avoid tanning beds and protect their skin from the sun with a hat, long-sleeved shirts, long pants, and sunscreen with an SPF of at least 30. Patients should speak with the doctor or nurse if they experience any skin changes. A list of tips to help patients care for their skin during and after radiation therapy is provided on the following page.
Skin Care During and After Radiation Therapy

- Be gentle with your skin; do not rub, scrub, or scratch.
- Use lotions and other skin products 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).
- Take a shower or bathe in lukewarm water. If you bathe, do it every other day and soak for less than 30 minutes; always use a mild, unscented soap; pat your skin dry; and do not 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 clothes and use soft sheets, such as those made with cotton.
- Do not wear tight clothes because they do not allow your skin to breathe.
- 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; protect your skin from the sun every day (use a wide-brimmed hat, long-sleeved shirt, and long pants or skirt outside) regardless of the time elapsed from the radiation treatment.
- Do not use tanning beds.
- 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 with an electric razor. 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. Ensure that you don’t become dehydrated during treatment. Difficulty swallowing will usually go away a few weeks after treatment is completed. The tips listed below may help ease throat irritation during radiation therapy.

Easing Throat Irritation During Radiation Therapy
- Eat bland foods that are soft, smooth, and easy to digest, such as pudding, yogurt, and milkshakes.
- Take small bites and swallow each bite completely before taking another bite.
- Try using thicker liquids, such as foods that have been pureed in a blender, which are easier to swallow.
- Avoid citrus fruits, especially juices.

Will Radiation Treatment Make the Body Radioactive?
External beam radiation does not cause a patient’s tissues to become radioactive. 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 will remain in the hospital and shielded from others during short exposures to internal radiation therapy. With permanent internal radiation and systemic radiation treatment, patients will be 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 will provide more information to patients, family members, and caregivers about special precautions...
that should be taken. The radioactivity will break down over time to the point where no radiation can be measured outside the patient’s body.

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 in most patients. These side effects may be prolonged in duration and last up to several months, which can leave patients susceptible to infections. Reactions at the site of the treatment infusion are also possible. These reactions can be severe and serious 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 Brentuximab Vedotin (Adcetris)?
The most common side effects reported in patients treated with brentuximab vedotin include a depressed immune system, low blood counts, peripheral neuropathy (numbness or tingling in the hands and/or feet), fatigue, nausea, anemia, upper respiratory tract infection, diarrhea, fever, rash, thrombocytopenia, cough, and vomiting. Patients may also experience reactions at the site of the treatment infusion. Hair loss is possible.

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 104 and the section “What Side Effects Are Caused by Radiation Therapy?” on page 121).

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 (mucositis), infection, anemia, and bleeding. 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 condition where the donated bone marrow attacks the patient’s tissues. 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. This represents a substantial risk to patients undergoing this procedure.

For more information, view the Transplantation in Lymphoma fact sheet on LRF’s website at www.lymphoma.org.

**When Should a Patient’s Doctor Be Contacted?**

As a general rule, a patient’s doctor should be contacted if:

- The patient experiences a side effect that is unexpected or lasts longer than expected.
- The patient experiences a medical problem—such as fever, shortness of breath, prolonged or constant nausea and vomiting, chest pains, and/or dizziness—that cannot wait for a regularly scheduled appointment.
Chapter 8: Managing Life During and After Treatment

This chapter discusses some general issues that patients may encounter while they live their life during and after treatment.

Coping Strategies

Each person’s experience with cancer is different, and how he or she copes with the physical and emotional impacts of having non-Hodgkin lymphoma (NHL) is unique to a patient’s personality and situation. Table 8.1 lists some suggestions for how to cope with some issues that patients may face.

Table 8.1. Coping Strategies

<table>
<thead>
<tr>
<th>Maintain a Strong Support System</th>
<th>Get Help For Depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>■ Communicate your fears and concerns about your disease by talking to your family, friends, doctors, and counselors.</td>
<td>■ Feeling sad or depressed is not unusual in patients living with cancer.</td>
</tr>
<tr>
<td>■ Writing down your concerns in a journal may also help.</td>
<td>■ Watch out for signs of depression: sleeping more or less than usual; feeling a lack of energy; crying; inability to concentrate.</td>
</tr>
<tr>
<td>■ Find a support group or other individuals who are also coping with cancer.</td>
<td>■ 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.</td>
</tr>
<tr>
<td></td>
<td>■ Find a support group of people who have had similar experiences.</td>
</tr>
</tbody>
</table>
### Table 8.1. Coping Strategies (continued)

<table>
<thead>
<tr>
<th>Deal With Physical Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Some patients with cancer may feel unattractive because of hair loss and other changes in appearance caused by their treatment.</td>
</tr>
<tr>
<td>- Ask your doctor what changes you should expect; plan ahead and buy a wig or head covering if hair loss is a possibility.</td>
</tr>
<tr>
<td>- Seek advice from a beautician about makeup for the areas that you consider a problem.</td>
</tr>
<tr>
<td>- Ask your healthcare team for advice on how to manage temporary changes such as dry skin, brittle nails, and a blotchy complexion.</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Maintain a Healthy Lifestyle</th>
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<tbody>
<tr>
<td>- Eat a healthy diet that includes fruits, vegetables, proteins, and whole grains.</td>
</tr>
<tr>
<td>- Engage in regular physical exercise, which can help reduce anxiety, depression, and fatigue, and improve mood.</td>
</tr>
<tr>
<td>- Get sufficient rest to help combat the stress and fatigue of your disease and its treatment.</td>
</tr>
<tr>
<td>- Quit smoking and reduce alcohol consumption.</td>
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<table>
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<tr>
<th>Set Reasonable Goals</th>
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<tbody>
<tr>
<td>- Having goals for how you want to live your life during and after treatment can help you maintain a sense of purpose.</td>
</tr>
<tr>
<td>- Avoid setting unreasonable goals; such as deciding to work full-time when part-time would be much better for your health.</td>
</tr>
<tr>
<td>- Stay as active and involved as you can in work and other activities that interest you.</td>
</tr>
</tbody>
</table>

### The Importance of Pain Control

In some situations, patients may experience pain from the cancer itself or from treatments and procedures. Cancer pain is very treatable, and there is no reason for a patient to endure this pain without help. Patients should tell their doctors and nurses if they have any pain because they can offer advice regarding medications and other ways to relieve the pain, as some medications may not be appropriate for their disease.
Different types of pain are best controlled by different types of pain relievers. Patients should ask their healthcare team which options are best to help manage their pain. Please see the tips below for managing pain.

**Managing Pain**

- Tell your doctor or nurse about your pain. Be specific when you describe it.
- Where do you feel the pain?
- When did the pain start?
- What type of pain is it (sharp, dull, throbbing)?
- Does it come and go, or is it steady?
- How strong is it? How long does it last?
- Does anything make the pain feel better or worse?
- Which 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, you have nothing to prove!

Several types of exercise are 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 remedy 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 will help patients keep up their strength and energy, tolerate treatment-related side effects, decrease their risk of infections, and heal and recover more quickly. Patients should aim for a diet high in fruits and vegetables, protein (poultry, fish, and eggs), and whole grains. During chemotherapy and after a stem cell transplant, the patient may be asked to temporarily avoid raw fruits and vegetables that may increase the risk of infection if they have a low white blood cell count ("neutropenic diet"). The healthcare team can help develop an eating plan that is appropriate. Patients should talk to their doctor before taking any dietary supplements, such as multivitamins or individual vitamin supplements, as well as any herbal or "natural" supplements, because they may interfere with treatments or have unexpected side effects.
The Importance of Follow-up Care
At the first visit following the completion of treatment, patients should discuss their follow-up schedule with the doctor. This schedule will be different for each patient depending on their disease type and stage, age, and overall health. Patients should adhere to their schedule of follow-up visits—these are very important for monitoring disease recurrence and detecting and treating any new health problems that might have been caused by the treatment.

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

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

- Copies of all medical records and a written summary of their treatment(s) in case the patient switches doctors or needs to see a primary care physician for routine medical care
- A list of signs of disease recurrence and late side effects from treatment
At the follow-up care appointments, patients should inform their doctor of:

- Any new symptoms
- Pain
- Physical problems that disrupt their daily life, such as fatigue, insomnia, sexual dysfunction, and weight gain or loss
- Any new health problems, such as heart disease, diabetes, and high blood pressure
- Any new medications and vitamins they are taking, including over-the-counter preparations
- Emotional problems, such as anxiety and depression
- Any other questions or concerns
Chapter 9: Preparing to Go to the Hospital

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

Hospital admission usually occurs either in the emergency room or through direct admission by the patient’s doctor for diagnostic testing or for treatment, if needed. In the case of a direct admission, the patient has seen their doctor and he/she feels that the patient should be admitted to the hospital. The doctor will call ahead and reserve a bed for the patient.

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

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

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

When being admitted to the hospital, being prepared can ease the process of admission and positively impact patients’ care. A brief list of items for patients to take with them is identified in the Patient Tip on the following page.
What to Bring if You Are Being Admitted to the Hospital

- Identification (driver’s license, student ID) and emergency contacts (relatives and friends’ names and phone numbers).

- List of all allergies and the reaction that occurs in response to allergen exposure (especially important for latex and pharmaceutical allergies).

- List of all current medications (name, strength, frequency) and “treatments” (include over-the-counter medications, such as Tylenol, vitamins, herbals, and any other items such as energy enhancers). If you do not have a list, place all medications in a bag and bring them with you.

- List all surgeries (even elective plastic surgeries) regardless of how long ago they occurred.

- Name 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, and/or a credit card.

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

If the patient has access to an up-to-date and complete medical record through a patient portal, flash drive, or phone app, bring the security code for these medical records and the name of the website, or the flash drive or phone app or device that contains the health information.
What Is the Purpose of an Advance Healthcare Directive and Appointing a Healthcare Proxy?

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

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

Besides stating medical care instructions, people may also consider naming a *healthcare proxy*, or a decision maker, in an Advance Healthcare Directive. This person should be someone who will carry out their wishes, including any do-not-resuscitate (DNR) instructions. It is best to have both an Advance Healthcare Directive and a healthcare proxy.

Before writing an Advance Healthcare Directive, it is important to understand patients’ rights and laws regarding Advance Healthcare Directives in each state. Consulting an attorney can provide legal information, but an attorney is not required to write an advance directive. An Advance Healthcare Directive may include:

- Specific instructions on medical care, including the type of special treatment that is or is not desired, such as cardiopulmonary resuscitation (CPR), artificial respiration, 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 for your state, please visit the “Planning Ahead” section of the National Hospice and Palliative Care Organization website at www.caringinfo.org.
What Are Patient’s Rights?
A patient’s rights are listed in the hospital’s Patient’s Bill of Rights. See the tips below for more information about these rights.

Your Rights As a Patient

- You must be given a medical screening examination and be evaluated for care whenever you are admitted to a hospital.
- You have the right to considerate and respectful care.
- You have the right to complete information regarding all aspects of your current condition.
- You have the right to know the names of all doctors and healthcare personnel providing your care.
- Sufficient information about the benefits and risks for all treatments or procedures to enable you to provide informed consent.
- You have the right to refuse any treatment.
- You have the right to privacy—none of your healthcare team can talk about your condition.
- If you must be transferred to another facility, the information on why you require transfer must be provided and the institution that you are being transferred to must have accepted you prior to transfer.
- You also 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 examine and receive an explanation of your bill.
- You have the right to know what hospital rules and regulations apply to your conduct.
What Do Patients Need to Know About Informed Consent Documents When in the Hospital?
If the patient is admitted to a teaching hospital, he/she may receive informed consent documents. These documents should enable patients to decide which treatments/procedures they are willing to receive. Signing these documents indicates that the patient understands the risks and benefits of the treatments/procedures being performed. The tips below will help patients know what to look for in informed consent.

What to Look For On the Hospital Informed Consent Document

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

What Do Patients Need to Know at Discharge?
When the patient is to be discharged, make sure the case manager addresses the issues identified in the following Patient Tip.
Issues For the Case Manager to Resolve Before Discharge

- Are there any new limitations to what you can do at work or at home? If so, your doctor can provide a note for your employer if needed.
- Will you need physical therapy to maintain functions?
- If you need any new medical equipment, where can it be obtained? Who will order it? Obtain a phone number to ensure you can follow up if there are any problems with equipment delivery.
- Will you need home nursing care or other arrangements?
- What new medication will you need to take, and for how long?
- Does your insurance cover the new medication as an outpatient? If not, or if you don’t have insurance, what will the cost be?
- If you don’t have insurance, does the hospital have a sliding-scale fee or charity care?
- Are there alternative medications if the cost is beyond your capacity to pay?
- What are the side effects of the new medications?
- Will they interact with any medications you currently are on?
- Are there other instructions from your doctor or the hospital physician?
- Whom should you follow up with and when?
- If you are to schedule your own follow-up, whom do you call?
- Who is responsible for paying for your care?
For itemized bills, make sure no mistakes were made. If there are discrepancies in the bill and the care patients receive, bring it to the attention of both the hospital and the insurance company.

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

Hospitals may send patient satisfaction surveys to patients after discharge. This survey is an opportunity for patients to share issues they had with their care during their stay and/or to recognize those staff members whose care and support they felt were exceptional. Believe it or not, hospitals and their administrators pay close attention to these surveys so it is worth the time to complete and return the survey so issues can be addressed and staff members providing excellent care can be acknowledged. If no survey is sent and you still want to report problems or satisfaction with the patient’s care, you can write a letter to the hospital administrator or appropriate department director.
Chapter 10: Overview of Clinical Trials

There are hundreds of 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 people who volunteer to participate. Clinical trials are also sometimes referred to as clinical studies. However, the term “clinical study” is broadly used to describe many different types of studies in addition to those described in this chapter.

The purpose of clinical trials in cancer is to answer specific questions about new ways to prevent, diagnose, treat, or manage a disease or the side effects caused by a new or existing treatment. 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 people. 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 determine the correctness of the study.
As shown below 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 are conducted after a drug has received FDA approval; these trials are sometimes called postmarketing studies. Each phase is designed to find out certain information, building upon the information learned from the previous phase. Patients may be eligible to participate in different types of clinical trials depending on their health status, type and stage of NHL, and the type of treatment, if any, they previously received.

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

<table>
<thead>
<tr>
<th>Phase</th>
<th>Purpose</th>
<th>Number of Volunteer Patients</th>
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<tbody>
<tr>
<td>Phase I</td>
<td>■ To identify a safe dose.</td>
<td>■ 15–30 people with one or more different types of cancer.</td>
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<tr>
<td></td>
<td>■ To decide on a schedule.</td>
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<tr>
<td></td>
<td>■ To see what side effects are related to the therapy.</td>
<td></td>
</tr>
<tr>
<td>Phase II</td>
<td>■ To find out if a new treatment has an effect against a certain type of cancer.</td>
<td>■ Usually less than 100 people with the same type of cancer.</td>
</tr>
<tr>
<td></td>
<td>■ To see if the treatment causes any side effects.</td>
<td>■ Randomized Phase II studies involve more than 100 people in two study arms.</td>
</tr>
<tr>
<td>Phase III</td>
<td>■ To compare new treatments or new uses of existing treatments with current standard treatments.</td>
<td>■ From 100 to several thousand people with the same type of cancer.</td>
</tr>
<tr>
<td></td>
<td>■ The main comparisons are usually how well the treatment works and what types of side effects it causes.</td>
<td>■ Patients are randomly assigned to a treatment group; one group receives the standard therapy and the other group receives the experimental treatment.</td>
</tr>
<tr>
<td>Phase IV</td>
<td>■ To find out more information about the long-term safety and effectiveness of a new treatment.</td>
<td>■ Several hundred to several thousand people with the same type of cancer.</td>
</tr>
<tr>
<td></td>
<td>■ These trials take place after the drug has been marketed.</td>
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</table>
Why Is a Placebo Sometimes Used in Phase III Trials?

In cancer clinical trials, patients are never given a placebo in place of an effective standard therapy. Placebo-controlled trials are NEVER DONE in a manner that would deny patients an effective therapy. In most cases, a placebo may be added to a standard regimen to compare an investigational agent with that same standard regimen.

A placebo, or sugar pill, is an inactive ingredient that is used as a comparator in some clinical trials. The placebo is made to look and taste the same as the experimental pill or have the same appearance as an intravenous agent. The patients and the doctors and nurses treating them may not know what type of treatment is being given. In Phase III trials, patients are usually selected at random for either the experimental group receiving the study drug or the control group receiving the current standard treatment(s) for their particular lymphoma. Many patients who are in the placebo group will still benefit from the standard of care.

Should a Patient Participate in a Clinical Trial?

Clinical trials are not a “last resort” for patients and it may be important to note that all approved drugs underwent evaluation before they were approved through the clinical trials process. Patients with all stages of NHL can participate in clinical trials, whether at the time of initial diagnosis or at relapse. Clinical trials may offer many benefits and risks. Patients in clinical trials may be able to try new treatments that are not otherwise available to all patients. However, being part of the trial may mean that the patient receives the standard therapy. If the patient receives the new treatment, it may or may not be more effective than the standard therapy. An advantage of clinical trials is that the health of enrolled patients is monitored very closely. The healthcare team studying the new treatment will explain all of the possible benefits and risks of a specific clinical trial.

Every clinical trial is led by a principal investigator, who is usually a medical doctor. Clinical trials also have a research team that may
include nurses, social workers, and other healthcare professionals. Patients usually continue regular visits with their current healthcare provider who may work with the research team to ensure that any investigational treatment would not interfere with current medication or treatments.

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

Some professional organizations, like the National Comprehensive Cancer Network (NCCN, which develops guidelines for doctors to use in treating patients with all types of cancers), actively encourage the participation of patients with cancer in clinical trials because they provide the best management for any patient with cancer.

**What Is Informed Consent In a Clinical Trial?**

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

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

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

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

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, other 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 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 undertakings 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 will cover, and the patient’s health insurance coverage. A patient should ask his or her doctor about the potential cost of participating in any clinical trial under consideration.

In most instances the law requires the healthcare plan to cover clinical trials. The March 2010 Affordable Care Act (ACA) states that all healthcare plans (offered through an employer or purchased through an ACA exchange) that were newly issued or renewed on or after January 1, 2014, are not allowed to limit or deny coverage to people who decide to participate in an approved clinical trial. However, this patient protection provision does not apply to healthcare plans that existed before January 1, 2014. Some of these “grandfathered” plans do pay for the basic medical procedures associated with the trial, such as laboratory tests, scans, and hospitalization when required, while others may define clinical trials as “experimental” or “investigational” and not cover some of the routine costs, such as doctor visits, tests, or treatments. Medicare provides coverage for patient care associated with most clinical trials.

If a patient is taking part in an NCI trial being conducted at the National Institutes of Health (NIH) campus located in Bethesda, Maryland, the NCI will pay for the study drug and the costs related to the study. Additional funding to assist with travel, food, and lodging expenses is also provided. Some cancer centers provide financial assistance or discounted rates for lodging and meals and have special research units that will pay for some study-related costs. Some organizations, including the Lymphoma Research Foundation (LRF), provide some financial assistance for treatment-related expenses. For more information on financial aid, please view the Resources for Financial Assistance fact sheet on LRF’s website at www.lymphoma.org.
Patients should ask their doctor what clinical trials may be most appropriate for them. Here are some additional sources of clinical trial information:

- The LRF Helpline at (800) 500-9976 or email 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
- Cancer centers in the area
Chapter 11: Advances in Treatment of Patients With Non-Hodgkin Lymphoma

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

Drugs that are not yet approved for sale 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 using tissue culture cells and laboratory animals. 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 and are then 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 the website at www.clinicaltrials.gov to search for trials using a particular drug or to find clinical trials nearby.

Remember that today’s science is moving very quickly. Check with your doctor or the Lymphoma Research Foundation 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 booklet.
Chemotherapy
Researchers are trying to develop new chemotherapy drugs, improve versions of existing drugs, and find better ways to combine different doses and sequences of existing drugs. The goal is to develop drugs that are better at eradicating NHL cells while leaving healthy cells alone (decreasing the chance of side effects).

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) transplantations; improving ways to remove all lymphoma cells from stem cell samples used for autologous (self) transplants; and developing more effective reduced-intensity stem cell transplantations.

Monoclonal Antibodies and Immunoconjugates
Monoclonal antibodies, which are drugs that mimic our own immune proteins, are designed to recognize and stick to specific target molecules on cancer cells. When a monoclonal antibody attaches itself to a cancer cell, it can stop or slow down its growth or make it easier for the immune system to recognize the cell and kill it. 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 ocaratuzumab (AME-133v), otlertuzumab (TRU-016), ublituximab (TG-1101), mogamulizumab (Poteligeo), MOR00208, and others. A different family of monoclonal antibodies targeting “checkpoints”, which put the brakes on immune cells’ ability to attack tumor cells, have recently been developed. These antibodies against PD-1, nivolumab (Opdivo) or pembrolizumab (Keytruda) take the brakes off of the immune system, and have generated enthusiasm among lymphoma specialists given the early responses observed in clinical trials for patients with B-cell malignancies.
Immunoconjugates, which are monoclonal antibodies attached to toxins or radioactive or other particles that can help kill cancer cells, are also in early development. Examples of such antibody-drug and antibody-toxin conjugates are polatuzumab vedotin (DCDS4501A), pinatuzumab vedotin (DCDT2980S), coltuximab ravtansine (SAR3419), IMGN529, and betalutin ($^{177}$Lu-tetraxetan-tetulomab).

**Targeted Therapies**

In addition to monoclonal antibodies that target molecules on the surface of cancer cells, many drugs are in development that target molecules inside cancer cells. 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. These specific molecules usually have important roles in controlling the growth and survival of lymphoma cells. The drugs that target these molecules are broadly called targeted, novel, or biologic therapies. These drugs may kill the lymphoma cells or slow down or stop their growth. Targeted therapies attack cancer cells in a more specific way than chemotherapy drugs and are less likely to kill or damage healthy cells. This characteristic makes it less likely that these agents will cause serious side effects.

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

- Histone deacetylase (HDAC) inhibitors such as panobinostat (Farydak), which targets molecules that help control which proteins are produced by a cell

- Mammalian target of rapamycin (mTOR) inhibitors, such as temsirolimus (Torisel) and everolimus (Afinitor), which target molecules in cell biochemistry pathways involved in cell growth and division

- Inhibitors of B-cell lymphoma-2 (Bcl2), such as venetoclax (ABT-199) and navitoclax (ABT-263), which target molecules that prevent cancer cells from dying
Kinase inhibitors, which block the transmission of signals from the surface of the cell to the cell’s control center (the nucleus), including:

– Aurora A kinase inhibitors such as alisertib (MLN8237) or AKT inhibitors such as MK2206, which interfere with normal cell division

– Bruton’s tyrosine kinase (BTK) inhibitors such as CC-292 (formerly AVL-292), which stop signals in cancer cells related to growth and survival

– The phosphoinositide-3 kinase (PI3K) delta inhibitor TGR-1202, which blocks signals in B-cells related to growth and survival

– The spleen tyrosine kinase (Syk) inhibitor entospletinib (GS-9973), which interferes with B-cell receptor signaling

Purine nucleoside phosphorylase (PNP) inhibitors such as forodesine (BCX-1777), which result in T- and B-cell-specific apoptosis (programmed cell death)

**Proteasome Inhibitors**

Bortezomib (Velcade) is a proteasome inhibitor currently approved for multiple myeloma and mantle cell lymphoma. Bortezomib targets the 26S proteasome and is currently being investigated, either alone or in combination with other drugs, for other NHL types including follicular lymphoma, marginal zone lymphoma, Waldenström macroglobulinemia, and several other lymphomas.

Carfilzomib (Kyprolis), a proteasome inhibitor approved for patients with relapsed/refractory multiple myeloma, is also being tested in clinical trials in various types of NHL. It targets certain active sites of the 20S proteasome, the proteolytic core particle of the 26S proteasome.
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, not prevent, lymphomas. The hope is that these vaccines might boost a person’s own immune system to recognize and kill lymphoma cells early during the course of the disease.

Genetically Engineered T Cells

Researchers have treated a small number of patients with NHL, chronic lymphocytic leukemia (CLL), and acute lymphoblastic lymphoma (ALL) with genetically engineered immune cells, or T cells. T cells are removed from patients and genetically modified to produce special receptors on their surface called chimeric antigen receptors (CARs), which allow them to recognize and kill malignant cells. The genetically engineered CAR-T cells are grown in the laboratory until they number in the billions and are then infused back into the patient. The CARs on the surface of T cells allow them to recognize a specific protein (antigen) on the tumor cells such as CD19, so that the patient’s own immune system can selectively kill them. CD19 may be an ideal tumor target for CAR therapy because it is expressed on almost all NHL, CLL, and ALL cells.

Once infused into the body, the genetically modified T cells can grow to large numbers and amplify the antitumor response, persisting for long periods of time and providing ongoing tumor control and possible protection against recurrence. Some patients have had very good responses, with no malignant tumor cells detected after treatment. However, this therapy can also result in significant side effects, such as tumor lysis syndrome or “cytokine release syndrome” after treatment. Some patients have reduced immunoglobulin and require monthly gamma globulin supplementation. Although this treatment approach looks very promising, much more research needs to be done to investigate the long-term effects of this kind of therapy and to better manage/control the side effects.
Nanoparticle drug delivery
Trials are beginning in nanoparticle delivery systems. Drugs are attached on to nanoparticles, which will potentially deliver drugs more efficiently.

ABOUT THE LYMPHOMA RESEARCH FOUNDATION
At the Lymphoma Research Foundation (LRF), our goal is to change the future for everyone whose life has been affected by a lymphoma diagnosis. We are dedicated to funding biomedical research; training the next generation of lymphoma investigators; raising public awareness of the disease; and providing education and support to people with lymphoma, their families and caregivers.

Advocacy Program
LRF supports public policies which seek to increase federal funding for lymphoma research and ensure access to high quality cancer care. The LRF Advocacy Program provides volunteer advocates with the resources necessary to garner attention and support for those public policies most important to the lymphoma community. There are currently more than 5,000 LRF advocates in all 50 states and the District of Columbia.

Outreach and Awareness
LRF offers numerous fundraising and awareness programs – including the signature Lymphoma Walk program and Team LRF – which allow members of the lymphoma community to become involved with the organization and support the LRF mission.

Patient Education and Services
LRF provides a comprehensive series of programs and services for members of the lymphoma community, including: Clinical Trials Information Service; Disease-Specific e-Newsletters, Publications, Videos, and Websites; Financial Assistance Programs; In-Person Education Conferences; Lymphoma Helpline; Lymphoma Support Network; Mobile App (www.focusonlymphoma.org); Teleconferences; and Webcasts/Podcasts.
Professional Education
LRF is committed to educating healthcare professionals on the latest developments in lymphoma 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 remains dedicated to finding a cure for lymphoma through an aggressively-funded research program and by supporting the next generation of lymphoma investigators. LRF supports these goals through Clinical Investigator Career Development Awards, 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.

Contact Information
LRF National Headquarters
115 Broadway, Suite 1301
New York, NY 10006
Phone: (212) 349-2910
Fax: (212) 349-2886
Email: LRF@lymphoma.org
Website: www.lymphoma.org

LRF Helpline
Phone: (800) 500-9976
Email: helpline@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

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National Headquarters
115 Broadway, Suite 1301
New York, NY 10006
(212) 349-2910 phone • (212) 349-2886 fax
Helpline: (800) 500-9976; helpline@lymphoma.org
Website: www.lymphoma.org - Email: LRF@lymphoma.org