

Getting the Facts

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Non-Hodgkin Lymphoma (Lymphoid Neoplasms)

Overview

Lymphoma is the most common blood cancer. The two main forms of lymphoma are Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). Lymphoma occurs when cells of the immune system called lymphocytes, a type of white blood cell, grow and multiply uncontrollably. Cancerous lymphocytes can travel to many parts of the body, including the lymph nodes, spleen, bone marrow, blood, or other organs, and form a mass called a tumor. The body has two main types of lymphocytes that can develop into lymphomas: B lymphocytes (B cells) and T lymphocytes (T cells).

NHL is the seventh most common cancer affecting adults in the United States. The incidence of NHL in the United States nearly doubled between 1975 and 2013, and more than 72,000 new cases are expected to be diagnosed in 2016.

NHL is not a single disease but rather a group of several closely related cancers, called lymphoid neoplasms. The most recent 2016 revision of the World Health Organization classification of lymphoid neoplasms estimates that there are at least 86 types of NHL. Three lymphoma subtypes make up the majority of NHLs. Three of the most common types of NHL in the U.S. are diffuse large B-cell lymphoma (22%), chronic lymphocytic leukemia/small lymphocytic lymphoma (18%), and follicular lymphoma (11%). Although the various types of NHL share many common characteristics, they differ in certain features, including their appearance under the microscope, their molecular features and growth patterns, their impact on the body, and how they respond to different types of treatment. For more in-depth information on NHL, please see the Lymphoma Research Foundation's (LRF's) booklet *Understanding Non-Hodgkin Lymphoma: A Guide for Patients, Survivors, and Loved Ones* at www.lymphoma.org/publications or call the LRF Lymphoma Helpline to order a copy.

NHL is broadly categorized into two groups: B-cell lymphomas and natural killer (NK)/T-cell lymphomas. B-cell lymphomas develop from abnormal B cells and account for about 85 percent of all NHLs. NK/T-cell lymphomas develop from abnormal T cells or NK cells and account for about 15 percent of all NHLs. NHL types are also classified as either *indolent* (slow-growing) or *aggressive* (fast-growing).

Common signs and symptoms of NHL include swelling of the lymph nodes (which is often but not always painless), fever, night sweats, unexplained weight loss, and lack of energy. While most people with these symptoms will not have NHL, anyone with persistent symptoms (lasting more than two weeks) should be seen by a physician.

Diagnosis and Staging

A biopsy of an affected lymph node or a sample of the tumor is the only way to make a definite diagnosis of NHL. A *pathologist* (doctor who specializes in diagnosing disease by looking at tumor tissue under the microscope) or a *hematopathologist* (physician who specializes in diagnosing diseases of the blood) who is experienced in diagnosing lymphoma should review the biopsy. This is because there are several different types of lymphoma, many of which are very uncommon, and special procedures and tests may be needed in order to make an accurate diagnosis. A correct diagnosis is important so that appropriate treatments can be used to effectively treat the patient's particular type of lymphoma.

Staging, which is done to determine how far the disease has spread, is important for selecting the best course of treatment. The Lugano Classification of the Ann Arbor staging system is used for most NHLs. In order to stage a patient's disease, the physician may order imaging tests such as abdominal and chest computed tomography (CT) scans or a positron emission tomography (PET)/CT scan. Other tests may include a bone marrow biopsy and additional blood tests.

Risk Factors

The characteristics that make a person possibly more susceptible to developing any type of disease are called risk factors. Having one or more of these risk factors does not necessarily mean a person will develop NHL. In fact, most people with the known risk factors never develop the disease, and many people diagnosed with NHL do not have any of these risk factors. The causes of NHL in most cases remain unknown. Nevertheless, known risk factors for NHL include:

- Infections with certain viruses such as the human immunodeficiency virus (HIV; the virus that can cause acquired immune deficiency syndrome [AIDS]), Epstein-Barr virus, human T-lymphotropic virus type 1 (HTLV-1), and/or hepatitis C virus

- An autoimmune disease (such as Crohn's disease, rheumatoid arthritis, or psoriasis) that may or may not have been treated with immunosuppressive agents, or treatment with certain drugs used after an organ transplant
- Infection with the bacteria *Helicobacter pylori* (a microbial pathogen that may cause stomach ulcers and may increase the risk of developing lymphoma in the stomach lining)
- A weakened immune system caused by an inherited immune disorder (such as hypogammaglobulinemia or Wiskott-Aldrich syndrome)
- Older age — NHL can develop in children and adults of all ages but, like most cancers, is more common in adults older than 65 years
- Male gender — For unknown reasons, NHL is slightly more common in men than in women
- Being exposed to particular chemicals such as certain herbicides and pesticides
- Treatment with radiation therapy for some other cancers, including NHL
- Previous treatment (such as chemotherapy and/or radiation) for NHL, other cancers, or autoimmune diseases

Types of NHL

The classification of lymphoma is complicated and has evolved over the years. NHL types are grouped according to which kind of lymphocyte is affected (B cells or NK/T cells) and how quickly the cancer grows (aggressive or indolent). There are more types of NHL than those listed here. Please consult with a physician if you are not sure of your type. New next-generation molecular sequencing studies and cytogenetic studies are defining different subsets that are clinically meaningful. The following list includes selected lymphoid malignancies in the current WHO classification.

Aggressive B-cell NHLs include the following types:

- Diffuse large B-cell lymphoma (DLBCL), not otherwise specified
 - Germinal center B-cell type
 - Activated B-cell type
- High-grade B-cell lymphoma, with *MYC* and *BCL2* and/or *BCL6* rearrangements
- High-grade B-cell lymphoma, not otherwise specified
- Burkitt lymphoma
- Intravascular large B-cell lymphoma
- Lymphomatoid granulomatosis

- Mantle cell lymphoma (MCL; can also be classified as indolent in certain circumstances)
- Primary mediastinal (thymic) large B-cell lymphoma
- Posttransplant lymphoproliferative disorders (PTLD)
- Primary effusion lymphoma (PEL)

Aggressive T-cell NHLs include the following types:

- Anaplastic large cell lymphoma (ALCL), systemic type
- Angioimmunoblastic T-cell lymphoma (AITL)
- Peripheral T-cell lymphoma (PTCL), not otherwise specified
- Extranodal NK/T-cell lymphoma, nasal type
- Enteropathy-associated T-cell lymphoma
- Sézary syndrome

Aggressive NHLs of histiocytic and dendritic cell types include the following types:

- Langerhans cell histiocytosis
- Follicular dendritic cell sarcoma
- Histiocytic sarcoma

Indolent B-cell NHLs include the following types:

- Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL)
- Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT)
- Follicular lymphoma (FL)
- Hairy cell leukemia
- Lymphoplasmacytic lymphoma (Waldenström macroglobulinemia)
- Nodal marginal zone lymphoma (MZL)
- Splenic MZL

Indolent T-cell NHLs include the following types:

- Mycosis fungoides
- Primary cutaneous anaplastic large cell lymphoma (ALCL)

Treatment Options

Many effective treatment options exist for patients with NHL, including:

- Chemotherapy (common treatments are bendamustine [Treanda] or CHOP [cyclophosphamide, doxorubicin, vincristine, and prednisone])
- Immunochemotherapy (includes the use of monoclonal antibodies such as rituximab in combination with chemotherapy agents)

- Monoclonal antibodies (rituximab [Rituxan] is commonly used)
- Radiation therapy
- Stem cell transplantation
- Targeted or biologic agents
- Watchful waiting (approach in which no treatment is given but patients are closely monitored)

The physician considers many factors when deciding the most appropriate form of treatment for each patient including the type of NHL, whether or not the lymphoma is aggressive or indolent, the stage of the lymphoma, the patient's symptoms (if any), whether the NHL is aggressive or indolent, prior therapies received, the patient's age, overall health (e.g., other disease/conditions the patient may have), and the patient's goals for treatment.

Sometimes after a patient has received an initial treatment, the disease may *relapse* (return after treatment) or become *refractory* (does not respond to treatment). However, numerous treatment options – often referred to as secondary therapies – exist for patients with relapsed/refractory NHL. In fact, many of the new therapeutic agents that have been approved by the U.S. Food and Drug Administration, as well as many of those being investigated in clinical trials, focus specifically on treating patients with relapsed/refractory disease.

Treatments Under Investigation

Many treatments at different stages of drug development are currently being tested in clinical trials for various types of NHL. It is critical to remember that today's scientific research is continuously evolving. Treatment options may change as new treatments are discovered and current treatments are improved. Therefore, it is important that patients check with their physician or with LRF for any treatment updates that may have recently emerged.

Clinical Trials

Clinical trials are crucial in identifying effective drugs and determining optimal doses for patients with lymphoma. Patients interested in participating in a clinical trial should view the *Understanding Clinical Trials* fact sheet on LRF's website at www.lymphoma.org, talk to their physician, or contact the LRF Helpline for an individualized clinical trial search by calling (800) 500-9976 or emailing helpline@lymphoma.org.

Follow-up

Patients with lymphoma should have regular visits with a physician who is familiar with their medical history and the treatments they

have received. Medical tests (such as blood tests, CT scans, and PET scans) may be required at various times during remission to evaluate the need for additional treatment.

Some treatments can cause long-term effects or late effects, which can vary based on duration and frequency of treatments, age, gender, and the overall health of each patient at the time of treatment. A physician will check for these effects during follow-up care. Visits may become less frequent the longer the disease remains in remission.

Patients and their caregivers are encouraged to keep copies of all medical records and test results as well as information on the types, amounts, and duration of all treatments received. This documentation will be important for keeping track of any effects resulting from treatment or potential disease recurrences. LRF's *Focus On Lymphoma* mobile application (app) (www.FocusOnLymphoma.org) can help patients manage this documentation.

Resources

LRF offers a wide range of resources that address treatment options, the latest research advances, and ways to cope with all aspects of lymphoma, including our award-winning mobile app. LRF also provides many educational activities, from in-person meetings to teleconferences and webcasts, as well as disease-specific websites, videos, and e-Updates for current lymphoma information and treatment options. These resources are described below and on the back page, or please visit our website at www.lymphoma.org, or contact the LRF Helpline at (800) 500-9976 or helpline@lymphoma.org.

Patient Education

LRF offers a wide range of opportunities to learn about lymphoma.

Ask the Doctor About Lymphoma is a national series of two-hour, topic-specific community-based programs that combine a presentation by a medical doctor with an extensive question and answer session.

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

The North American Educational Forum on Lymphoma is held annually and provides critical information on treatment options, patient support issues, and the latest in lymphoma research.

Webcasts are available on specific types of lymphoma, treatment options, and support topics.

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Teleconferences are hour-long, interactive telephone programs that provide an opportunity to learn more about lymphoma, treatments, and promising research from leading lymphoma experts.

Patient Services and Support

LRF can support you and your loved ones in many ways. LRF Helpline staff members are available to answer your general questions about a lymphoma diagnosis and treatment information, as well as to provide individual support and referrals to you and your loved ones. Callers may request the services of a language interpreter.

LRF's Clinical Trials Information Service increases awareness about novel and emerging treatments for lymphoma. The LRF Helpline staff will conduct a search for clinical trials based upon your specific diagnosis and medical information so you and your physician can discuss and make important decisions about clinical trial options.

LRF's Lymphoma Support Network is a national, one-to-one peer support program that matches lymphoma patients or caregivers with volunteers who have had similar lymphoma-related experiences.

Financial Assistance Grant Program offers limited financial assistance to eligible patients currently undergoing treatment for lymphoma.

Stories of Hope are personal stories written by members of the lymphoma community who have shared their experiences to help provide hope and inspiration to others. You too can be a source of inspiration by posting your story to the LRF website.

Patient Publications

LRF offers a series of print and digital patient education publications. LRF offers comprehensive guides on non-Hodgkin lymphoma (NHL), Hodgkin lymphoma (HL), chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), and the *Understanding the Stem Cell Transplantation Process* booklet along with a variety of disease- and topic-specific fact sheets.

The goal of these publications is to provide an overview of lymphoma, as well as specific information about the diagnosis and treatment of more than 25 lymphoma types and a variety of supportive care topics. Each guide and fact sheet is updated annually, including a medical review by an expert in that particular type of lymphoma. These publications are available in print and web format and are provided free of charge to patients, survivors, caregivers, and loved ones. LRF will also supply bulk quantities of these publications to healthcare providers interested in sharing the information with their patients. Contact the LRF Helpline at (800) 500-9976 or visit our website at www.lymphoma.org/publications.

Mobile App

LRF also has an award-winning app for smartphones and tablets. *Focus On Lymphoma* is the first mobile app that provides patients and caregivers comprehensive content based on their lymphoma type and tools to help manage their diagnosis, including a medication manager and side effects tracker. The *Focus On Lymphoma* mobile app is now available for free download for iOS and Android devices in the Apple App Store and Google Play. For additional information on the mobile app, visit www.FocusOnLymphoma.org.