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Non-Hodgkin Lymphoma

Tom, non-Hodgkin lymphoma survivor

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A Message from Louis J. DeGennaro, PhD

President and CEO of The Leukemia & Lymphoma Society

The Leukemia & Lymphoma Society (LLS) is the world's largest voluntary health organization dedicated to finding cures for blood cancer patients. Our research grants have funded many of today's most promising advances; we are the leading source of free blood cancer information, education and support; and we advocate for blood cancer patients and their families, helping to ensure they have access to quality, affordable and coordinated care.

Since 1954, we have been a driving force behind nearly every treatment breakthrough for blood cancer patients. We have invested more than $1 billion in research to advance therapies and save lives. Thanks to research and access to better treatments, survival rates for many blood cancer patients have doubled, tripled and even quadrupled.

Yet we are far from done.

Until there is a cure for cancer, we will continue to work hard—to fund new research, to create new patient programs and services, and to share information and resources about blood cancer.

This booklet has information that can help you understand non-Hodgkin lymphoma, prepare your questions, find answers and resources, and communicate better with members of your healthcare team. Our vision is that, one day, all people with non-Hodgkin lymphoma will be cured or will be able to manage their disease so that they can experience a great quality of life. Today, we hope that our sharing of expertise, knowledge and resources will make a difference in your journey.

Louis J. DeGennaro, PhD
President and Chief Executive Officer
The Leukemia & Lymphoma Society

Inside This Booklet

Acknowledgement

The Leukemia & Lymphoma Society gratefully acknowledges, for her critical review and important contributions to the material presented in this booklet,

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Introduction

This booklet provides information about non-Hodgkin lymphoma (NHL) for patients and their families. Lymphoma is a general term for a group of blood cancers that start in the lymphatic system. Brief descriptions of normal blood and bone marrow, the lymphatic system, and definitions of medical terms are included in this booklet.

An estimated 606,972 people in the United States are either living with or in remission from NHL in 2016. About 72,580 people were expected to be diagnosed with NHL in 2016. Advances in the treatment of NHL are resulting in improved remission and cure rates. New approaches to therapy are being studied in clinical trials for patients of all ages and for all disease stages.

Resources and Information

LLS offers free information and services to patients and families affected by blood cancers. This section of the booklet lists various resources available to you. Use this information to learn more, to ask questions, and to make the most of your healthcare team members' knowledge and skills.

For Help and Information

Consult with an LLS Information Specialist. Information Specialists are master's level oncology social workers, nurses and health educators. They offer up-to-date disease and treatment information. Language services are available. For more information, please

- Call: (800) 955-4572 (Monday through Friday, 9 a.m. to 9 p.m. EST)
- Email: infocenter@LLS.org
- Live chat: www.LLS.org
- Visit: www.LLS.org/informationspecialists.

Free Information Booklets. LLS offers free education and support booklets that can be either read online or ordered in print versions. For more information, please visit www.LLS.org/booklets.

Telephone/Web Education Programs. LLS offers free telephone/Web education programs for patients, caregivers and healthcare professionals. For more information, please visit www.LLS.org/programs.

Co-Pay Assistance Program. LLS offers insurance premium and medication co-pay assistance for eligible patients. For more information, please

- Call: (877) 557-2672
- Visit: www.LLS.org/copay.

Sign Up for an E-newsletter. Read the latest disease-specific news, learn about research studies and clinical trials, and find support for living with blood cancer. Please visit www.LLS.org/signup.

Community Resources and Networking

Online Blood Cancer Discussion Boards and Chats. Online discussion boards and moderated online chats can provide support and help cancer patients to reach out and share information. For more information, please visit www.LLS.org/discussionboard and www.LLS.org/chat.

LLS Community. LLS Community is an online social network and registry for patients, caregivers, and supporters of those with blood cancer. It is a place to ask questions, get informed, share your experience and connect with others. To join visit www.LLS.org/community.

LLS Chapters. LLS offers community support and services in the United States and Canada including the *Patti Robinson Kaufmann First Connection Program* (a peer-to-peer support program), in-person support groups, and other great resources. For more information about these programs or to contact your chapter, please

- Call: (800) 955-4572
- Visit: www.LLS.org/chapterfind.

Other Helpful Organizations. LLS offers an extensive list of resources for patients and families. There are resources that provide help with financial assistance, counseling, transportation, locating summer camps and other needs. For more information, please visit www.LLS.org/resourcedirectory.

Clinical Trials (Research Studies). New treatments for patients are under way. Patients can learn about clinical trials and how to access them. For more information, please call (800) 955-4572 to speak with an LLS Information Specialist who can help conduct clinical-trial searches.

Advocacy. The LLS Office of Public Policy (OPP) engages volunteers in advocating for policies and laws that encourage the development of new treatments and improve access to quality medical care. For more information, please

- Call: (800) 955-4572
- Visit: www.LLS.org/advocacy.

Additional Help for Specific Populations

Información en Español (LLS information in Spanish). For more information, please visit www.LLS.org/espanol.

Language Services. Let your doctor know if you need a language interpreter or other resource, such as a sign language interpreter. Often, these services are free.

World Trade Center (WTC) Survivors. People involved in the aftermath of the 9/11 attacks and subsequently diagnosed with a blood cancer may be eligible for help from the World Trade Center (WTC) Health Program. People eligible for help include

- Responders
- Workers and volunteers who helped with rescue, recovery and cleanup at the WTC-related sites in New York City (NYC)
- Survivors who were in the NYC disaster area, lived, worked or were in school in the area
- Responders to the Pentagon and the Shanksville, PA crashes.
- For more information, please
  - Call: WTC Health Program at (888) 982-4748
  - Visit: www.cdc.gov/wtc/faq.html.

People Suffering from Depression. Treating depression has benefits for cancer patients. Seek medical advice if your mood does not improve over time—for example, if you feel depressed every day for a two-week period. For more information, please

- Call: the National Institute of Mental Health (NIMH) at (866) 615-6464
- Visit: NIMH at www.nimh.nih.gov. Enter "depression" in the search box.

Feedback. To give suggestions about this booklet, visit www.LLS.org/publicationfeedback.

Lymphoma

"Lymphoma" is a general term for a group of blood cancers that start in the lymphatic system, which is part of the body's immune system. The two major types of lymphoma are Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL).

Both Hodgkin and non-Hodgkin lymphoma are further classified into subtypes. Knowing the subtype of your disease is important because the treatment approach is based on the subtype. A discusssion of NHL subtypes begins on page 5.

About Non-Hodgkin Lymphoma

"Non-Hodgkin lymphoma" (NHL) is the term used for a diverse group of blood cancers that share a single characteristic—they arise from lymphocytes. Lymphocytes are white blood cells that are part of our immune system. They can be either B-cells, T-cells or NK cells (called "natural killer" cells). In lymphoma, a lymphocyte undergoes a malignant change and multiplies, eventually crowding out healthy cells and creating tumors.

These tumors generally develop in the lymph nodes or in lymphatic tissue found in organs such as the stomach, intestines or skin. In some cases, NHL involves the bone marrow (the spongy tissue in the hollow central cavity of the bones that is the site of blood cell formation) and blood. Lymphoma cells may develop in one place or in many sites in the body (see *Signs and Symptoms* on page 10).

More than 60 specific NHL subtypes have been identified and assigned names (called "diagnostic designations") by the World Health Organization (WHO). The REAL/WHO (Revised European-American Lymphoma/World Health Organization) classification categorizes NHL subtypes by the characteristics of the lymphoma cells, including their appearance, the presence of proteins on the surface of the cells and their genetic features. A hematopathologist, a doctor who specializes in the diagnosis of blood disorders and blood cancers, should review biopsy specimens since the prognosis and the approach to treatment are influenced by histopathology, the study of diseased cells and tissues viewed under a microscope.

Specialists further characterize the NHL subtypes according to how the disease progresses: the progression may be fast moving (aggressive) or slow moving (indolent). The subtype of NHL and whether it is aggressive or indolent determines the appropriate treatment; so, getting an accurate diagnosis is very important. Table 1, on page 6, provides a list of some of the NHL subtypes designated as either aggressive or indolent; Table 2, on page 7, lists some of the diagnostic designations for NHL subtypes, based on the WHO classification.

Lymphocytic or lymphoblastic leukemias are closely related. A cancer that originates in the lymphatic tissue within the marrow is designated "lymphoblastic" or "lymphocytic" leukemia. Acute lymphoblastic leukemia and chronic lymphocytic leukemia are the two major examples of this type of blood cancer. (For more information, see the free LLS booklets *Acute Lymphoblastic Leukemia* and *Chronic Lymphocytic Leukemia*). In contrast to leukemia, a cancer that begins in a lymph node or other lymphatic structure in the skin, in the gastrointestinal tract, or in another site in the body is called a "lymphoma." It is important to recognize that leukemias, which originate in the marrow, often involve lymph nodes or other organs; similarly, lymphomas, which originate in lymphatic tissue outside the bone marrow, often involve the bone marrow.

This booklet covers many NHL subtypes and provides detailed information (including diagnosis, staging and treatment) about the more common ones. It also provides a brief description of normal blood and marrow and the lymphatic system,

as well as a list of medical terms that will help readers understand information that may be new to them.

NHL can grow and spread at different rates and is grouped into two subtypes: aggressive or indolent. Aggressive lymphomas are rapidly progressing or high-grade NHL subtypes and account for about 60 percent of all NHL cases. Diffuse large B-cell lymphoma (DLBCL) is the most common aggressive NHL subtype. Indolent lymphomas tend to grow more slowly and have fewer signs and symptoms when first diagnosed. Slow-growing or indolent subtypes represent about 40 percent of all NHL cases. Follicular lymphoma (FL) is the most common subtype of indolent NHL.

The treatments for aggressive and indolent lymphomas are different. Some of the most common aggressive and indolent NHL subtypes are listed in Table 1. When a patient's rate of disease progression is between indolent and aggressive, he or she are considered to have "intermediate grade" disease. Some cases of indolent NHL can transform into aggressive NHL.

Table 1. Most common subtypes of non-Hodgkin lymphoma

Aggressive

- Diffuse large B-cell lymphoma (DLBCL)
- Anaplastic large cell lymphoma
- Burkitt lymphoma
- Lymphoblastic lymphoma
- Mantle cell lymphoma
- Peripheral T-cell lymphoma
- Transformed follicular and transformed mucosa-associated lymphoid tissue (MALT) lymphomas

Indolent

- Follicular lymphoma
- Cutaneous T-cell lymphoma (mycosis fungoides and Sézary syndrome)
- Lymphoplasmacytic lymphoma/Waldenström macroglobulinemia
- Marginal zone B-cell lymphoma
- MALT lymphoma
- Small cell lymphocytic lymphoma/chronic lymphocytic leukemia (SLL/CLL)

Table 2 on page 7 lists the NHL diagnostic designations of the subtypes for non-Hodgkin lymphoma. The descriptive part of the names (eg, follicular, mantle cell or marginal zone) in some disease subtypes refers to the specific areas of the lymph nodes (the follicle, mantle and marginal zones) where the lymphoma appears to have originated.

Table 2. Diagnostic designations for non-Hodgkin lymphoma (NHL): NHL subtypes

Mature B-cell lymphomas

- B-cell chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL)
- Lymphoplasmacytic lymphoma
  - Waldenström macroglobulinemia
- Marginal zone B-cell lymphoma
  - Monocytoid B-cell lymphoma (nodal marginal zone lymphoma)
  - Gastric mucosa-associated lymphoid tissue (MALT) lymphoma
  - Extragastric MALT lymphoma
  - Splenic marginal zone lymphoma
- Follicular lymphoma
- Mantle cell lymphoma
- Diffuse large B-cell lymphoma (DLBCL)
  - Primary cutaneous DLBCL, leg type
  - Primary DLBCL of the central nervous system
- Lymphomatoid granulomatosis
- Primary mediastinal (thymic) large B-cell lymphoma
- Intravascular large B-cell lymphoma
- Primary effusion lymphoma
- Burkitt lymphoma
- B-cell lymphoma unclassifiable (BCLU)

Mature T-cell and NK-cell lymphomas

- Peripheral T-cell lymphoma
  - Hepatosplenic gamma/delta T-cell lymphoma
  - Subcutaneous panniculitis-like T-cell lymphoma
  - Enteropathy-type intestinal T-cell lymphoma
- Cutaneous T-cell lymphoma
  - Mycosis fungoides
  - Sézary syndrome
- Angioimmunoblastic T-cell lymphoma
- Adult T-cell leukemia/lymphoma (human T-lymphotrophic virus [HTLV 1]+)
- Extranodal T-/NK-cell lymphoma, nasal type
- Anaplastic large cell lymphoma
- Primary cutaneous anaplastic large cell lymphoma
- Systemic anaplastic large cell lymphoma

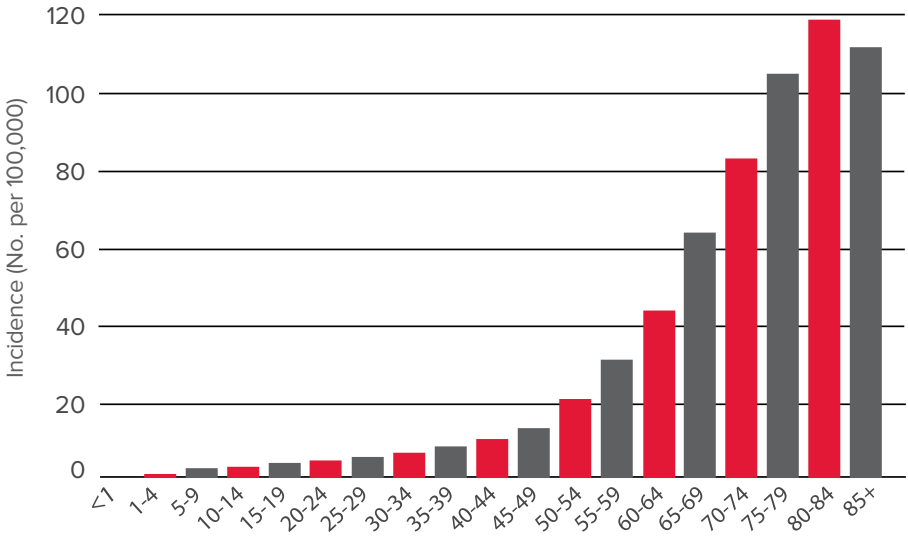
Source: World Health Organization (WHO) Classification of the Mature B-cell, T-cell and NK-cell Neoplasms (2008).

Incidence, Causes and Risk Factors

Incidence. About 72,580 new cases of NHL were expected to be diagnosed in the United States in 2016. Most of these (about 80 to 85 percent) comprise one of 14 different types of NHL that involve lymphocytes called "B cells." The two most common subtypes of NHL, diffuse large B-cell lymphoma and follicular lymphoma, are examples of B-cell lymphomas. The other approximately 15 to 20 percent of cases of NHL involve lymphocytes called "T cells" or "natural killer (NK) cells." T-cell lymphoma includes peripheral T-cell lymphoma and cutaneous T-cell lymphoma.

NHL occurs in individuals at virtually all ages, but it is uncommon in children. The disease is more common in men than women, and among whites. NHL is most frequently diagnosed among people 80 to 84 years old (see Figure 1).

Figure 1. Non-Hodgkin Lymphoma: Age-Specific Incidence Rates 2009-2013



The horizontal axis shows 5-year age intervals. The vertical axis shows the frequency of new cases of non-Hodgkin lymphoma each year per 100,000 people, by age-group. The incidence of non-Hodgkin lymphoma significantly increases with age. Fewer than 8 cases per 100,000 occur in people in their late 30s. Incidence increases progressively to 119.3 cases per 100,000 in persons age 80 to 84. Source: Surveillance, Epidemiology and End Results (SEER) Program; National Cancer Institute; 2016.

Causes and Risk Factors. The exact cause of NHL is not known but there are risk factors that may increase a person's likelihood of developing the disease.

Immune suppression is one of the most clearly established risk factors for NHL. People with autoimmune disease, acquired immunodeficiencies including human immunodeficiency virus infection and acquired immune deficiency syndrome (HIV/AIDS), and organ transplant recipients have an elevated risk for NHL. In addition, factors that suppress the immune system, such as chemical exposures or treatments for autoimmune diseases, may contribute to the development of NHL.

A number of occupational and environmental factors have also been associated with NHL. Farming communities have a higher incidence of NHL, and farming has been linked to NHL overall and to major NHL subtypes. This observation has led to research on agricultural chemicals, such as pesticides, solvents, fuels, oils and other agents that are potentially carcinogenic. Some studies suggest that specific ingredients in herbicides and pesticides such as organochlorine, organophosphate and phenoxy acid compounds, are linked to lymphoma. For example, the occupational exposure to nonarsenical insecticides during spraying and application has been classified by the International Agency for Research on Cancer (IARC) as a "probable human carcinogen" for NHL. The number of lymphoma cases caused by such exposures has not been determined. More studies are needed to understand these associations.

Exposure to certain viruses and bacteria is associated with NHL. It is thought that infection with either a virus or a bacterium can lead to intense lymphoid cell proliferation, increasing the probability of a cancer-causing event in a cell. Here are some examples:

- Epstein-Barr virus (EBV) infection in patients from specific geographic regions is strongly associated with Burkitt lymphoma in Africa. The role of the virus is unclear, since Burkitt lymphoma in Africa also occurs among people who have not been infected with EBV.
- Epstein-Barr virus infection may play a role in the increased risk of NHL in persons whose immune systems are suppressed as a result of organ transplantation and its associated therapy.
- Human T-cell lymphotropic virus-1 (HTLV-1) is associated with a type of T-cell lymphoma in patients from certain geographic regions in southern Japan, the Caribbean, South America and Africa.
- Human immunodeficiency virus infection and acquired immune deficiency syndrome (HIV/AIDS) is associated with the development of certain types of NHL. Generally, this occurs in older patients.
- The bacterium *Helicobacter Pylori (H Pylori)* causes ulcers in the stomach and is associated with the development of mucosa-associated lymphoid tissue (MALT) lymphoma in the stomach wall.
- Hepatitis C is associated with the development of splenic marginal zone lymphoma. Associations with other types of lymphoma are being explored.

Other conditions, such as Sjögren syndrome, Wiskott-Aldrich syndrome and Klinefelter syndrome can predispose individuals to later development of NHL. These inherited disorders are uncommon, but the concept of predisposition genes is under study to determine if they play a role in the random occurrence of NHL in otherwise healthy individuals.

For more information, contact an LLS Information Specialist at (800) 955-4572 or visit www.LLS.org/resourcedirectory under "Blood Cancer—General Information" and then click on "Disease registries and other disease studies."

Signs and Symptoms

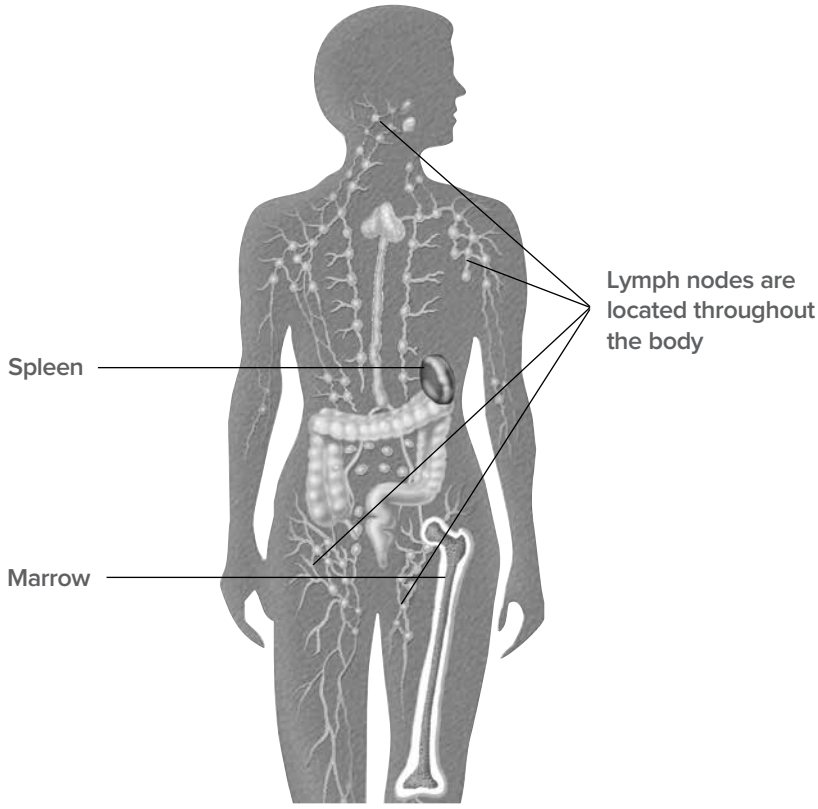
A person with signs or symptoms that suggest the possibility of NHL is usually referred to a specialist. This may be a hematologist-oncologist. The doctor will order additional tests and a tissue biopsy to make a diagnosis (see *Diagnosis* on page 12). The signs and symptoms of NHL are also associated with a number of other, less serious diseases.

There are about 600 lymph nodes in the body. The most common early sign of NHL is painless swelling of one or more lymph node(s).

- Most patients with NHL have one or more enlarged lymph nodes in the neck, armpit or groin.
- Less often, a swollen node appears near the ears, the elbow or in the throat near the tonsils.

Occasionally, the disease starts in a site other than the lymph nodes, such as a bone, a lung, the gastrointestinal tract or the skin. In these circumstances, patients may experience symptoms that are associated with that specific site (see Figure 2 on page 11).

Figure 2. Non-Hodgkin Lymphoma and the Lymphatic System



The lymphatic system is part of the immune system. The normal immune system helps to protect the body from infection. The marrow, lymph nodes and spleen are some of the parts of the immune system. There are about 600 lymph nodes throughout the body.

Lymph nodes and other lymphoid tissues that are commonly involved in lymphoma include those around the ears and jaw, in the tonsils and adenoids, in the front and back of the neck, above and below the collar bone, in the armpit, near the elbow, in the chest, in the abdomen, in the pelvis and in the groin. The spleen contains many clusters of lymphocytes that can become malignant and grow, leading to the enlargement of the spleen. The gut-associated (intestinal) lymph tissue may also be the site of lymphoma development.

Common symptoms of NHL include

- Painless swelling in one or more lymph node(s)
- Unexplained fever
- Drenching night sweats
- Persistent fatigue
- Loss of appetite

- Unexplained weight loss
- Cough or chest pain
- Abdominal pain
- Sensation of bloating or fullness (due to an enlarged spleen)
- Itchy skin
- Enlargement of the spleen or liver
- Rashes or skin lumps.

Some people have no symptoms and the disease may only be discovered during a routine medical examination or while the patient is under care for an unrelated condition.

B Symptoms. Fever, drenching night sweats and loss of more than 10 percent of body weight over six months are sometimes termed "B symptoms" and are significant to the prognosis and staging of the disease. Other NHL symptoms, such as itching and fatigue, do not have the same prognostic importance as the symptoms designated as B symptoms. Further, they are not considered to be B symptoms.

Diagnosis

An accurate diagnosis includes determination of the specific subtype of NHL, and is one of the most important aspects of a person's care. Obtaining a precise diagnosis will help the doctor to

- Estimate how the disease will progress
- Determine the appropriate treatment.

Evaluation. The doctor will take a comprehensive medical history and ask questions regarding the absence or presence of B symptoms. Physical examination will include measurement of all accessible lymph node groups as well as the size of organs such as the spleen and liver.

A diagnosis of NHL is usually made by examining a lymph node biopsy specimen (piece of node taken and studied under the microscope). The biopsy examination includes tests called "immunophenotyping" and "cytogenetic analysis." More information about these tests is found on page 13. It is important that all patients receive an accurate diagnosis and know their NHL subtype. Patients can ask the doctor to write down the name of the subtype for them.

Lymph Node Biopsy. Making an accurate diagnosis of the patient's specific subtype of NHL can be challenging. Since there are many subtypes of NHL

and the treatment approach and prognosis are specific to each subtype, a precise diagnosis is needed. It requires an experienced hematopathologist (a doctor who specializes in diagnosing diseases of the blood and marrow) to prepare the tissue samples from a biopsy. Then the hematopathologist will look at the slides under the microscope and analyze the findings. A second opinion by another hematopathologist may be necessary if there is any doubt about the diagnosis, or to confirm the diagnosis in the case of a rarer lymphoma.

A biopsy (microscopic examination and testing of a sample of lymph node tissue) of an involved lymph node or other tumor site is needed to confirm the NHL diagnosis and the subtype. A needle biopsy may be done, but the specimen of the lymph node that can be obtained through a needle is usually not sufficient to make a firm diagnosis. Generally, either the lymph node or part of the lymph node is surgically removed so that the hematopathologist has enough tissue to make an accurate diagnosis. The tissue can generally be removed using a local anesthetic.

NHL can develop in parts of the body that do not involve lymph nodes, such as the lung or bone. When lymphoma is detected exclusively outside of the lymph nodes, it is called "primary extranodal lymphoma," and the biopsy specimen is taken from that involved tissue.

The biopsy specimen is placed on a slide with a preservative and then stained with dyes. Next, the slide is examined under a microscope, and the doctor studies the size and shape of the cells and how they are arranged. This may confirm not only if the person has lymphoma but also the type of lymphoma. Sometimes, hematopathologists can tell which subtype of lymphoma a person has just by looking at the cells from the lymph node, but usually other types of tests are needed to confirm the diagnosis. If cancer is found, the hematopathologist will note the distinctive patterns of changed cells and use that information to identify the NHL subtype. Additional tests that may be necessary include

- Immunophenotyping—a dye is used directly on very thin slices of the tissue to determine which proteins or markers (antigens) are expressed in the lymphoma cells. Immunophenotyping can provide additional evidence that these cells are lymphoma cells and, further, whether they are B cells, T cells or NK cells. The pattern of protein expression helps to determine the identity of the lymphoma cells, and can also provide important information on the biology of the lymphoma.

- Flow cytometry—similar to immunophenotyping, this technique takes cells from the blood or tissue biopsy and sends them through a machine that will detect which proteins or markers (antigens) are expressed in the lymphoma cells.

- Cytogenetic analysis—dividing cells are studied to see if any chromosomal abnormalities are present. Fluorescent in situ hybridization (FISH) is a type of lab test that uses special dyes to look for abnormal chromosomes in cells. Chromosomal abnormalities are important considerations in identifying specific subtypes of NHL and choosing the most effective treatment approach.

- Gene expression profiling and microarray analysis—these tests identify cancer subtypes and risk factors. The tests help predict how patients will respond to treatment and which patients may be at increased risk for relapse. For example, gene expression profiling is used to identify different forms of diffuse large B-cell lymphoma. However, gene expression profiling and microarray analysis are not generally used in clinical practice and these tests are still mostly used as research tools.

- Polymerase chain reaction (PCR)—a technique to expand trace amounts of DNA or RNA so that the specific type of the DNA or RNA can be determined. This method has become useful in detecting a very low concentration of residual lymphoma cells—too few to be seen by using a microscope. The technique can detect the presence of one lymphoma cell among 500,000 to 1 million healthy cells. This test is a possible predictor of how well a patient will respond to treatment with specific therapies. The use of PCR requires a specific DNA abnormality or marker, such as an oncogene, in the lymphoma cells.

Staging

Doctors use physical examinations, imaging and lab tests to determine the extent of the disease. When imaging is used and the "stage" of the disease is determined, this is called "staging" (see Table 3 on page 16 and Figure 3 on page 17). Staging provides important information for treatment planning.

Imaging Tests. The physical examination and imaging tests help the doctor evaluate

- The location and distribution of lymph node enlargement

- Whether organs other than the lymph nodes are involved

- If there are very large masses of tumors in one site or another.

Imaging is a very important part of the staging and management of NHL. A doctor may first order imaging tests when a patient's medical history and physical examination suggest a possible diagnosis of NHL. The imaging test(s) may show enlarged lymph nodes in either the chest or abdomen, or both. Tumor masses may also occur outside the lymph nodes in lung, bone or other body tissue.

The imaging tests may include

- Chest x-rays

- CT (computed tomography) scan—A CT scan uses special x-ray equipment to take multiple images from different angles around the body. A computer then processes the information from the images and produces an image that shows a cross section of the area being examined. Patients have CT scans of the neck,

chest, abdomen and pelvis—all the areas where lymph nodes are present—to identify areas of disease. A CT scan can also show whether there is involvement of the lungs, liver and other organs, which is helpful staging information. A CT scan shows where the lymphoma is located and can measure the size of the mass.

- FDG-PET (fluorodeoxyglucose (FDG) positron emission tomography) scan—A PET scan is an imaging technique that produces a 3D image of functional processes in the body. This type of scan uses a small amount of a radioactive sugar (FDG) to show differences between healthy and nonhealthy tissue. A small amount of FDG is injected into the patient. Cancer grows at a faster rate than healthy tissue, so cancer cells absorb more of the radioactive substance FDG. The PET scanner detects the radiation given off by the FDG and produces color-coded images of the body that show both normal and cancerous tissue.
- Magnetic resonance imaging (MRI)—Magnetic resonance is used in select cases. MRI uses a powerful magnet and radio waves linked to a computer to create clear and detailed cross-sectional images (slices) of the body. The "slices" can then be displayed on a video monitor and saved on a disk for future analysis.
- PET-CT scan—This test combines the techniques of both CT and PET imaging into one machine. A PET-CT scan reveals information about both the structure and function of cells and tissues in the body during a single imaging session. It provides a more detailed picture of where the cancer is located in the body than either test does by itself.

  PET scans are increasingly being used not only to stage the disease precisely, but also to determine the margins of radiotherapy (when needed), to confirm response to treatment and to provide a baseline to assess future treatment response.

Blood Tests. Blood tests are used to

- Determine whether lymphoma cells are present in the blood and if the special proteins (called "immunoglobulins") made by lymphocytes are either deficient or abnormal
- Check indicators of disease severity by examining blood protein levels, uric acid levels and erythrocyte sedimentation rate (ESR)
- Assess kidney and liver functions
- Measure two important biological markers, lactate dehydrogenase (LDH) and beta$_2$-microglobulin which are helpful prognostic indicators for several NHL subtypes.

A complete blood count (CBC) may show

- Anemia (low red blood cell counts)
- Neutropenia (low levels of neutrophils, a type of white blood cells)
- Thrombocytopenia (low platelet levels).

Bone Marrow Biopsy. Most patients diagnosed with NHL undergo a bone marrow biopsy to make sure there is no spread of the disease to the bone marrow and to evaluate the use of specific therapies including radioimmunotherapy (a combination of radiation therapy and immunotherapy). A bone marrow biopsy may not always be required for patients with early-stage disease who also have low-risk features, for example, NHL with no B symptoms and no large masses.

Other Tests. Some tests are associated with a specific subtype and are not necessary for all patients with NHL. Examples of specific testing include a

- Full evaluation of the gastrointestinal (GI) tract, including upper and lower endoscopies for patients who have disease involving the GI tract, such as MALT lymphoma
- Colonoscopy for patients with mantle cell lymphoma (routine colonoscopy is important for all persons beginning at age 50, or earlier if there is a family history of colon cancer)
- Testicular ultrasound for patients who have a testicular mass
- Spinal tap (lumbar puncture) and/or MRI of the brain or spinal column may be required for patients with certain subtypes or symptoms that suggest central nervous system involvement.

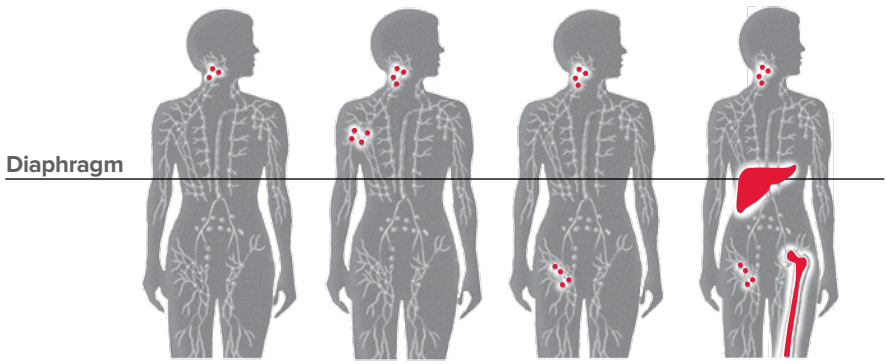
Table 3. Stages of Non-Hodgkin Lymphoma

Stage	Modifying Features
I – Involvement of one lymph node or a group of adjacent nodes	**A** – No symptoms
II – Involvement of two or more lymph node regions on the same side of the diaphragm	**B** – Presence of fever, drenching sweats, loss of more than 10 percent of body weight over the previous six months (without dieting)
III – Involvement of two or more lymph node regions above and below the diaphragm (for example, neck, chest and abdomen)	**X** – Bulky disease. This is a nodal mass whose greatest size is usually more than 10 cm or more than one-third of the chest diameter by x-ray
IV – Involvement of lymph node regions on both sides of the diaphragm and involvement of organs such as the lungs, liver or bones	**E** – Involvement of organs or tissues beyond the lymph system

The stage and modifying features direct the treatment approach. For example, stage IIB indicates that the patient has

- Two lymph node sites near each other with disease involvement (for example, enlarged lymph nodes in the neck and near the collarbone or in the neck and the armpit)
- Fever, excessive sweating and/or weight loss (any one of these symptoms).

Figure 3. Non-Hodgkin Lymphoma Stages



Stage I
Localized disease; single lymph node region or single organ

Stage II
Two or more lymph node regions on the same side of the diaphragm

Stage III
Two or more lymph node regions above and below the diaphragm

Stage IV
Widespread disease; multiple organs, with or without lymph node involvement

This illustration shows the location of non-Hodgkin lymphoma in the body for each stage.

Keep in mind that "stage IV" does not have the same implications in NHL as it does for many other cancers. NHL does not necessarily start at stage I and then continue to spread to stage II and so forth. In lymphoma, the stage reflects where the disease is located, not how well or how poorly a patient may respond to treatment. More than 50 percent of patients with intermediate or aggressive disease and more than 80 percent of patients with indolent types of NHL are diagnosed with stage III or stage IV disease. A diagnosis of stage IV NHL may be highly treatable, depending on the patient's specific subtype of disease.

When all the diagnostic and staging tests are completed, the doctor will evaluate the information, identify the NHL subtype, determine which areas of the body are involved and begin to discuss treatment options with the patient.

Treatment Overview

The initial therapy and intensity of treatment indicated for a patient are based on the subtype and stage of disease. In general, the goal of treatment is to destroy as many lymphoma cells as possible and to induce a "complete remission." Complete remission means that all evidence of disease is eliminated. Patients who go into remission are sometimes cured of their disease. Treatment can also keep NHL in check for many years, even though imaging or other studies show remaining sites of disease. This situation may be referred to as a "partial remission."

For patients without symptoms and with indolent subtypes of NHL, the treatment may be the "watch-and-wait" approach, meaning treatment is deferred or delayed until signs of disease progression occur. Frequent and careful observation is required so that effective treatment can be started if the disease starts advancing. Some patients have a long slow-growing disease, while others have a disease that evolves into more aggressive types of NHL requiring immediate treatment.

In general, chemotherapy and radiation therapy are the two principal forms of treatment for NHL (See Table 4 and Table 5, on pages 19 and 20). Although radiation therapy is often neither the sole nor the principal curative therapy, it is an important additional treatment in some cases.

Stem cell transplantation may also be used to treat some NHL subtypes. You can see more information on stem cell transplantation on page 37 and in the free LLS booklet *Blood and Marrow Stem Cell Transplantation*. Other forms of treatment are emerging, and some are already approved for specific subtypess of NHL. Many other new therapies are being developed in clinical trials.

Table 4. Some Drugs Used in the Treatment of Non-Hodgkin Lymphoma

Alkylating Agents (DNA-Damaging Drugs)

- Bendamustine hydrochloride (Bendeka™)
- Carboplatin (Paraplatin®)
- Carmustine (BCNU, BiCNU®)
- Chlorambucil (Leukeran®)
- Cisplatin (Platinol®)
- Cyclophosphamide (Cytoxan®)
- Dacarbazine (DTIC, DTIC-Dome®)
- Ifosfamide (Ifex®)
- Melphalan (Alkeran®)
- Procarbazine HCl (Matulane®)

Antifolate

- Pralatrexate (Folotyn®)

Antitumor Antibiotics

- Doxorubicin (Adriamycin®)
- Idarubicin (Idamycin®)
- Mitoxantrone (Novantrone®)

Antimetabolites

- Cladribine (Leustatin®)
- Cytarabine (Cytosine arabinoside, Ara-C, Cytosar-U®)
- Fludarabine (Fludara®)
- Gemcitabine (Gemzar®)
- Nelarabine (Arranon®)
- Methotrexate (Rheumatrex®, Trexall®)
- Thioguanine, (6-TG, 6-Thioguanine, Tabloid®)

Proteasome Inhibitor

- Bortezomib (Velcade®)

DNA Repair Enzyme Inhibitors

- Etoposide (Etopophos®, VePesid®, Topopsar®)

Drugs That Prevent Cell Division by Blocking Mitosis

- Paclitaxel (Abraxane®, Onxol®, Taxol®)
- Vinblastine (Velban®)
- Vincristine (Oncovin®)

Hormones That Can Kill Lymphocytes

- Dexamethasone (Decadron®)
- Methylprednisolone (Medrol®)
- Prednisone

Immunotherapy

- Alemtuzumab (Campath®)
- Brentuximab vedotin (Adcetris®)
- Obinutuzumab (Gazyva®)
- Ofatumumab (Arzerra®)
- Rituximab (Rituxan®)
- Yttrium-90+ibritumomab tiuxetan (Zevalin®)

Retinoid

- Bexarotene (Targretin®)

Histone Deacetylase Inhibitor

- Vorinostat (Zolinza®)
- Romidepsin (Istodax®)

Other Biologic Agents

- Bruton's tyrosine kinase (BTK) inhibitor
  - Ibrutinib (Imbruvica®)
- P13K inhibitor
  - Idelalisib (Zydelig®)
- *BCL-2* inhibitor
  - Venetoclax (Venclaxta™)

Immunomodulator

- Lenalidomide (Revlimid®)

Table 5 on page 20 contains examples of drug combinations used to treat NHL. Researchers in clinical trials continue to study the most effective combinations of drugs for the treatment of all types of NHL including newly diagnosed, refractory or relapsed cases.

Table 5. Some Drug Combinations Used to Treat Non-Hodgkin Lymphoma

CHOP: Cyclophosphamide, hydroxydoxorubicin (doxorubicin), Oncovin® (vincristine), prednisone

R-CHOP: Rituximab (Rituxan®) plus cyclophosphamide, hydroxydoxorubicin (doxorubicin), Oncovin® (vincristine) and prednisone

R-HCVAD: Rituximab plus cyclophosphamide, vincristine, Adriamycin® (doxorubicin), dexamethasone

DHAP: Dexamethasone, high-dose cytarabine (Ara-C®), Platinol® (cisplatin)

ICE: Ifosfamide, carboplatin, etoposide

EPOCH: Etoposide, prednisone, Oncovin® (vincristine), cyclophosphamide, doxorubicin (hydroxydoxorubicin)

BR: Bendamustine and rituximab

CNOP: Cyclophosphamide, Novantrone® (mitoxantrone), Oncovin ® (vincristine), prednisone

Monoclonal antibodies. Monoclonal antibodies are immunotherapy drugs specially designed to target specific proteins (antigens) in cancer cells. Once the antibody finds and attaches to its target, it can recruit other parts of the immune system to destroy the cell that contains the antigen. Some monoclonal antibodies (known as "naked" antibodies) work by themselves, while others are coupled with a chemotherapy drug or attached to a radioactive particle and are called "conjugated monoclonal antibodies" (antibody-drug conjugates or ADC). They circulate throughout the body until they attach to the target antigen and then deliver the toxic substance to the cancer cell.

Over the last two decades, the FDA has approved several monoclonal antibodies to treat NHL as well as several types of cancer. They include

- **Rituximab** (Rituxan®), which has been an important addition to traditional drug therapy programs and is approved for treating several types of B-cell NHL including follicular lymphoma and diffuse large B-cell lymphoma.
- **Alemtuzumab** (Campath®), which is an anti-CD52 antibody. It is used as therapy for some NHLs including Waldenström macroglobulinemia.

- **Brentuximab vedotin** (Adcetris®), which targets CD30 and releases a chemotherapy drug called "MMAE" (monomethyl auristatin E) into the cell. Brentuximab vedotin is used for treating peripheral T-cell lymphoma and Hodgkin lymphoma.

- **Yttrium-90+ibritumomab tiuxetan** (Zevalin®), which attaches to CD20 and releases radioactive substances into the cell to kill it. Yttrium-90+ibritumomab tiuxetan is used in the treatment of follicular lymphoma.

- **Obinutuzumab** (Gazyva®), which targets CD20 and is being used for some types of NHL, including refractory follicular lymphoma.

- **Ofatumumab** (Arzerra®), which is an anti-CD20 antibody approved for refractory/relapsed CLL. It is now being studied in combination with other agents for the treatment of Waldenström macroglobulinemia and other types of NHL.

Factors That Influence Treatment. Each person should discuss treatment options with his or her doctor and ask for help understanding the benefits and risks of different treatment approaches. The most effective treatment plan for a patient with NHL is individualized and depends on

- The subtype of NHL (knowing whether the lymphoma cells are most closely related to T cells, B cells or natural killer [NK] cells gives the doctor important clues about appropriate treatments to use)

- The stage and category of the disease, which is important information in forming decisions about treatment (see Table 3 on page 16)

- Factors such as fever, drenching night sweats and weight loss of more than 10 percent of body weight, referred to as "B symptoms"

- The presence of lymphoma in areas of the body outside of the lymph nodes (extranodal involvement)

- Other prognostic factors such as age and any underlying medical conditions.

The patient's age may be a factor, but older age is no longer a major determinant in treatment for most patients. However, medical problems, including the patient's overall health status, and the patient's decisions about treatment are all important considerations.

The International Prognostic Index (IPI). An international collaboration among several cancer research groups in North America and Europe that evaluated thousands of patients with aggressive NHL and identified several unfavorable prognostic factors.

One point is assigned for each of the following risk factors:

- Age greater than 60 years

- Stage III or stage IV disease
- More than one lymph node involved
- Elevated serum lactate dehydrogenase (LDH)
- Level performance status, a scale used to evaluate a person's ability to perform daily tasks of living without help.

These factors help predict overall survival and the risk of relapse, and provide a basis for recommending either more or less aggressive treatment for high-risk patients.

The number of IPI risk factors a person has defines the corresponding IPI risk group to help predict the risk of relapse. Each point represents some increased risk for disease relapse. The total number of points identifies the following risk groups:

- Low risk (0 to 1 point)
- Low-intermediate risk (2 points)
- High-intermediate risk (3 points)
- High risk (4 to 5 points).

For patients younger than 60 years, the risk categories are slightly different. They are

- Low risk (0 points)
- Low-intermediate risk (1 point)
- High-intermediate risk (2 points)
- High risk (3 points).

Patients may want to discuss risk factors with their doctor in order to understand treatment options, including participation in clinical trials.

Pretreatment Considerations. Adults of childbearing age and parents of children diagnosed with NHL should ask their doctor for information about possible long-term and late effects, including effects on fertility (see *Long-Term and Late Effects of Treatment for Non-Hodgkin Lymphoma*, page 40. For more information, see the free LLS fact sheets *Fertility Facts; Long-Term and Late Effects of Treatment in Adults Facts;* and *Long-Term and Late Effects of Treatment for Childhood Leukemia or Lymphoma Facts*).

Treatment Setting. Patients may undergo treatments over long periods, but most therapy can be administered in an outpatient setting. Radiation therapy, chemotherapy or immunotherapy can be administered in an outpatient clinic of an oncology center. Short periods of hospitalization are sometimes required. Particularly intensive therapy can cause prolonged or severe decreases in red blood cell, white blood cell and/or platelet counts. Therefore, transfusion of appropriate

blood products and administration of cytokines (hormones that enhance blood cell production) may be needed. Outpatient treatment is still possible in some cases that require blood transfusion and/or cytokine treatment. If fever or other signs of infection occur, hospitalization and administration of antibiotics may be necessary. For more information, see the free LLS booklet *Blood Transfusion*.

Treatment Considerations for Children, Adolescents and Young Adults. NHL accounts for an estimated 5 percent of cancers in children younger than 15 years. Burkitt lymphoma is the predominant NHL subtype in children aged 5 through 14 years.

Children and adolescents with NHL should be referred to medical centers that have a specialized pediatric oncology team to ensure that young patients receive optimal treatment, support and follow-up care. Young adults and parents of children diagnosed with NHL should talk to members of the oncology team about the stage and the specific subtype of NHL. Doctors use this information about the patient's disease in order to determine the most effective therapy. It is also important to discuss the planned therapy with members of the oncology team to learn about the drugs, potential side effects and long-term effects and the treatment schedule. See *Pretreatment Considerations*, on page 22.

Different treatment strategies may be used for children and for adults with NHL. The choice of therapy for adolescents and young adults can be challenging and it is a topic of ongoing research. Pediatric treatment strategies are currently used to treat adults who have certain subtypes of NHL, including Burkitt lymphoma and lymphoblastic lymphoma. Adolescents and young adults should consider being evaluated and treated in a pediatric oncology setting or with a pediatric protocol as part of a clinical trial. With current treatments, NHL in most children is highly curable. The results depend on achieving a precise diagnosis thorough staging of the disease and using complex multi-drug treatments.

Childhood, adolescent and young adult cancer survivors require close follow-up care because cancer therapy side effects may persist or develop months or even years after treatment. For more information, see the free LLS fact sheet *Long-Term and Late Effects of Treatment for Childhood Leukemia or Lymphoma Facts*.

Treatment of Aggressive Subtypes

Every patient's situation should be evaluated individually by an oncologist who specializes in treating NHL and who will discuss the disease subtype, stage and treatment options with the patient. It is also important to seek treatment at a center that has experience in treating NHL.

Treatment for aggressive B-cell NHL subtypes starts at the time of diagnosis. Patients with fast-growing NHL are frequently treated with chemotherapy that consists of four or more drugs. In most cases this is the combination therapy called R-CHOP (rituximab [Rituxan®], cyclophosphamide [Cytoxan®], doxorubicin [hydroxydoxorubicin], Oncovin® [vincristine] and prednisone). This intensive, multidrug chemotherapy can be very effective for aggressive lymphoma, and cures have been achieved.

Chemotherapy can be supplemented by radiation therapy in select cases, for instance, when large NHL masses are found during the diagnostic and staging process.

Diffuse Large B-Cell Lymphoma (DLBCL). This is the most common NHL subtype and represents about 30 percent of cases of NHL diagnosed in the United States. DLBCL grows rapidly in the lymph nodes and frequently involves the spleen, liver, bone marrow or other organs. DLBCL development usually starts in lymph nodes in the neck or abdomen and is characterized by masses of large B cells (lymphocytes). In addition, patients with DLBCL often experience B symptoms (fever, night sweats and weight loss).

For some patients, DLBCL may be the initial diagnosis. For other patients, their indolent lymphomas, such as small lymphocytic lymphoma or follicular lymphoma, transform and became DLBCL. DLBCL most commonly occurs in middle-aged and older persons, but it can occur at any age. Most cases have no known cause.

Gene expression profiling has been used to define groups of patients who may have different responses to therapy or who may have a different clinical presentation based on the number and types of genes that are either more active or less active in the tumor sample. To date, gene expression profiling studies have distinguished three molecular subtypes of DLBCL. They are

- Germinal center B-cell-like (GCB)
- Non-germinal center B-cell-like (non-GCB)
- Primary mediastinal B-cell lymphoma (PMBL)

These distinct DLBCL subtypes arise due to specific genetic changes. Because gene expression profiling is not commercially available, most oncologists, working with hematopathologists, perform immunophenotyping to identify the specific proteins that are associated with GCB or non-GCB subtype of DLBCL.

According to some studies, DLBCL patients who appear to have the GCB subtype experience significantly better treatment outcomes than patients who do not have the GCB subtype. A number of clinical trials are under way to investigate whether using novel approaches to therapy improves treatment outcomes for non-GCB DLBCL patients.

Primary mediastinal B-cell lymphoma (PMBL) is a subtype of DLBCL that shows a pattern of gene expression similar to that of classical Hodgkin lymphoma. It is marked by the overgrowth of scar like lymph tissue. A tumor generally forms behind the breastbone and may cause coughing and difficult breathing. The tumor is often very large and can cause pressure on the blood vessels or the heart and lungs. It occurs in young adults around age 35 and it affects slightly more women than men.

DLBCL is frequently treated with a chemotherapy regimen that is made up of four or more drugs. Patients with PMBL often need more intense treatment than other patients with DLBCL. The standard chemotherapy combination used for PMBL is R-CHOP. It is a combination of rituximab (Rituxan®), cyclophosphamide (Cytoxan®), doxorubicin (hydroxydoxorubicin), vincristine (Oncovin®) and prednisone, but this is increasingly being replaced by more intense regimens including DA-EPOCH-R, which comprises dose-adjusted etoposide, prednisone, vincristine (Oncovin®), cyclophosphamide, hydroxydoxorubicin (doxorubicin) plus rituximab.

Rituximab is indicated for previously untreated DLBCL, CD20-positive NHL in combination with CHOP or other anthracycline-based chemotherapy regimens. This combination can be very effective, and most patients with early-stage DLBCL are cured with this treatment regimen. At this time, there is no standard maintenance treatment for DLBCL. Studies are ongoing to see if maintenance treatment is an appropriate option for patients.

About 30 to 40 percent of patients relapse after their first chemotherapy treatment. For these patients, additional chemotherapy (called "salvage" treatment) is given, which may include drugs that were not used previously. The goal of salvage treatment is to achieve a remission so that there is no need to use high-dose chemotherapy or perform autologous stem-cell transplantation.

"Double-hit lymphoma" is the term used to describe a lymphoma in which the malignant cells exhibit mutations on two significant genes. Double-hit lymphoma has been observed in 2 to 11 percent of newly diagnosed patients with DLBCL. These patients have rearrangements (mutations) of the *MYC* gene and the *BCL2* and/or *BCL6* gene arrangements. This lymphoma subtype responds poorly to the standard R-CHOP therapy and the prognosis for patients is unfavorable. Thus, the treatment of double-hit lymphoma has become the subject of ongoing clinical trials.

Peripheral T-Cell Lymphoma (PTCL). PTCL refers to a group of aggressive NHL subtypes that originate in mature T-cell lymphocytes. PTCL generally affects people age 60 and older and are diagnosed slightly more often in men than in women. However, younger adults and children are also sometimes diagnosed with PTCL. PTCL is a rare disease in the United States. Some forms of PTCL are more common in Asia, Africa and the Caribbean, possibly as a result of exposure to specific viruses, such as the Epstein-Barr virus (EBV) and the human T-cell leukemia virus-1 (HTLV-1).

The most common subtypes of PTCL include

- Peripheral T-cell, not otherwise specified (PTCL NOS)—This is the most common subtype of PTCL. It often involves lymph node sites, but other areas such as the liver, bone marrow, GI tract and skin can be involved.
- Anaplastic large cell lymphoma (ALCL)—This subtype usually starts in lymph nodes and can spread to the skin. The cancer cells express a marker called "CD30" on the surface of the cells. There are two main subtypes of ALCL.
  - Systemic ALCL ALK-1 positive anaplastic large cell lymphoma—This subtype begins in the lymph nodes and the disease may spread to other parts of the body. There is a protein called "anaplastic lymphoma kinase" (ALK-1) inside the lymphoma cells. About 80 percent of patients with this subtype are cured. This disease is more common in young people.
  - Systemic ALCL ALK-1 negative anaplastic large cell lymphoma—This subtype, which does not express the ALK-1 protein, occurs mainly in older patients. Treatment with chemotherapy or radiation therapy is often less successful and a stem cell transplant may be discussed.
- Primary cutaneous anaplastic large cell lymphoma—This subtype mostly affects the skin, but other parts of the body may be involved.
- Hepatosplenic T-cell lymphoma—This uncommon type of PTCL usually affects young men. It starts in the liver and spleen and theses cancer cells have a receptor called "gamma/delta" on the surface of the cell.
- Angioimmunoblastic T-cell lymphoma—This type of T-cell lymphoma often involves lymph nodes and the bone marrow. Many patients have "paraneoplastic symptoms" including fevers, rash and abnormal protein levels in their blood.
- Enteropathy-type intestinal T-cell lymphoma—It develops in the small bowel of patients with untreated celiac disease.
- Extranodal natural killer/T-cell lymphoma (ENK/TCL)—This is an uncommon type of lymphoma that can occur in the nasal sinuses or in other parts of the body. It is usually a very aggressive lymphoma that requires both chemotherapy and radiation. ENK/TCL is more common in people of Asian origin.

PTCL is one of the most difficult types of lymphoma to treat. It is commonly treated with the regimens used for DLBCL. Chemotherapy with CHOP [cyclophosphamide (Cytoxan®), doxorubicin (hydroxydoxorubicin), vincristine (Oncovin®), and prednisone] is the standard treatment for newly diagnosed PTCL; however, the treatment outcomes are not as favorable as they are for DLBCL. Studies are under way to try to develop new treatment approaches, and patients are encouraged to seek out these trials.

Some new drugs approved for the treatment of PTCL include

- **Pralatrexate** (Folotyn®), an antifolate drug, has been FDA approved for the treatment of patients with relapsed or refractory PTCL.
- **Romidepsin** (Istodax®), a type of histone deacetylase (HDAC) inhibitor, has been approved by the FDA for the treatment of PTCL patients who have received at least one prior therapy.
- **Brentuximab vedotin** (Adcetris®), given by injection, is FDA-approved for the treatment of patients with systemic ALCL after failure of at least one prior multi-agent chemotherapy regimen. This drug is a type of conjugated monoclonal antibody, which targets CD30 and releases a chemotherapy drug called "MMAE" (monomethyl auristatin E) into the cell.
- **Belinostat** (Beleodaq®) is an HDAC inhibitor that has been FDA approved for the treatment of patients who have either relapsed or refractory PTCL.

For more information about PTCL, including treatment options, see the free LLS fact sheet *Peripheral T-Cell Lymphoma Facts.*

AIDS-associated Lymphoma. The types of NHL that are most often seen in people with AIDS are DLBCL, Burkitt lymphoma and primary central nervous system (CNS) lymphoma. Treatment outcomes are affected by how well the patient with AIDS is responding to treatment and managing the effects of chemotherapy on blood counts. The number of people developing AIDS-associated NHL has decreased in the last several years because of improved HIV treatment.

Burkitt Lymphoma. This aggressive B-cell subtype grows and spreads very quickly and represents about 2.5 percent of NHL cases. It may involve the jaw, bones of the face, bowel, kidneys, ovaries, marrow, blood, central nervous system (CNS) and other organs. More than half of those treated can be cured with current therapies. This disease is also known as "diffuse small noncleaved-cell lymphoma." It develops mostly in children and young adults.

Burkitt lymphoma was named after Dr. Dennis Burkitt, a surgeon working in equatorial Africa. There, the disease usually appears in children as a mass in a facial bone, especially the jaw, and signs of the Epstein-Barr virus are usually found in the lymphoma cells along with an abnormality of chromosome 8. In Africa, both

the chromosomal abnormality and viral infection are thought to play a causal role in the onset of Burkitt lymphoma. Burkitt lymphoma occurs far less frequently in other parts of the world. There are three main types.

- Endemic Burkitt lymphoma—occurs commonly in Africa and is associated with the Epstein-Barr virus
- Sporadic Burkitt lymphoma—occurs throughout the world
- Immunodeficiency-related Burkitt lymphoma—often seen in patients with AIDS.

Burkitt lymphoma may spread to the brain and spinal cord (central nervous system, CNS), therefore, treatment to prevent CNS spread may be administered. CHOP or CHOP-like chemotherapy does not produce favorable results. Instead, highly aggressive chemotherapy is used to treat this subtype of NHL, often requiring admission to the hospital. Commonly used regimens include

- **CODOX-M/IVAC** (cyclophosphamide, vincristine (Oncovin®), doxorubicin and high-dose methotrexate) alternating with IVAC (ifosfamide, etoposide and high-dose cytarabine)
- **Hyper-CVAD** (hyperfractionated cyclophosphamide, vincristine, doxorubicin [Adriamycin®] and dexamethasone) alternating with methotrexate and cytarabine)
- **DA-EPOCH-R** (dose-adjusted etoposide, prednisone, vincristine [Oncovin®], cyclophosphamide, doxorubicin plus rituximab)

Participation in clinical trials is recommended for all patients.

Central Nervous System (CNS) Lymphoma. Primary CNS lymphoma forms in the brain and/or the spinal cord. It is often a feature of AIDS-associated lymphoma, but most patients who have primary CNS lymphoma in the United States do not have a clear predisposing cause. Secondary CNS lymphoma starts with lymphoma in other parts of the body and then spreads to the brain and/or the spinal cord.

Both primary and secondary CNS lymphomas are uncommon. Treatment options depend on the stage, location of the disease within the central nervous system, whether the disease has just been diagnosed or has relapsed, and the patient's age and general health. Treatment may consist of standard therapy or treatment that is being studied in a clinical trial. Standard treatment may include chemotherapy, glucocorticoid drugs and/or radiation therapy. Immunotherapy and high-dose chemotherapy with stem cell transplantation for CNS lymphoma are being studied in clinical trials.

Mantle Cell Lymphoma. Mantle cell lymphoma (MCL) represents about 6 percent of NHL cases. The malignant cells originate from a lymphocyte in the mantle zone of a lymph node. This subtype usually occurs in people over age 50

and is found more frequently in men than in women. The disease begins in the lymph nodes and spreads to the spleen, blood, bone marrow and sometimes the esophagus, stomach and intestines.

MCL cells express too much of a protein called "cyclin-D1." Some patients do not show signs or symptoms of the disease, so delaying treatment may be an option for them. Most patients need to start treatment after diagnosis. Standard treatment is combination chemotherapy, either with or without an autologous stem cell transplant.

The drug ibrutinib (Imbruvica®), a small-molecule Bruton's tyrosine kinase (BTK) inhibitor, was approved by the FDA for the treatment of patients with MCL who have received at least one prior therapy. In addition, lenalidomide (Revlimid®) and bortezomib (Velcade®) are approved for use in relapsed MCL.

For more information about mantle cell lymphoma, including treatment options, see the free LLS fact sheet *Mantle Cell Lymphoma Facts*.

Angioimmunoblastic Lymphoma. Patients with this diagnosis are treated like patients with acute lymphoblastic leukemia (ALL). ALL diagnosis and treatment is described in detail in the free LLS booklet *Acute Lymphoblastic Leukemia*.

Approaches to Therapy for Advanced-stage Aggressive NHL Subtypes. The standard of care for advanced-stage disease is R-CHOP. The number of chemotherapy cycles used depends upon the stage and extent of disease. If the lymphoma is in the bone marrow, nasal sinuses or testicles, or if it is near the spinal cord, it may spread to the central nervous system. Therefore, chemotherapy may be given into the spinal fluid.

Patients with high-risk disease based on prognostic factors may benefit from more aggressive initial treatment and should discuss clinical-trial options with their doctors.

Treatment of Indolent Subtypes

The management of indolent lymphoma subtypes at initial diagnosis ranges from observation with careful monitoring (the watch-and-wait approach) to aggressive therapy.

Appropriate management for any given patient is highly individual and depends on factors that include the patient's

- Prognostic factors
- Stage of disease
- Age and other medical conditions.

Treatment Options. Standard treatment for indolent NHL include the following options:

For early-stage disease

- The watch-and-wait approach
- Radiation therapy
- Rituximab with or without chemotherapy.

For advanced-stage disease

- The watch-and-wait approach for asymptomatic patients
- Monoclonal antibodies (rituximab, obinutuzumab, yttrium-90+ibritumomab tiuxetan)
- Alkylating agents (cyclophosphamide, chlorambucil, bendamustine)
- Combination chemotherapy.

The Watch-and-Wait Approach. Many doctors consider observation (the watch-and-wait approach) an active form of therapy, involving careful monitoring and follow-up care. Patients need to discuss with their doctors the potential benefits of the watch-and-wait approach versus initiating chemotherapy and/or other therapies. Studies comparing watch-and-wait to initial therapy have shown no survival advantage in the group of patients who were treated at diagnosis compared to those who were observed. Studies are ongoing, and one trial showed that when the watch-and-wait approach and treatment with rituximab (Rituxan®) were compared, the rituximab treatment increased the time until a patient needed chemotherapy. However, no major difference in quality of life was observed, and the overall survival was the same. More studies need to be done to confirm this data.

There are some patients with indolent lymphoma who need aggressive initial therapy. However, patients with no symptoms and limited extent of disease frequently can be observed over long periods of time. Sometimes their condition may remain stable for years and these patients can avoid the side effects of unnecessary therapy. Therapy should be started for a patient who shows signs of lymphoma progression, such as newly involved or enlarging lymph nodes; bone or other organ involvement; or a decrease in blood cell formation that causes low red blood cell, low white blood cell or low platelet counts. The specific decision to treat indolent lymphoma is made collaboratively by the oncologist and patient. Each case is evaluated individually and approaches vary among patients.

Relapsed Indolent Lymphoma. Slow-growing lymphoma often comes back after treatment, and new drug combinations may be required. A series of remissions lasting a number of years often occurs and patients can continue their usual

activities for very long periods of time. Patients with low-grade lymphoma whose disease continues to progress after receiving other forms of treatment may benefit from autologous stem cell transplantation.

Bendamustine hydrochloride (Bendeka™) has been approved by the FDA for patients with indolent B-cell NHL that has progressed during or within six months of treatment with rituximab or with a rituximab-containing regimen.

Follicular Lymphoma (FL). This is the second most frequent type of lymphoma, accounting for about 22 percent of cases of NHL. Most FL cells have a specific chromosome abnormality (a translocation between parts of chromosomes 14 and 18) that causes the overexpression of a gene, *BCL-2*, and makes the cells resistant to therapy. FL is a very slow-growing disease. Some patients may not need treatment for several years, whereas others may have extensive lymph node or organ involvement and need treatment right away. Most patients with FL are age 50 or older at diagnosis. In a small percentage of patients, FL may transform into a more aggressive disease.

Follicular Lymphoma Treatment. Stage I or stage II FL may be treated with

- The watch-and-wait approach; patients with less advanced disease can be observed with periodic examinations and imaging tests
- Radiation therapy
- Chemotherapy with rituximab followed by radiation therapy.

Some patients with FL who respond to treatment may be followed without any need for further therapy. However, periodic observation continues to be important so that doctors can identify patients who need additional treatment.

For patients with stage II FL who have large lymph nodes, stage III or stage IV FL, or advanced-stage relapsed FL, treatment will be based on symptoms, the patient's age and health status, the extent of disease and the patient's choice. A patient who requires treatment may want to consider taking part in a clinical trial.

Other treatment options include

- Radiation therapy to lymph nodes that are causing symptoms, or to a large localized mass, if one is present
- Single chemotherapy drugs in combination with rituximab. Examples of drugs used for treatment include cyclophosphamide, chlorambucil or bendamustine (Bendeka™)
- Chemotherapy combinations plus Rituxan®, such as R-CVP (rituximab plus cyclophosphamide, vincristine, and prednisone) or R-CHOP (rituximab plus cyclophosphamide, hydroxydoxorubicin [doxorubicin], vincristine [Oncovin®] and prednisone)

- A radioactive monoclonal antibody, such as yttrium-90+ibritumomab tiuxetan (Zevalin®). Zevalin is a radioimmunotherapeutic agent that is approved for relapsed or refractory CD20-positive, low-grade, follicular or transformed B-cell lymphoma and for previously untreated follicular NHL patients who achieve a partial or complete response to first-line chemotherapy
- Stem cell transplantation for some patients (see the free LLS booklet *Blood and Marrow Stem Cell Transplantation*)
- The watch-and-wait approach
- Maintenance rituximab after completion of initial therapy with either rituximab alone or rituximab in combination with chemotherapy. This involves a single dose of rituximab administered on a prescribed schedule (generally every two to three months). Rituximab maintenance may last for two years.
- Idelalisib (Zydelig®), which has been FDA approved to treat patients with relapsed follicular B-cell NHL and relapsed small lymphocytic lymphoma (SLL), another subtype of NHL. Idelalisib is intended for patients who have received at least two prior therapies.

Transformed Follicular Lymphoma (FL). FL has a small risk of transforming into an aggressive large B-cell lymphoma such as DLBCL. Patients with transformed FL appear to benefit from high-dose therapies along with autologous stem cell transplantation. (See *Diffuse Large B-Cell Lymphoma* on page 24.)

A clinical trial may be a good option for patients with disease that transforms after several different treatment approaches have been tried. Other options include

- Chemotherapy either with or without rituximab (Rituxan®)
- Treatment with a radioimmunotherapeutic monoclonal antibody, such as yttrium-90+ibritumomab tiuxetan (Zevalin®)
- Radiation therapy
- Supportive care
- Autologous stem cell transplantation within a clinical trial. When an autologous stem cell transplant is an option, stem cells should be collected before treatment with radioimmunotherapy.

The Follicular Lymphoma International Prognostic Index (FLIPI). The FLIPI is a scoring system used to predict which patients with follicular lymphoma may be at higher risk for disease recurrence. This information helps doctors determine appropriate care for patients who have been treated for follicular lymphoma. One point is assigned for each of the following risk factors (known by the acronym NoLASH):

- **No**des involved—5 or more
- **L**actate dehydrogenase (LDH) level—higher than the upper limit of normal

- **A**ge older than 60 years
- **S**tage III or stage IV disease
- **H**emoglobin concentration—less than 12 g/dL.

Each point represents an increased risk for disease recurrence. The total number of points identifies the following risk groups: low risk (0 to 1 point); intermediate risk (2 points); high risk (3 to 5 points). Patients may want to discuss risk factors with their doctor in order to understand treatment options, including participation in clinical trials.

Cutaneous T-Cell Lymphoma (Mycosis Fungoides and Sézary Syndrome). Cutaneous T-cell lymphomas (CTCLs) are a group of non-Hodgkin lymphomas that develop primarily in the skin and may grow to involve lymph nodes, blood and other organs. This type of lymphoma originates in a T cell. Mycosis fungoides (MF) is the most common type of CTCL, and is characterized by prominent skin involvement. MF accounts for 50 to 70 percent of all CTCL cases. When the malignant lymphocytes enter and accumulate in the blood, the disease is called "Sézary syndrome" (SS). SS accounts for only 1 to 3 percent of all CTCL cases.

Therapy for CTCL depends on the nature of the skin lesions and whether disease is present in the lymph nodes. Topical therapies are among the approaches used to treat the skin lesions. These include drugs applied directly to the skin and two different forms of therapy based on exposing skin lesions to light—ultraviolet light therapy and electron beam therapy. Ultraviolet light is used in conjunction with psoralen (a drug that becomes active when it is exposed to light); the combination therapy is often referred to as "PUVA" (psoralen and ultraviolet A) therapy.

If there is widespread involvement of lymph nodes and other sites, single- or multi-drug chemotherapy or photopheresis can be used, depending on the objective of therapy and the rate of disease progression. Extracorporeal photopheresis (ECP) is an immunomodulatory therapy that uses psoralen and UVA. Leukocytes are removed by leukapheresis, then treated with psoralen, exposed to UVA and then returned to the patient. ECP is recommended for patients either with, or at risk for, blood involvement such as that seen in Sézary syndrome.

For more information about CTCL, see the free LLS fact sheet *Cutaneous T-Cell Lymphoma Facts*.

Lymphoplasmacytic Lymphoma and Waldenström Macroglobulinemia. Waldenström macroglobulinemia (WM) is a type of lymphoplasmacytic lymphoma. Lymphoplasmacytic lymphoma and WM are both slow-growing types of lymphoma that originate in a B-lymphocyte precursor.

In lymphoplasmacytic lymphoma, the lymph nodes are more involved than in Waldenström macroglobulinemia. Both disorders show malignant

lymphoplasmacytic cells in the marrow and spleen. Lymphoplasmacytic lymphoma is usually diagnosed by lymph node biopsy, while Waldenström macroglobulinemia is diagnosed by marrow examination. These two types of lymphoma account for less than 2 percent of NHL cases.

The malignant lymphoplasmacytic cells in both disorders secrete an abnormal protein called "monoclonal immunoglobulin M (IgM)." If the monoclonal IgM levels in the blood become elevated enough, patients experience increased blood viscosity (thickening of the blood), inadequate blood flow, and symptoms and signs of limited blood flow (for example, headache, visual blurring, mental confusion). This is referred to as "hyperviscosity syndrome," which may require urgent intervention.

Hyperviscosity syndrome can be treated by plasmapheresis (a process in which plasma is separated from whole blood and the rest is returned to the patient). Plasmapheresis can reverse acute symptoms and signs, but long-term control requires a reduction in the mass of lymphoma cells that make the protein.

One option for patients without symptoms is to take a watch-and-wait approach. Active treatment begins for these patients only if symptoms develop. Progressive disease may also involve the lungs, the gastrointestinal tract and other organs.

Therapy regimens include a combination of biological agents (monoclonal antibodies such as rituximab), signaling inhibitors (drugs that block cell growth and survival signals), and chemotherapy with alkylating agents such as chlorambucil, melphalan and cyclophosphamide.

The Bruton tyrosine kinase (BTK) inhibitor ibrutinib (Imbruvica®) has been approved by the FDA for the treatment of patients with symptomatic WM. Ofatumumab (Arzerra®) is an anti-CD20 antibody approved for relapsed CLL. It is now being studied in clinical trials in various combinations for the treatment of Waldenström macroglobulinemia and other types of NHL.

For more information about Waldenström macroglobulinemia, see the free LLS fact sheet *Waldenström Macroglobulinemia Facts.*

Marginal Zone Lymphoma. This indolent B-cell lymphoma subtype may be extranodal (disease outside of the lymph nodes) or nodal (disease within the lymph nodes). It begins in B lymphocytes in a part of the lymph tissue called the "marginal zone." The disease tends to remain localized. Marginal zone lymphoma includes several subtypes, each categorized by the type of tissue where the lymphoma forms.

- Gastric mucosa-associated lymphoid tissue (MALT) lymphoma usually begins in the stomach. It forms in cells in the mucosa that help make antibodies. Patients with MALT lymphoma may have a history of autoimmune disease, such as Hashimoto thyroiditis or Sjögren syndrome. A higher incidence of MALT lymphoma involving the stomach is seen in patients who have been infected with the bacterium *H Pylori.* Bacteria have also been implicated in other

forms of MALT lymphoma. Treatment often includes potent combinations of antibiotics, which both eradicate the *H Pylori* infection and cause the lymphoma to regress. Many patients with *H Pylori* have been cured of MALT lymphoma without radiation or chemotherapy. For a small subset of patients, MALT lymphoma can transform into diffuse large B-cell lymphoma (DLBCL), and if this happens, patients can benefit from treatments used for DLBCL. See *Diffuse Large B-Cell Lymphoma* on page 24.

- Extragastric MALT lymphoma forms in cells of the mucosa that help make antibodies. It begins outside the stomach in almost every part of the body including other areas of the GI tract, salivary glands, thyroid, lung, skin and around the eye.
- Monocytoid B-cell lymphoma, also known as "nodal marginal zone B-cell lymphoma," may be found in the spleen and blood. This form of NHL is rare, accounting for less than 2 percent of NHL cases, and is generally treated like follicular lymphoma. See *Follicular Lymphoma* on page 31.
- Splenic marginal zone lymphoma (SMZL) is diagnosed in less than 1 percent of all NHL cases. SMZL typically affects patients older than 50 years. This type of lymphoma begins in the spleen and may spread to the peripheral blood and bone marrow. One of the first signs of SMZL is an enlarged spleen; however, symptoms can be slow to develop. SMZL has been associated with hepatitis C infection. Treatment for hepatitis C with interferon (either alone or in combination with ribavirin) may result in a remission of the patient's lymphoma.

  For patients with SMZL who do not have hepatitis C or any symptoms of lymphoma, the first treatment may be the watch-and-wait approach. Treatment is generally started when an enlarged spleen starts to cause symptoms or produces low white blood cell counts. For symptomatic patients who are hepatitis-C negative, treatment may include

  - Splenectomy (removal of the spleen)
  - Single-agent chemotherapy
  - Combination chemotherapy
    - R-CVP (rituximab, cyclophosphamide, vincristine and prednisone)
    - R-CHOP (rituximab, cyclophosphamide, doxorubicin [hydroxydoxorubicin], vincristine [Oncovin®] and prednisone)
    - BR (bendamustine, rituximab)
  - Immunotherapy with rituximab
  - Rituximab combined with chemotherapy.

  Researchers in clinical trials are currently investigating new treatment approaches for SMZL. Speak to your doctor or an LLS Information Specialist to find out more about clinical trials.

Small Cell Lymphocytic Lymphoma (SLL) and Chronic Lymphocytic Leukemia (CLL). Small cell lymphocytic lymphoma and chronic lymphocytic leukemia are highly similar subtypes with regard to

- Incidence—median age of patients is 65 years
- Signs and symptoms—usually widespread enlarged lymph nodes (lymphadenopathy) and slight marrow and blood involvement
- Disease progression—may be very slow
- Treatment.

SLL primarily involves lymph nodes or lymphoid tissue, and it represents about 7 percent of NHL cases. CLL is primarily a disease of the blood and marrow, but CLL cells may travel to the lymph nodes.

The Bruton's tyrosine kinase (BTK) inhibitor ibrutinib (Imbruvica®) has been FDA-approved as first-line therapy for CLL/SLL. The PI3K inhibitor idelalisib (Zydelig®) in combination with rituximab and the BCL-2 inhibitor venetoclax (Venclexta®) have been approved for use in patients with relapsed CLL/SLL.

Bendamustine hydrochloride (Bendeka™) is a chemotherapy agent that has been approved by the FDA for the treatment of patients with CLL and for patients with indolent B-cell NHL who have progressed during or within six months of treatment with rituximab or a rituximab-containing regimen.

Localized SLL is an uncommon disease. Radiation alone (to the specific site) is a treatment option that should be discussed with the doctor.

For more information about CLL, see the free LLS booklet *Chronic Lymphocytic Leukemia.*

Refractory or Relapsed Non-Hodgkin Lymphoma

In some patients, NHL does not respond to initial treatment. This is called "refractory" disease. There are other patients who have a return of their lymphoma after achieving a remission. This is referred to as "relapsed" disease.

Most patients with refractory or relapsed disease receive second-line therapy, in some cases followed by allogeneic (from a donor) or autologous (from the patient) stem cell transplantation. Second-line regimens may include

- ICE—Ifosfamide, carboplatin, and etoposide
- RICE—Rituximab, ifosfamide, carboplatin and etoposide

- DHAP—Dexamethasone, high-dose cytarabine (Ara-C®) and cisplatin (Platinol®)
- ESHAP—Etoposide, methylprednisolone, high-dose cytarabine (Ara-C®) and cisplatin (Platinol®)
- R-ESHAP—Rituximab, etoposide, methylprednisolone, high-dose cytarabine (Ara-C®) and cisplatin (Platinol®).

An elevated beta$_2$-microglobulin level, a high serum lactate dehydrogenase (LDH) level, expression of survivin (a protein that inhibits cell death), expression of cyclin D3, *p53* gene mutation and certain other factors are associated with higher risk for relapse after standard therapy. Imaging with a fluorodeoxyglucose positron emission (FDG-PET) scan may be used to assess response after therapy to determine if there is a need for more aggressive therapy. Relapse is more common in the first two to three years after diagnosis but is rare four years after diagnosis.

Autologous stem cell transplantation after high-dose chemotherapy may be an option for some patients with lymphoma who have relapsed after R-CHOP chemotherapy. Autologous stem cell transplant is a treatment that uses a patient's own stem cells to delay the progression of certain blood cancers. Autologous stem cell transplantation allows more patients and older patients with relapsed disease to receive intensive chemotherapy and rescue of their marrow function by infusion of stem cells. If an autologous transplant is not an option because of older age or medical complications, then treatment in clinical trials can be explored.

An allogeneic stem cell transplantation is a treatment that uses donor stem cells to restore a patient's marrow and blood cells. However, allogeneic transplant is not used as often as autologous stem cell transplantation because it is more toxic and is considered a last option.

Increasingly, there are less aggressive treatments being used for relapsed or refractory lymphomas. Examples include idelalisib (Zydelig®), which is FDA approved for use in indolent lymphomas that have relapsed despite prior monoclonal antibodies against CD20, and chemotherapy with alkylating agents. New combinations are being tested in clinical trials for relapsed lymphomas.

Side Effects of Treatment for Non-Hodgkin Lymphoma

The side effects of treatment for lymphoma depend on the intensity and type of treatment such as the location of the radiation therapy, the age of the patient, and coexisting medical conditions (for example, diabetes mellitus and chronic renal disease). In addition, certain drugs have a tendency to affect certain tissues—for example, vincristine typically affects nerve tissue.

In recent years, new drugs and other therapies have increased doctors' ability to control side effects such as nausea and vomiting that trouble many patients. When side effects do occur, most are short-lived and resolve when therapy is completed. The benefits of treatment, with the goal of remission (and in some cases, cure) generally outweigh the risks and discomfort associated with NHL therapy. For more information, see the free LLS booklet *Understanding Side Effects of Drug Therapy.*

Suppressed Blood Cell Formation. Decreases in blood cell counts may occur in patients treated with chemotherapy. Blood transfusions may be necessary for some patients with low blood cell counts. If decreases in white blood cell counts are severe and continue over extended periods of time, infection may develop and require antibiotic treatment. Sometimes, chemotherapy dosages or the time between chemotherapy cycles must be altered to allow the patient's blood counts to recover from the effects of treatment. To stimulate the production of depleted white blood cells, a granulocyte-colony stimulating factor (G-CSF) such as Neupogen® or Neulasta® is sometimes used. This subcutaneous injection is given to increase the number of white blood cells that help prevent infection.

Infections. Chemotherapy and radiation therapy can make patients more susceptible to infection because these treatments weaken immune cell function and can lower the number of normal white blood cells. Removal of the spleen, a treatment option for some types of NHL such as splenic marginal zone lymphoma (SMZL), also contributes to the risk of severe infection. However, when patients are cured, their immune function may improve.

Improvement in the treatment of patients with NHL, increased awareness of the risk of infectious diseases and better antimicrobial therapy have made infectious complications less of a medical problem for patients.

NHL patients are advised to receive certain vaccinations once they have finished their treatment, including vaccinations for pneumococcal pneumonia and influenza. There are two types of pneumococcal vaccines available for adults: a pneumococcal polysaccharide vaccine (PPSV23) and a pneumococcal conjugate vaccine (PCV13). Immunizations that should not be administered include those using live organisms or those with high viral loads, such as the herpes zoster (also known as "shingles") vaccine. Your doctor can give you more information.

Viral Reactivation. Hepatitis B virus (HBV, Hep B) reactivation has been reported in some patients treated with chemotherapy either with or without immunotherapy drugs. Carriers of the Hepatitis B virus, especially those treated with anti-CD20 monoclonal antibodies (rituximab, ofatumumab, obinutuzumab), have a high risk of virus reactivation and disease. Preventive antiviral therapy is recommended for patients who test positive for HBV if they are going to receive NHL therapy.

Neuropathy. Some chemotherapeutic agents such as the drug vincristine (Oncovin®) or brentuximab vedotin (Adcetris®) can cause nerve damage called "neuropathy." Initially, the patient experiences numbness and tingling in the fingertips and toes. The sensation might come and go, but if it continues, it may become permanent. In general, treatment options are limited. The patient should be monitored for these side effects between each cycle of chemotherapy that includes vincristine. If the neuropathy becomes severe, the dose of vincristine may need to be adjusted.

Progressive Multifocal Leukoencephalopathy (PML). This is a rare but serious and potentially fatal central nervous system infection caused by the reactivation of the latent John Cunningham (JC) virus. Cases of PML typically occur in severely immunocompromised individuals such as AIDS patients or blood cancer patients who have profound immunosuppression due to the underlying disease or its treatment. The use of rituximab (used in combination with chemotherapy) may be associated with an increased risk of PML in immunocompromised patients with CLL/SLL and other types of NHL. Signs and symptoms of PML include confusion, poor coordination, motor weakness and visual and/or speech changes. To date, there is no effective treatment for this condition. Patients at risk should be carefully monitored for the development of any neurological symptoms.

Tumor Lysis Syndrome. Patients with NHL, especially those with very high white blood cell counts before the beginning of treatment, may be at high risk for developing acute tumor lysis syndrome (TLS). TLS is characterized by metabolic abnormalities that are caused by the sudden release of the cellular contents of dying cells into the bloodstream, a phenomenon induced by chemotherapy. If untreated, TLS can lead to heart arrhythmias, seizures, loss of muscle control, acute kidney failure and even death. Patients with a high level of uric acid may be given the drug allopurinol (Zyloprim®) to minimize the buildup of uric acid in the blood. Allopurinol is taken by mouth. Another drug, rasburicase (Elitek®), is given in a single intravenous dose and can rapidly lower an elevated uric acid level.

Other Side Effects. Chemotherapy affects tissues that normally have a high rate of cell turnover. Thus, the lining of the mouth, the lining of the intestines, the skin and the hair follicles may be affected. Common side effects of therapy include

- Mouth sores
- Nausea and vomiting
- Diarrhea

- Temporary hair loss
- Fatigue
- Cough
- Fever
- Rash.

Side effects can range from mild to severe. They depend on the medications and dosages used and the individual patient's susceptibility. Fortunately, there are drugs and other supportive measures to either prevent or manage many side effects.

Children may experience side effects of treatment for a short time or longer periods that can affect learning. For more information, see the free LLS booklet *Learning & Living With Cancer: Advocating for your child's educational needs.*

Long-Term and Late Effects of Treatment for Non-Hodgkin Lymphoma

Long-term effects of cancer therapy are medical problems that persist for months or years after treatment ends. Late effects are medical problems that do not develop or become apparent until years after treatment ends.

It is important to know about the potential for long-term and late effects of treatment so that any problems may be identified early and managed. Various factors can influence the risk, including

- Type and duration of treatment
- Age at time of treatment
- Gender and overall health

Many survivors of NHL do not develop significant long-term or late effects of treatment. However, it is important for all adult patients and for parents of children who will be treated for NHL to discuss possible long-term and late effects with members of the treatment team so that the proper planning, evaluation and follow-up care can take place.

Heart Disease. Radiation therapy to the chest and treatment with chemotherapy containing alkylating agents (eg, cyclophosphamide) or anthracyclines (eg, doxorubicin) have been linked to heart disease, including inflammation of the sac surrounding the heart (the pericardium), valve dysfunction or classic heart attack (myocardial infarction).

Secondary Cancers. For as long as three decades after diagnosis, patients are at a significantly elevated risk for second primary cancers, such as lung, brain and kidney cancers, melanoma, and Hodgkin lymphoma. Therapy with autologous bone marrow or peripheral blood stem cell transplant and treatment with chemotherapy-containing alkylating agents are associated with an increased risk of developing myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML).

Fertility. Patients may be less fertile after treatment for NHL. The risk of infertility varies according to the nature of the treatment, including the type and amount of chemotherapy, the location of radiation therapy and the patient's age. Men who are at risk of infertility should consider sperm banking before treatment. Women who have ovarian failure after treatment experience premature menopause and require hormone replacement therapy. Since frozen-egg storage is generally a time-consuming process, it may not be recommended to patients who need to start treatment without delay.

It is important to discuss all your options and treatment concerns with your doctor. If possible, you may also want to discuss these options with a doctor who specializes in fertility and reproduction. Many cancer centers have reproductive specialists who will suggest specific options for each patient. In couples of childbearing age in which one partner has received treatment, the incidence of pregnancy loss and the health of a newborn are very similar to those of healthy couples.

For more information, see the free LLS fact sheets *Fertility Facts; Long-Term and Late Effects of Treatment for Childhood Leukemia or Lymphoma Facts*; and *Long-Term and Late Effects of Treatment in Adults Facts.*

Follow-up Care. Follow-up care is important with both aggressive and indolent forms of NHL because if the disease recurs, curative options are still available for many people. Follow-up care needs to be individualized and should be based on several factors, including how the disease initially manifested. Patients who are in remission should continue to be monitored by clinical assessment as determined by their doctor. In the past, CT scans or other diagnostic imaging were done routinely in an attempt to detect relapse. However, there is an increasing awareness that too many scans may be harmful, and that CT scans performed in otherwise asymptomatic patients have a relatively low chance of finding recurrent lymphoma. The frequency of clinical visits, laboratory tests, and CT scans or other imaging should be discussed with the treating doctor.

Periodic assessment of the patient's state of health, blood cell counts and, if indicated, bone marrow, is important. Over time, the interval between assessments may be lengthened, but assessments should be continued indefinitely for most patients.

Research and Clinical Trials

New approaches under study in clinical trials for NHL treatment, many of which are being supported by LLS research programs, hold the promise of increasing the rate of remission and finding a cure for NHL.

Clinical Trials. Every new drug or treatment regimen goes through a series of studies called "clinical trials" before it becomes part of standard therapy. Clinical trials are carefully designed and rigorously reviewed by expert clinicians and researchers to ensure as much safety and scientific accuracy as possible. Participation in a carefully conducted clinical trial may be the best available therapy. Patient participation in past clinical trials has resulted in the therapies we have today.

LLS Information Specialists, at (800) 955-4572, can offer guidance on how patients can work with their doctors to determine if a specific clinical trial is an appropriate treatment option. Information Specialists will conduct individualized clinical-trial searches for patients, family members and healthcare professionals.

Research Approaches. There are clinical trials for newly diagnosed patients and for patients with relapsed or refractory disease. A number of approaches are under study in clinical trials for the treatment of patients with NHL.

Agents Under Study. The following drugs are examples of specific agents under study:

- Agents called "histone deacetylase (HDAC) inhibitors" are a class of drugs that address "epigenetic" changes in the DNA. Examples include vorinostat (Zolinza®), romidepsin (Istodax®) and belinostat (Beleodaq®), among others.
- The immunomodulatory drug lenalidomide (Revlimid®) is being studied as a single agent and in combination with other drugs for the treatment of diffuse large B-cell lymphoma, mantle cell lymphoma, follicular lymphoma and chronic lymphocytic leukemia (CLL).
- Pralatrexate (Folotyn®), approved for various T-cell lymphoma subtypes, is being studied as a single agent and in combination with other chemotherapy drugs for treating various relapsed and refractory B-cell and T-cell NHLs. Pralatrexate is an antifolate drug that disrupts processes in cells that are required for cell replication.
- There are several other drugs under investigation that target B-cell receptor signaling pathways inside the lymphoma cells. Some of these drugs include
    - Ibrutinib (Imbruvica®), a BTK inhibitor that is approved for treating Waldenström macroglobulinemia and previously-treated mantle cell lymphoma (MCL). It is now being studied in combination with other drugs to treat various indolent and aggressive NHLs.

- The PI3K inhibitor idelalisib (Zydelig®), approved for the treatment of patients with relapsed CLL/SLL, is being studied in combination with other agents for relapsed or refractory indolent B-cell NHL and MCL.

- Immunotherapy with monoclonal antibodies
  - Brentuximab vedotin (Adcetris®) targets CD30 and is used for treating peripheral T cell lymphomas and Hodgkin lymphomas. It is under study in clinical trials for treating systemic anaplastic large cell lymphoma and other previously treated NHLs.
  - Yttrium-90+ibritumomab tiuxetan (Zevalin®) has been approved for previously untreated follicular NHL patients who achieve a partial or complete response to first-line chemotherapy. The effectiveness of this agent is now being studied in the retreatment of lymphoma, as therapy for newly diagnosed indolent lymphoma, as therapy for aggressive forms of NHL in combination with or following other drug regimens, and as part of high-dose therapy programs along with autologous stem cell transplantation.
  - Ofatumumab (Arzerra®) is an anti-CD20 antibody approved for relapsed CLL. It is now being studied in clinical trials in various combinations for the treatment of Waldenström macroglobulinemia, DLBCL and follicular lymphoma.
  - Obinutuzumab (Gazyva®) is an antibody that targets CD20. It is being used in the treatment of some types of NHLs including refractory follicular lymphoma. It is currently being studied in clinical trials (in combination with other agents) for treating relapsed and refractory CLL/SLL.

Reduced-Intensity Stem Cell Transplantation (Nonmyeloablative Allogeneic Transplantation). Clinical trials are under way to determine the usefulness of this approach in older and sicker patients for many blood cancers, including some NHL subtypes. As a result, stem cell transplantation may be an option for patients aged 60 to 70 years and older. Patients being conditioned for a reduced-intensity transplant receive lower doses of chemotherapy drugs and/or radiation in preparation for the transplant. Immunosuppressive drugs are used to prevent rejection of the graft (the donor immune cells), thereby allowing the engrafted immune cells to attack the recipient's disease. The effectiveness of reduced-intensity transplantation is due to the graft-versus-lymphoma effect of the donor's lymphocytes rather than to high doses of chemotherapy.

CAR T-Cell Therapy. This is a type of immunotherapy that consists of engineering a patient's own immune cells to recognize and then attack cancerous tumors. This approach has shown very promising results in patients with blood cancers. The patient's T cells are genetically engineered to produce receptors on their surface called "chimeric antigen receptors (CARs)." These receptors recognize and bind to a specific target found on the cancer cells. In an ongoing clinical trial, researchers are studying the role of CAR T-cell therapy in patients with relapsed or refractory aggressive B-cell NHL.

For more information on this type of therapy, please see the LLS fact sheet *Chimeric Antigen Receptor (CAR) T-Cell Therapy Facts.*

PD-1 Checkpoint Inhibitors. A vital part of the immune system is its ability to tell the difference between healthy cells in the body from those that are foreign or harmful. The immune system depends on multiple "checkpoints," in which molecules on certain immune cells need to be activated or inactivated in order to start an immune response. Cancer cells sometimes take advantage of these checkpoints to escape the detection of active immune cells.

Programmed cell death 1 (PD-1) is a checkpoint protein that is found on the surface of T cells. It normally acts as a type of "off switch" that helps prevent immune cells from attacking healthy cells in the body. It accomplishes this when it attaches to PD-L1, a protein found on some normal cells and also in some cancer cells. When PD1 binds to PD-L1, a message is sent to the T cell to leave the other cell alone. Some cancer cells have large amounts of PD-L1 receptors, which help them avoid an immune attack.

Checkpoint inhibitors are drugs created to target the PD1 or PD-L1, blocking their actions, and allowing the immune system to recognize and eliminate cancer cells. One example of this type of drug is nivolumab (Opdivo®), which has shown positive results in other cancers such as melanoma and is now being studied as a single agent and in combination with other drugs for the treatment of B-cell and T-cell non-Hodgkin lymphomas. Another checkpoint inhibitor drug is pidilizumab, which is now being studied in trials for the treatment of relapsed follicular lymphoma.

We encourage you to contact an Information Specialist and visit www.LLS.org/clinicaltrials for more information about specific treatments under study in clinical trials.

Normal Blood and Marrow and the Lymphatic System

Blood and Marrow. Blood is composed of plasma and cells suspended in plasma. Plasma is largely made up of water in which many chemicals are dissolved. These chemicals include

- Proteins of various types
  - Albumin, the most common protein in blood
  - Blood-clotting proteins, made by the liver
  - Erythropoietin, a protein made by the kidneys that stimulates red cell production
  - Immunoglobulins, antibodies made by plasma cells in response to infections including those we develop from our vaccinations (such as poliovirus antibodies, which are made by normal plasma cells in the bone marrow)

- Hormones, such as thyroid hormone and cortisol
- Minerals, such as iron and magnesium
- Vitamins, such as folate and vitamin B_{12}
- Electrolytes, such as calcium, potassium and sodium
- Antibodies, which are made by plasma cells.

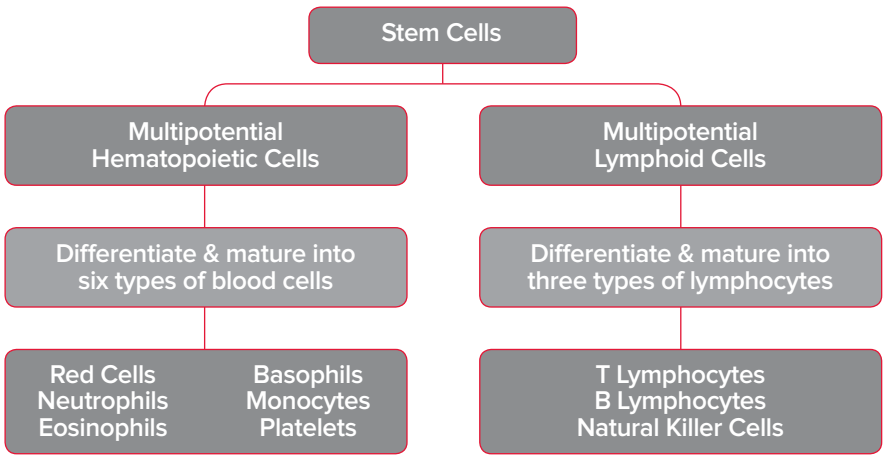
The cells suspended in plasma include red blood cells, platelets and white blood cells (neutrophils, monocytes, eosinophils, basophils, and lymphocytes).

- Red blood cells
  - Make up a little less than half the volume of the blood
  - Are filled with hemoglobin, which gets oxygen from the lungs and delivers it to the cells throughout the body
  - Hemoglobin gets carbon dioxide from the cells and takes it back to the lungs
  - In the lungs, carbon dioxide is removed when we exhale.
- Platelets
  - Are small cells (one-tenth the size of red blood cells)
  - Help stop bleeding at the site of an injury in the body
  - If there is a cut, the blood vessels are torn open
  - Platelets stick to the tear, clump together, and plug up the bleeding site
  - They use blood-clotting proteins such as fibrin, and electrolytes such as calcium
  - Later, a firm clot forms
  - The vessel wall heals at the site of the clot and returns to its normal state.
- Neutrophils and monocytes
  - Are white blood cells
  - Called “phagocytes” (eating cells), can ingest bacteria or fungi and kill them
  - Unlike the red blood cells and platelets, monocytes can leave the blood and enter tissue
  - In tissue they can attack invading organisms and help combat infection.
- Eosinophils and basophils
  - Are white blood cells
  - They respond to allergens or parasites.

- Lymphocytes
  - Are white blood cells
  - Are found in the lymph nodes, the spleen and the lymphatic channels
  - Some lymphocytes enter the blood
  - Are a key part of the immune system
  - There are three major types of lymphocytes:
    - T lymphocytes (T cells)
    - B lymphocytes (B cells)
    - Natural killer (NK) cells.

Marrow is a spongy tissue where blood cell development takes place. It occupies the central cavity of bones. In newborns, all bones have active marrow. By the time a person reaches young adulthood, the bones of the hands, feet, arms and legs no longer have functioning marrow. The spine (vertebrae), hip and shoulder bones, ribs, breastbone and skull contain the marrow that makes blood cells in adults. The process of blood cell formation is called "hematopoiesis." A small group of cells, the stem cells, develop into all the blood cells in the marrow by the process of differentiation (see Figure 4).

Figure 4. Blood Cell & Lymphocyte Development



Stem cells develop into blood cells (hematopoiesis) and lymphoid cells.

In healthy individuals, there are enough stem cells to keep producing new blood cells continuously. Blood passes through the marrow and picks up the fully developed and functional red and white blood cells and platelets for circulation in the blood.

Some stem cells enter the bloodstream and circulate. They are present in such small numbers that they cannot be counted or identified by standard blood count tests. Their presence in the blood is important because they can be collected by a special technique. There are also methods to induce more stem cells to leave their home in the marrow and circulate in the blood, allowing a greater stem cell collection to occur. If enough stem cells are harvested from a compatible donor, they can be transplanted into a recipient.

Stem cell circulation, from marrow to blood and back, also occurs in the fetus. After birth, placental and umbilical cord blood can be collected, stored and used as a source of stem cells for transplantation.

The Lymphatic System. The marrow is really two organs in one. The first is marrow as the blood cell-forming organ. The second is marrow as the lymphocyte-forming organ that is a part of the immune system.

The marrow produces three main types of lymphocytes (white blood cells). They are

- B lymphocytes (B cells), which make antibodies in response to foreign substances (antigens), especially microbes
- T lymphocytes (T cells), which mature in the thymus. The T lymphocytes have several functions, including assisting B lymphocytes to make antibodies against invading bacteria, viruses or other microbes. The antibody attaches to the microbe, making it possible for another white blood cell to recognize the antibody and "ingest it," that is, pull it into the cell along with its attached microbe. The white cell then kills and digests the microbe.
- Natural killer (NK) cells, which attack virus-infected cells without requiring antibody or other mediation. T cells and NK cells have other functions as well and are important elements in research efforts to design immunotherapies to treat lymphoma and other cancers.

The lymphocytes circulate through channels called "lymphatics," which connect the lymph nodes to each other throughout the body. The lymphatic channels collect into large ducts that empty into blood vessels. Lymphocytes enter the blood via these ducts. Most lymphocytes are found in the lymph nodes and other parts of the lymphatic system such as the skin, spleen, tonsils and adenoids (special lymph nodes), intestinal lining, and in young people, the thymus.

Medical Terms

Allogeneic Stem Cell Transplantation. A treatment that uses donor stem cells to restore a patient's marrow and blood cells. Allogeneic transplantation may be considered in the treatment of indolent NHL, particularly for younger patients whose disease behaves more aggressively than the average indolent lymphoma. A type of allogeneic transplant called a "reduced-intensity" or "nonmyeloablative" transplant is under study. It uses lower doses of conditioning therapy and may be safer, especially for older patients. For more information, see the free LLS booklet *Blood and Marrow Stem Cell Transplantation*.

Anemia. A decrease in the number of red blood cells and, therefore, the hemoglobin concentration of the blood. This results in a diminished ability of the blood to carry oxygen. Severe anemia can cause a pale complexion, weakness, fatigue and shortness of breath on exertion.

Antibodies. Proteins released by plasma cells (derived from B lymphocytes) that recognize and bind to specific foreign substances called "antigens." Antibodies coat, mark for destruction or inactivate foreign particles such as bacteria, viruses or harmful toxins.

Antigen. A foreign substance, usually a protein, that stimulates an immune response when it is ingested, inhaled or comes into contact with the skin or mucous membranes. Examples of antigens are bacteria, viruses or allergens. Antigens stimulate plasma cells to produce antibodies.

Antioncogene. See Tumor Suppressor Gene.

Apheresis. The process of removing certain components of a donor's blood and returning the unneeded parts to the donor. The process, also called "hemapheresis," uses continuous circulation of blood from a donor through a specialized machine and then back to the donor. Apheresis makes it possible to remove desired elements from large volumes of blood. Platelets, red blood cells, white blood cells and plasma can be removed separately.

Autologous Stem Cell Transplantation. A treatment that uses a patient's own stem cells to delay the progression of certain blood cancers. The autologous transplantation process takes place after the patient achieves a complete response (remission), or a good partial response, to induction drug therapy. For diffuse large B-cell lymphoma, mantle cell lymphoma, and follicular lymphoma, an autologous transplant in first remission may be a good treatment option. For more information, see the free LLS booklet *Blood and Marrow Stem Cell Transplantation.*

***BCL-2* Gene Rearrangement.** Rearrangement in the *BCL2* gene that occurs in B cells and is present in many cases of follicular lymphoma, diffuse large B-cell lymphoma and other cancers.

Biopsy. A procedure to obtain tissue for diagnosis. In many cases, a special needle can be used to obtain the tissue. In some cases, a larger piece of tissue may be surgically removed. Since the appearance of a lymph node is important in categorizing the type of lymphoma that may be present, surgical removal of an entire, swollen lymph node or nodes may be necessary (lymph node biopsy).

Bone Marrow. A spongy tissue in the hollow central cavity of the bones that is the site of blood cell formation. By puberty, the marrow in the spine, ribs, breastbone, hips, shoulders and skull is most active in blood cell formation. In these sites, the marrow is filled with fat cells. When marrow cells have matured into blood cells, they enter the blood that passes through the marrow and are carried throughout the body.

Bone Marrow Aspiration. A test to examine marrow cells to detect cell abnormalities. A marrow sample is usually taken from the patient's hip bone. After medication is given to numb the skin, the liquid sample is removed using a special needle inserted through the bone into the bone marrow.

Bone Marrow Biopsy. A test to examine marrow cells to detect cell abnormalities. This test differs from a bone marrow aspiration in that a small amount of bone filled with marrow is removed, usually from the hip (pelvic) bone. After medication is given to numb the skin, a special hollow biopsy needle is used to remove a core of bone containing marrow. Bone marrow aspiration and bone marrow biopsy may be done in the doctor's office or in a hospital. The two tests are almost always done together.

Bone Marrow Transplantation. See Allogeneic Stem Cell Transplantation and Autologous Stem Cell Transplantation.

Central Line (Indwelling Catheter). A special tubing inserted into a large vein in the upper chest. The central line (the indwelling catheter), is tunneled under the skin of the chest to keep it firmly in place. The external end of the catheter can be used to administer medications, fluids or blood products or to withdraw blood samples. See Port.

Chemotherapy. The use of chemicals (drugs or medications) to kill malignant cancer cells. Numerous chemicals have been developed for this purpose; most act to injure the DNA of the cancer cells. When the DNA is injured, the cancer cells cannot grow or survive.

Chromosome. Threadlike structures within cells that carry genes in a linear order. Human cells have 23 pairs of chromosomes: chromosome pairs 1 to 22 and one pair of sex chromosomes (X for women and Y for men). See Translocation.

Clonal. The designation for a population of cells derived from a single transformed parent cell. Virtually all cancers are derived from a single cell with an injury (mutation) to its DNA and thus are monoclonal. Leukemia, lymphoma

and myeloma are examples of clonal cancers, that is, cancers derived from a single abnormal cell.

Cluster Designation (CD). A term used with a number to identify a specific molecule on the surface of an immune cell. It is commonly used in its abbreviated form, for example: CD20 is the target of the monoclonal antibody therapy rituximab and CD52 is the target of the monoclonal antibody therapy alemtuzumab.

Colony-Stimulating Factor. See Growth Factor.

Computed Tomography (CT) Scan. A technique for imaging body tissues and organs. X-ray transmissions are converted to detailed images using a computer to synthesize x-ray data. The images are displayed as a cross-section of the body at any level from the head to the feet. A CT scan of the chest, abdomen or pelvis permits detection of an enlarged lymph node, liver or spleen. A CT scan can be used to measure the size of these and other structures during and after treatment.

CT Scan. See Computed Tomography (CT) Scan.

Cytogenetic Analysis. The process of analyzing the number and size of the chromosomes of cells. It detects chromosome alterations and, in some cases, may identify the actual genes that have been affected. These findings help healthcare professionals diagnose specific types of blood cancers, determine treatment approaches and monitor the response to treatment. The individual who prepares and examines the chromosomes and interprets the results is called a "cytogeneticist."

Differentiation. The process by which stem cells give rise to functional cells of a single blood cell line. For example, differentiation of stem cells forms red blood cells, platelets and white blood cells (neutrophils, monocytes, eosinophils, basophils and lymphocytes). See Hematopoiesis.

DNA. The genetic material in the cell. The scientific name for DNA is deoxyribonucleic acid. DNA is made up of a sugar-phosphate backbone with ladderlike "steps" composed of purines and pyrimidines (building blocks of nucleic acids). The sequence of the purines and pyrimidines in the DNA is responsible for passing genetic information to new cells during the process of cell division; for passing genetic information from one generation to the next during reproduction; and for providing the instructions for building proteins, which in turn carry out the major functions of a cell. A mutation is generally a change in, or loss of, the sequence of the purines or pyrimidines of the DNA. Mutations can lead to cell death, to changes in the way a cell functions or, in some cases, to cancer.

DNA-Gene Chip. See Microarray.

Eosinophil. A type of white blood cell that participates in allergic reactions and helps fight certain parasitic infections.

Epigenetic Change. Any change that alters gene activity without changing the DNA sequence. While epigenetic changes are natural and essential to many of the body's functions, certain epigenetic changes can cause major adverse health effects, including cancer.

Erythrocytes. Red blood cells that carry hemoglobin. See also Red Blood Cells.

Erythrocyte Sedimentation Rate. (ESR). See Sedimentation Rate.

Extranodal Lymphoma. Lymphoma that develops in parts of the body that are not lymph nodes—for example, the thyroid, lungs, gastrointestinal tract, liver, bones, stomach, or central nervous system. When lymphoma is detected exclusively in these non-lymph node areas, it is called "primary" extranodal lymphoma.

FISH. See Fluorescence In Situ Hybridization.

Flow Cytometry. A test that permits the identification of specific cell types within a sample of cells. The test may be used to examine blood cells, marrow cells or cells from a biopsy. One use of flow cytometry is to determine whether a sample of cells is composed of T cells or B cells. This permits the doctor to determine if the leukemia or lymphoma is the B-cell or T-cell type.

Fluorescence In Situ Hybridization (FISH). A technique for studying chromosomes in tissue using DNA probes tagged with fluorescent molecules that emit light of different wavelengths and in different colors. The probes match to the chromosomes within the cells and the chromosomes emit light (fluoresce) in color.

G-CSF (Granulocyte-Colony Stimulating Factor). See Growth Factor.

Gene Expression Profiling. A research method that uses microarray analysis to identify a combination of genes that are turned off or on in response to a specific condition. A set of genes in a blood or tissue sample can be used to monitor the levels of thousands of genes at once.

GM-CSF (Granulocyte-Macrophage Colony Stimulating Factor). See Growth Factor.

Granulocyte. A type of white blood cell that has a large number of granules in the cell body. Neutrophils, eosinophils and basophils are all types of granulocytes.

Growth Factor. A type of protein called a "glycoprotein" used to stimulate the production of neutrophils and shorten the period of low neutrophil counts in the blood after chemotherapy. Granulocyte-colony stimulating factor (G-CSF) and granulocyte-macrophage colony stimulating factor (GM-CSF) are examples of growth factors that are made commercially. GM-CSF can also stimulate monocytes.

Hemapheresis. Selective removal of certain components of the blood. See also Apheresis.

Hematologist. A doctor who specializes in the treatment of blood cell diseases. This is an internist who specializes in blood diseases in adults or a pediatrician who specializes in treating blood diseases in children.

Hematopathologist. A pathologist specializing in blood diseases. See also Pathologist.

Hematopoiesis. The process of blood cell development in the marrow. The most undeveloped cells in the marrow are stem cells. They start the process of blood cell development. The stem cells begin to develop into young or immature blood cells such as red blood cells or white blood cells of various types. This process is called "differentiation." The young or immature blood cells then further develop into fully functional blood cells. This process is called "maturation."

The mature cells leave the marrow, enter the blood and circulate throughout the body. Hematopoiesis is a continuous process that is active normally throughout life. When the marrow is invaded with cancer cells, the constant demand for new blood cells cannot be met, resulting in a severe deficiency in blood cell counts.

HLA. Human Leukocyte Antigen(s). These antigens are proteins on the surface of most tissue cells that give an individual his or her unique tissue type. HLA factors are inherited from mother and father, and the greatest chance of having the same HLA type is between siblings. On average, one in four siblings is expected to share the same HLA type. The testing for HLA antigens is referred to as "tissue typing."

Immunophenotyping. A method that uses the reaction of antibodies with cell antigens to determine a specific type of cell in a sample of blood cells, marrow cells or lymph node cells. The antibodies react with specific antigens on the cell. A tag is attached to an antibody so that it can be detected. The tag can be identified by the laboratory equipment used for the test so cells carrying antigens can be identified.

Immunotherapy. The term for several treatment approaches used by doctors to harness the body's immune system to treat lymphoma and other diseases. These therapies include monoclonal antibody therapy, radioimmunotherapy and vaccine therapy. Monoclonal antibodies are proteins made in the laboratory that either react with or attach to antigens on the target cells. The antibodies are used therapeutically in three ways: as "naked" antibodies (monoclonal antibodies), as antibodies to which radioactive isotopes are attached (radioimmunotherapy), and as antibodies to which toxins are attached (immunotoxins). For more information, see the free LLS fact sheet *Immunotherapy Facts*.

Indwelling Catheter. See Central Line (Indwelling Catheter).

Intrathecal. Designation for the space between the covering or lining of the central nervous system (CNS) and the brain or spinal cord. That lining is called the "meninges." In some situations, drugs have to be administered directly into the spinal canal when cancer cells are present in the meninges. This procedure is called "intrathecal therapy."

Lactate Dehydrogenase (LDH). An enzyme present in all normal and abnormal cells, LDH is released from cells into the blood and is present in normal amounts in the liquid portion of blood (the plasma). When blood is collected and allowed to clot, the fluid portion is called the "serum." Many chemicals are measured in the serum, including LDH. Normal serum contains low levels of LDH. The level may be elevated in many diseases, such as hepatitis and various cancers. The LDH level is often elevated in lymphoma and lymphocytic leukemias. Changes in LDH are nonspecific, but when the LDH level is elevated in the presence of lymphocytic cancers, the change may reflect the extent of the tumor and the rapidity of tumor growth. LDH monitoring is used in some cases along with other measures to plan the intensity of therapy for lymphoma. Burkitt lymphoma and other types of aggressive lymphoma are often associated with marked elevations in the serum LDH level. Also known as "lactic acid dehydrogenase."

Leukocytes. See White Blood Cells.

Leukopenia. A decrease below normal in the concentration of blood leukocytes (white blood cells).

Lymphadenopathy. Enlargement of lymph nodes.

Lymphatic System. The system comprising the lymph nodes, the thymus gland (in the first several decades of life), the lymphatic channels, the lymphatic tissue of the marrow, the gastrointestinal tract, the skin and the spleen, and the T lymphocytes, B lymphocytes and natural killer (NK) lymphocytes contained in these sites.

Lymph Nodes. Bean-sized structures that contain large numbers of lymphocytes and are connected with each other by small channels called "lymphatics." These nodes are distributed throughout the body. In patients with lymphoma and some types of lymphocytic leukemia, the malignant lymphocytes grow and the lymph nodes may become enlarged. This enlargement of lymph nodes can be seen, felt or measured by computed tomography (CT) scan or magnetic resonance imaging (MRI), depending on the degree of enlargement and the location of the nodes.

Lymphocyte. A type of white blood cell that is the essential cell type in the body's immune system. There are three major types of lymphocytes: B lymphocytes, which produce antibodies to help combat infectious agents like bacteria, viruses and fungi; T lymphocytes, which have several functions, including assisting B lymphocytes to make antibodies; and natural killer (NK) cells, which can attack virus-infected cells or tumor cells.

Macrophage. See Monocyte/Macrophage.

Magnetic Resonance Imaging (MRI). A testing technique that provides detailed images of body structures. It differs from the CT scan in that the patient is not exposed to x-rays. Signals are generated in the tissues in response to a magnetic field produced by a specialized instrument and are converted by computer into images of body structures. Healthcare professionals use MRI to measure the size, or a change in size, of organs such as the lymph nodes, liver and spleen, or tumor masses.

Marrow. See Bone Marrow.

Maturation. See Hematopoiesis.

Meninges. See Intrathecal.

Microarray. A two-dimensional grid of molecules (often but not always DNA genes or gene fragment spots), usually arranged on a glass slide or silicone wafer. A typical microarray (also called "DNA-gene chip") contains 10,000 to 200,000 microscopic DNA spots. Scientists use a microarray to study gene expression and to learn which genes are expressed or not expressed under given circumstances. See Gene Expression Profiling.

Monoclonal. See Clonal.

Monoclonal Antibody Therapy. See Immunotherapy.

Monocyte/Macrophage. A type of white blood cell that represents about 5 to 10 percent of the cells in normal human blood. The monocyte and the neutrophil are the two major microbe-eating and microbe-killing cells in the blood. When monocytes leave the bloodstream and enter the tissue, they are converted to macrophages. The macrophage is the monocyte-in-action: It can combat infection in the tissues, ingest dead cells (in this function it is called a "scavenger cell") and assist lymphocytes in their immune functions.

MRI. A type of imaging test. See Magnetic Resonance Imaging.

Mutation. An alteration in a gene that results from a change to a part of the stretch of DNA that represents the gene. A "germ cell mutation" is present in the egg or the sperm and can be transmitted from parent to offspring. A "somatic mutation" occurs in a specific tissue cell and can result in the growth of that cell into a tumor. Most cancers start after a somatic mutation. In leukemia, lymphoma or myeloma, a primitive marrow (blood-forming) or lymph node cell undergoes a somatic mutation or mutations that lead to the formation of a tumor. If a mutation results from a major abnormality of chromosomes such as a translocation, it can be detected by cytogenetic examination. Sometimes the alteration in the gene is more subtle and requires more sensitive tests to identify the oncogene.

Neutropenia. A decrease below normal in the concentration of neutrophils, a type of white blood cell.

Neutrophil. The principal phagocyte (microbe-eating cell) in the blood. The neutrophil is the main cell that combats infections. Patients with certain blood cancers or patients who have undergone chemotherapy often do not have sufficient quantities of neutrophils circulating in their bloodstream. A severe deficiency of neutrophils increases the patient's susceptibility to infection.

Nonmyeloablative Stem Cell Transplantation. See Reduced-Intensity Stem Cell Transplantation.

Oncogene. A mutated gene that is the cause of a cancer. Several subtypes of acute myeloid leukemia, acute lymphoblastic leukemia, lymphoma, and nearly all cases of chronic myeloid leukemia are associated with an oncogene.

Oncologist. A doctor who diagnoses and treats patients who have cancer. Oncologists are usually internists who undergo additional specialized training to treat people with cancer (pediatric oncologists treat children with cancer). Radiation oncologists specialize in the use of radiation to treat cancer, and surgical oncologists specialize in the use of surgical procedures to diagnose and treat cancer. These doctors cooperate and collaborate to provide the best treatment plan (surgery, radiation therapy, chemotherapy or immunotherapy) for the patient.

Pathologist. A doctor who identifies disease by studying tissues under a microscope. A hematopathologist is a pathologist who studies diseases of blood cells by looking at peripheral blood smears, bone marrow aspirates and biopsies, lymph nodes and other tissues and uses his or her expertise to identify diseases such as NHL. In addition to the microscope, a hematopathologist also uses laboratory values, flow cytometry and molecular diagnostic tests to make the most accurate diagnosis. The hematopathologist works closely with the hematologist or oncologist who sees the patient and decides on the best treatment based upon the diagnosis.

Percutaneously Inserted Central Venous Catheter (PICC or PIC Line). A long, thin, flexible tube that is inserted into the body and can be left in place for weeks or even months for administration of medications, fluids and nutrition. It can also be used to obtain blood samples. The PICC eliminates the need for standard intravenous (IV) administration.

Phagocytes. Cells that protect the body from infection by eating and killing microorganisms such as bacteria and fungi. The two principal phagocytes are neutrophils and monocytes. They leave the bloodstream and enter tissues in which an infection has developed. Chemotherapy and radiation can cause a severe decrease in the concentrations of these cells which makes patients more susceptible to infection. Treatment may suppress blood cell production in the marrow, resulting in deficiencies of the phagocytes.

PICC or PIC line. See Percutaneously Inserted Central Venous Catheter.

Platelets. Small blood cells (about one-tenth the volume of red blood cells) that stick to the site of blood vessel injury, aggregate and then seal off the injured blood vessel to stop bleeding. "Thrombocyte" is a synonym for platelet and is often used as the prefix in terms describing disorders of platelets, such as thrombocytopenia (too few platelets) or thrombocythemia (too many).

Polymerase Chain Reaction (PCR). A technique to expand trace amounts of DNA or RNA so that the specific type of DNA or RNA can be studied or determined. This technique has become useful in detecting a very low concentration of residual lymphoma cells, too few to be seen using a microscope. PCR can detect the presence of one lymphoma cell among 500,000 to 1 million nonlymphoma cells. PCR requires a specific DNA (or RNA) abnormality or marker, like an oncogene, in the lymphoma cells in order to be used for identifying residual abnormal cells.

Port. A small device used with a central line (catheter) used to access a vein. The port is placed under the skin of the chest. After the site heals, no dressings or any special home care is required. To give medicines or nutrition or to take blood samples, the doctor or nurse inserts a needle through the skin into the port. A numbing cream can be put on the skin before the port is used.

Positron Emission Tomography (PET) Scan. A procedure used to image lymphoma masses. In this technique, glucose, a type of sugar, is labeled with a positron particle emitting a radioisotope such as fluorine-18. The utilization of sugar is greater in lymphoma cells than in normal tissue, and the isotope thus becomes concentrated in areas of lymphoma. The location of the lymphoma sites in the body can be identified by scanning for intense positron particle emission. PET is combined with CT to establish the precise location of lymphoma masses; compared to other imaging procedures, PET can detect much smaller lymphoma masses. In some cases, successfully treated lymphoma may convert to fibrous tissue that looks like a mass in imaging studies, perhaps leading the doctor to think that the mass was not successfully treated. Since lymphoma tissue is not fibrous, and scars (primarily fibrous) do not take up the fluorine-18-labeled sugar, PET can distinguish residual lymphoma from healed scar tissue. PET is increasingly used for both staging of lymphoma and assessing response.

Radiation Therapy. The use of x-rays and other forms of radiation in treatment. Radiation therapy may be useful in the treatment of localized lymphoma. Few cases of NHL are treated solely with radiation therapy because lymphoma cells are likely to be spread widely throughout the body. Radiation therapy can be an important adjunct to therapy when there are particularly large masses of lymphoma in a localized area or when local large lymph nodes are compressing or invading normal organs or structures and chemotherapy cannot control the problem.

Radioimmunotherapy. See Immunotherapy.

Recurrence/Relapse. The return of a disease after it has been in remission following treatment.

Red Blood Cells. Blood cells (erythrocytes) that carry hemoglobin, which binds oxygen and carries it to the tissues of the body. The red blood cells make up about 40 to 45 percent of the volume of the blood in healthy individuals.

Reduced-Intensity Stem Cell Transplantation. A form of allogeneic transplantation. In reduced-intensity transplantation (also called "nonmyeloablative stem cell transplantation"), patients receive lower doses of chemotherapy drugs and/or radiation in preparation for the transplant. For more information about all types of stem cell transplantation, see the free LLS booklet *Blood and Marrow Stem Cell Transplantation*.

Remission. A disappearance of evidence of a disease, usually as a result of treatment. The terms "complete" and "partial" are used to modify the term "remission." Complete remission means that all evidence of the disease is gone. Partial remission means that the disease is markedly improved by treatment, but residual evidence of the disease is present. Long-term benefit usually requires a complete remission, especially in progressive lymphomas.

RNA. Abbreviation for ribonucleic acid, a molecule in cells that carries out DNA's instructions for making proteins.

Sedimentation Rate. A blood test that measures how quickly red blood cells (erythrocytes) settle in a test tube in one hour. A sedimentation rate test is done to find out if inflammation is present in the body, to check on the progress of a disease or to see how well a treatment is working. This test is also called a "sed rate" or "erythrocyte sedimentation rate (ESR)."

Serum. See Lactate Dehydrogenase (LDH).

Solitary Extranodal Lymphoma. See Extranodal Lymphoma.

Spleen. An organ located in the left upper portion of the abdomen just under the left side of the diaphragm. It contains clusters of lymphocytes and also filters old or worn-out cells from the blood. It is often affected in lymphocytic leukemias and lymphomas. Enlargement of the spleen is called "splenomegaly." Surgical removal of the spleen is known as "splenectomy."

Stem Cells. Primitive cells in marrow that are essential to the formation of red blood cells, white blood cells and platelets. Stem cells are largely found in the marrow, but some leave the marrow and circulate in the blood. Using special techniques, the stem cells in blood can be collected, preserved by freezing and later thawed and used for stem cell therapy. See Hematopoiesis.

Thrombocyte. See Platelets.

Thrombocythemia. An increase above normal in the concentration of platelets in the blood.

Thrombocytopenia. A decrease below normal in the concentration of platelets in the blood.

Toxin. A naturally derived substance that is poisonous to cells. A toxin can be attached to antibodies that then attach to cancer cells. The toxin may kill the cancer cells.

Translocation. An abnormality of chromosomes in marrow or lymph node cells that occurs when a piece of one chromosome breaks off and attaches to the end of another chromosome. In a balanced translocation, genetic material is exchanged between two different chromosomes with no gain or loss of genetic information. When a translocation takes place, the gene at which the break occurs is altered. This is one form of somatic mutation that may transform the gene into an oncogene (cancer-causing gene). See Mutation.

Tumor Suppressor Gene. A gene that acts to prevent cell growth. If a mutation occurs that "turns off" this gene and causes loss of function, it may make the individual more susceptible to the development of cancer in the tissue in which the mutation occurred. Another term for tumor suppressor gene is "antioncogene."

White Blood Cells. Any of the five major types of infection-fighting white cells in the blood: neutrophils, eosinophils, basophils, monocytes and lymphocytes. White cells are also called "leukocytes."

More Information

Free LLS booklets include

Blood and Marrow Stem Cell Transplantation
Blood Transfusion
Cutaneous T-Cell Lymphoma Facts
Fertility Facts
Immunotherapy Facts
Long-Term and Late Effects of Treatment in Adults Facts
Long-Term and Late Effects of Treatment for Childhood Leukemia or Lymphoma Facts
Mantle Cell Lymphoma Facts
Peripheral T-Cell Lymphoma Facts

Understanding Clinical Trials for Blood Cancers
Understanding Side Effects of Drug Therapy
Waldenström Macroglobulinemia Facts

Visit "Suggested Reading" at www.LLS.org/suggestedreading to see a list of helpful books on a wide range of topics.

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