HODGKIN'S LYMPHOMA

Authored by:

American Cancer Society

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COURSE OBJECTIVES

At the end of this course, you will be able to:

1.) Define what Non-Hodgkin's Lymphoma is.

2.) List the types of B Cell Lymphomas.

3.) List the types of T Cell Lymphomas.

4.) Discuss the causes and risk factors for Non-Hodgkin's Lymphoma.

5.) List the diagnostic options available for Non-Hodgkin's Lymphoma.

6.) Explain the different levels of staging for Non-Hodgkin's Lymphoma.

7.) List the detailed treatment options available for the different types of B and T cell lymphomas.

INTRODUCTION TO NON-HODGKIN'S LYMPHOMA

WHAT ARE THE KEY STATISTICS ABOUT NON-HODGKIN LYMPHOMA?

In the United States, about 54,370 people (28,850 men and 25,520 women) are expected to be diagnosed with non-Hodgkin lymphoma in 2004. These statistics include both adults and children. It is the fifth most common cancer in this country, not counting non-melanoma skin cancers. A person's risk of developing non-Hodgkin lymphoma during their lifetime is about 1 in 50.

Since the early 1970s, incidence rates for non-Hodgkin lymphoma have nearly doubled. This increase is not completely understood, although many people believe that it was partly due to human immunodeficiency virus (HIV) infections, while a small part of the increase was due to better methods of diagnosis. Since the end of the 1990s, however, the overall incidence rates have remained steady.

Although some types of non-Hodgkin lymphoma are among the most common childhood cancers, over 95% of the cases occur in adults, with the average age at diagnosis in the 60s. The risk of developing non-Hodgkin lymphoma increases throughout life, with the elderly having the highest risk. The increasing average age of the American population is expected to contribute to the increase in non-Hodgkin lymphoma cases during the coming years. It should be noted that the type of non-Hodgkin lymphoma seen in children is often very different from that seen in adults.

Non-Hodgkin lymphoma typically is more common in men than in women, while African Americans and Asian Americans are less likely than Caucasians to develop non-Hodgkin lymphoma.

The American Cancer Society estimates that approximately 19,410 people in the U.S. (10,390 men and 9,020 women) will die of non-Hodgkin lymphoma in 2004. A person's risk of dying of non-Hodgkin lymphoma during their lifetime is about 1 in 100.

Overall survival statistics for non-Hodgkin lymphoma are not very helpful because survival depends on the type of lymphoma. Nevertheless, the 5-year relative survival for all people with lymphoma is 55%. The 5-year survival rate refers to the percentage of patients who live at least 5 years after their cancer is diagnosed. (Five-year relative survival rates only count people who die of the cancer. People who die of other causes are not counted.) Although many of these patients live much longer than 5 years after diagnosis, 5-year rates are used to produce a standard way of discussing prognosis. Recent improvements in treatment often result in a more favorable outlook for recently diagnosed patients.

WHAT IS NON-HODGKIN LYMPHOMA?

Non-Hodgkin lymphoma (aka: non-Hodgkin's lymphoma, NHL, or lymphoma) is a cancer that starts in the lymphoid tissue.

Lymph nodes make and store the white blood cells called lymphocytes. Lymph nodes are connected throughout the body by narrow tubes similar to blood vessels called lymph vessels. These lymph vessels carry a colorless, watery fluid called lymphatic fluid, which contains these lymphocytes. Eventually the lymphatic fluid is emptied into a major blood vessel in the left upper chest.

Other types of cancer - lung or colon cancers, for example - can develop in other organs and then spread to lymphoid tissue. But cancers that spread to the lymph nodes from other areas are not lymphomas. Lymphomas start from lymphocytes in either the lymphoid tissue or lymphoid organs and can spread from there.

There are 2 main types of lymphomas: 1.) Hodgkin lymphoma (aka: Hodgkin's lymphoma, Hodgkin disease, or Hodgkin's disease) is named after Dr. Thomas Hodgkin, who first described it as a new disease in 1832. 2.) Non-Hodgkin lymphomas.

These 2 types of lymphoma can usually be distinguished from each other by examining the cancerous tissue under a microscope. In some cases, more tests to identify specific chemical components of the lymphoma cells may be needed.

Lymphoid Tissue

The main cell type found in lymphoid tissue is the lymphocyte. The 2 main types of lymphocytes are **B lymphocytes** (B cells) and **T lymphocytes** (T cells). Although both types can develop into lymphoma cells, B-cell lymphomas are much more common than T-cell lymphomas, with B-cell lymphomas accounting for 85% of the cases of NHL, while T Cells account for just 15% of the cases.

Differing Jobs

B cells normally help protect the body against pathogens, such as bacteria or viruses, by producing proteins called antibodies. The antibodies attach to the bacteria or viruses and attract immune system cells that surround and digest the antibody-coated germs. Antibodies also attract certain blood proteins that can kill bacteria.

There are several types of **T cells**, each with a specialized job. Some normal T cells help protect the body against viruses, fungi, and some bacteria. They recognize specific substances found in virus-infected cells and destroy these cells. T cells can also release substances called cytokines that attract certain other types of white blood cells, which then digest the infected cells. T cells are also thought to destroy some types of cancer cells, as well as the cells of transplanted organs. Some types of T cells play a role in stimulating or inhibiting the activity of other immune system cells.

Organs That Contain Lymphoid Tissue

Because lymphatic tissue is found in many parts of the body, lymphomas can start almost anywhere. The major sites of lymphatic tissue are listed below.

Lymph nodes are bean-sized organs located throughout the body and connected by a system of lymphatic vessels. These vessels are like veins, except that instead of carrying blood, they carry lymph fluid (a clear fluid containing waste products and excess fluid from tissues) and immune cells traveling to lymph nodes from other tissues.

Lymph nodes increase in size when they fight an infection. Lymph nodes that grow in reaction to infection are called **reactive nodes** or hyperplastic nodes and are often tender to the touch. In most cases, an enlarged lymph node is usually not serious. Enlarged lymph nodes in the neck are often felt in people with sore throats or colds. But a large lymph node is also the most common sign of lymphoma as well, so differentiation is important.

The **spleen** is found under the lower part of the rib cage on the left side of the body. An average adult spleen weighs about 5 ounces. The spleen produces lymphocytes and other immune system cells to help fight infection. It stores healthy blood cells and filters out damaged blood cells, bacteria, and cell waste.

The **thymus gland** is located in the front of the chest at the base of the neck. Before birth, the thymus plays a vital role in development of T lymphocytes. The thymus gland's size (about 1 ounce) and

function diminish over the first 20 years of life. Although its size and activity decline with age, the thymus continues to be active in immune system function throughout life.

Adenoids and **tonsils** are collections of lymphoid tissue located at the back of the throat. They produce antibodies against germs that are breathed in or swallowed. They are easy to see when they become enlarged during an infection or if they become cancerous.

The **stomach** and **intestinal tract** as well as many other organs also contain some lymphatic tissue.

The **bone marrow** produces B cell lymphocytes. Sometimes lymphomas start from these bone marrow lymphocytes.

CLASSIFICATION OF NON-HODGKIN LYMPHOMA

The classification of non-Hodgkin lymphoma seems quite confusing (even for many doctors) because there are so many types and because several different systems of classification have been developed. The most recent system is the **Revised European-American Lymphoma/World Health Organization (REAL/WHO)** classification.

The reason for the changes in classification is that the old systems of classifying lymphomas by their appearance alone no longer worked. Modern science has discovered many chemical and genetic characteristics that identify lymphoma cells better than just by their appearance alone. As we learn more about genes in humans, the genetic changes in lymphomas will play a larger role in classification, and new systems will be developed.

REAL/WHO system: The REAL/WHO system not only uses the appearance of the lymphoma cells for classification but also uses chromosome features of the cells and their chemistry. The chemistry is mainly evaluated by looking for certain proteins on the surface of the cells. This overview classifies the most common lymphomas according to whether they are B-cell or T-cell lymphomas and lists them by how common they are.

TYPES OF B-CELL LYMPHOMAS

Diffuse large B-cell lymphoma (DLBCL): This type of NHL makes up about 31% of all lymphomas. When viewed under the microscope these cells are very large. This is also a fast growing lymphoma.

The symptoms are usually a quick growing mass in the body or an enlarged lymph node that is palpable. Although this lymphoma usually starts in lymph nodes, it can spread into other areas such as the intestines, bone, the brain or spinal cord.

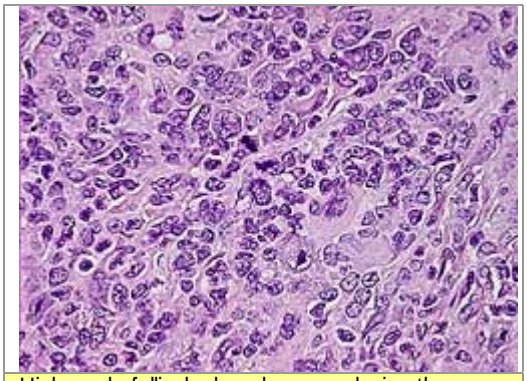
About one third of these lymphomas are confined (localized) to one part of the body. When it is localized this type of lymphoma is considered to be more curable than when it has spread to other parts of the body. Scientists, using genetic testing of the lymphomas, have also found that there are 2 types of DLBCL. One type has a very good outlook and responds well to treatment while the other does not. In spite of these genetic differences, however, the 2 types look alike under the microscope.

DLBCL can affect any age group but occurs mostly in older adults. The average age of occurrence is in the mid-60s, with about 40% to 50% of people with this lymphoma being cured with therapy.

Follicular lymphoma: About 22% of all lymphomas are follicular lymphomas. The term "follicular" is used because the cells tend to grow in a circular, or nodular, pattern in lymph nodes. This is a slow growing lymphoma.

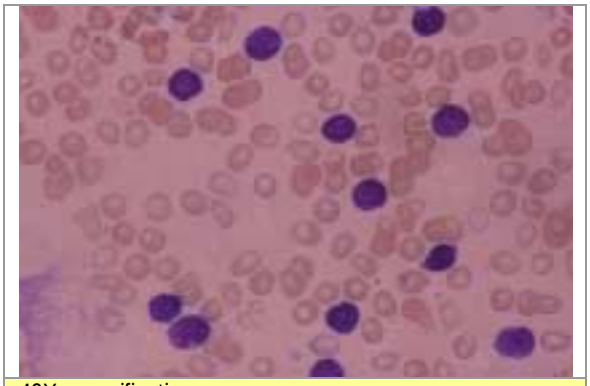
Most of the time, this lymphoma occurs at many lymph node sites in the body, as well as in the bone marrow.

The average age for people with this lymphoma is about 60 years of age and is very rare to find at younger ages. It is not considered to be curable by standard treatment, however, it is slow growing, and the 5-year survival rate is around 60% to 70%. Over time, many follicular lymphomas transform into fast growing diffuse B-cell lymphomas.



High grade follicular lymphoma replacing the normal B-cell areas in the spleen. Cells have a predominantly centroblastic morphology and exhibit marked pleomorphis. (Haematoxylin-eosin staining original magnification x600). Courtesy of Gordon Stamp, Transgenic Pathology Unit.

Chronic lymphocytic leukemia (CLL) / small lymphocytic lymphoma (SLL): These related diseases account for 7% of all lymphomas. In both, the same type of cell, the small lymphocyte, is involved. The only difference is the location that the cancer occurs. In CLL (the more common of the two) it is mostly in the blood, whereas in SLL it is mainly in the lymph nodes. Although both are slow growing diseases, CLL tends to be slower.



40X magnification

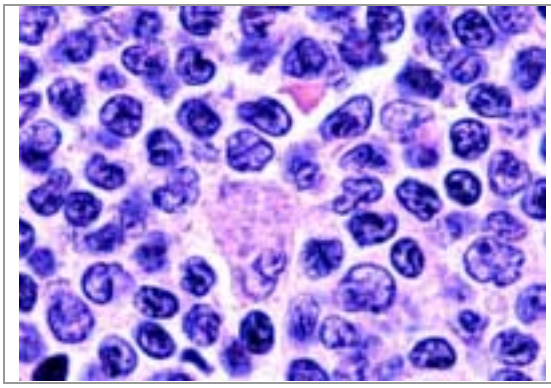
The lymphocytes in CLL are small with predominantly round, darkly staining nuclei and little cytoplasm.

Photo by: *Tulane University Medical Center*

CLL and SLL are not considered curable with standard treatments. But depending on the stage and growth rate of the disease, patients can live well over 10 years with this lymphoma. Occasionally over time, these slow growing lymphomas have the ability to transform into a more aggressive type of lymphoma.

Mantle cell lymphoma: These account for about 6% of lymphomas. The cells are small to medium in size. It is usually widespread when it is diagnosed, involving lymph nodes, bone marrow, and, very often, the spleen.

Men are most often affected. The average age of patients is about 63. Although this isn't a very fast growing lymphoma, it is a very serious one. Only 20% of patients survive at least 5 years.



MANTLE CELL LYMPHOMA

The lymphoid nuclei are irregular. Traditionally they are described as "angulated". In fact here the degree of indentation approaches what is seen in a different type of cell, the small-cleaved cell. In the center is a histiocyte with eosinophilic, granular cytoplasm, which is characteristic of many cases of mantle cell lymphoma.

Photo by: *University of Medicine and Dentistry of New Jersey*

Extranodal marginal zone B-cell lymphomas - mucosa-associated lymphoid tissue (MALT) lymphomas: These account for about 8% of lymphomas. The cells in these lymphomas are small.

Most MALT lymphomas arise in the stomach and are thought to stem from an infection by the bacteria *Helicobacter pylor*i. Other possible sites are lung, skin, thyroid, salivary gland, and tissues surrounding the eye. Usually it is confined to the area where it began and is not widespread.

The average age for patients with this lymphoma is about 60. It is a slow growing lymphoma and is often curable in its early stages.

Nodal marginal zone B-cell lymphoma: These account for about 2% of lymphomas. The cells in this lymphoma are small. Mostly lymph nodes are involved, although the cells can also sometimes be found in the bone marrow.

This is considered a slow growing lymphoma, and many patients are cured if they are diagnosed in the early stages.

Splenic marginal zone B-cell lymphoma: This is a rare lymphoma. The cells are small. Most often the lymphoma is found only in the spleen and bone marrow.

Patients are often elderly and male and suffer from fatigue and discomfort caused by an enlarged spleen. Because the disease is slow growing, treatment may not be necessary unless the symptoms become troublesome.

Primary mediastinal B-cell lymphoma: This type accounts for about 2% of all lymphomas. The cells are large. This lymphoma starts in the mediastinum (the area around the heart and behind the chest bone). It usually is localized at the beginning and rarely involves the bone marrow. It can cause patients to have trouble breathing because it often presses against the air passages leading into the lung. It may also block the superior vena cava (the large vein that returns blood to the heart from the arms and head), which can cause the arms and face to swell.

About two thirds of people with this lymphoma are women. Most are young - in their 30s. It is a fast growing lymphoma but it is treatable. About half the patients can be cured. Genetic studies have shown that this type of lymphoma is closely related to Hodgkin disease.

Burkitt lymphoma: This type makes up about 2% of all lymphomas. It is named after the doctor who first described this disease in African children and young adults. The cells are medium sized. Another kind of lymphoma, called Burkitt-like lymphoma, has slightly larger cells. Because this second

kind of lymphoma is hard to tell apart from Burkitt lymphoma, the REAL/WHO classification combines them.

This is a very fast growing lymphoma. In the African variety, it often starts as tumors of the jaws or other facial bones. In the more common types seen in the US, the lymphoma usually starts in the abdomen, where it forms a large tumor mass. It can also spread to the brain and spinal fluid.

Close to 90% of patients are male, and the average age is about 30. Although this is a fast growing lymphoma, about half of patients are cured by aggressive chemotherapy.

Lymphoplasmocytic lymphoma (Waldenstrom macroglobulinemia): This kind is not common, accounting for only 1% of lymphomas. The cells are small and found mainly in the bone marrow, lymph nodes, and spleen. It is slow growing. Most of the time the lymphoma cells produce an antibody called immunoglobulin M (IgM), which is a very large protein. This antibody circulates in the blood and causes it to thicken, leading to the symptoms typical of this disease.

Symptoms caused by high IgM levels include weakness, fatigue, problems with vision (due to poor circulation in blood vessels in the back of the eyes), a tendency to bleed easily, and neurological problems (such as headache, dizziness, and confusion) caused by poor blood flow within the brain. High blood IgM levels can also damage some organs, such as the kidneys.

Although this lymphoma isn't curable, most patients live longer than 5 years.

Hairy cell leukemia: This lymphoma is rare - about 500 people in the US are diagnosed with this type each year. The typical cell is small with projections around it that have a hair-like appearance. It typically is found in the bone marrow, spleen and circulating in the blood. It is slow growing, and some patients never need treatment. An enlarging spleen or dropping blood counts because of bone marrow replacement by lymphoma cells are the usual reasons to begin treatment. Patients with this disease are generally older.

Primary central nervous system (CNS) lymphoma: This lymphoma usually involves the brain (called primary brain lymphoma), but it also can be found in the spinal cord and in tissues around the spinal cord and the eye. Over time, it becomes widespread in the central nervous system. Although this was a rare tumor in the past, it has become more common in patients with acquired immune deficiency syndrome (AIDS). Most people with this disease develop headache and confusion. They can also have vision problems and, rarely, paralysis.

The outlook for people with this condition is poor. But about 30% of people can live at least 5 years with today's treatment.

TYPES OF T-CELL LYMPHOMAS

Precursor T-lymphoblastic lymphoma/leukemia: This disease can be considered either a lymphoma or leukemia. The distinction depends on whether more or less than 25% of bone marrow cells are lymphoma cells. Leukemias have more than 25% involvement; lymphomas have less. Usually there is a mass in the mediastinum (the area around the heart and behind the chest bone).

About 2% of all lymphomas fall into this category. Patients are most often (75%) men, and their average age is about 25. The typical cell is small to middle sized. The lymphoma is fast growing, but if it hasn't spread to the bone marrow when it is first diagnosed, the chance of cure with chemotherapy is quite good. Once it involves the bone marrow, only 20% of patients can be cured.

Peripheral T-cell lymphomas: There are several kinds of peripheral T-cell lymphomas, which, in total, account for about 7% of all lymphomas.

Cutaneous T-cell lymphoma (mycosis fungoides, Sezary syndrome): This T-cell lymphoma starts in the skin. It is rare, making up less than 1% of all lymphomas. Most patients are in their 50s or 60s.

Mycosis Fungoides lymphoma usually begins as patchy, scaly, red lesions on the skin. They then progress to more solid, raised tumors that can become bigger and mushroom-like (so first named mycosis fungoides). In time, the lymphoma can invade lymph nodes and then organs like the liver and spleen. The growth rate varies among patients.

In the Sezary syndrome, the lymphoma cells are found in the blood. Here the skin is involved all over instead of in patches. It usually appears thickened and very red, and it is often itchy. Survival depends on whether the lymphoma spreads. In Sezary syndrome the lymphoma has spread all over the body through the blood. Patient survival at 5 years ranges from 58% for slow-growing lymphomas to 5% for faster growing ones. The same is true for mycosis fungoides. If only the skin contains lymphoma as patches and not tumors, few patients die of this lymphoma. But once it forms tumors and invades lymph nodes, only about half of patients survive at least 5 years. Once it invades internal organs, very few patients survive 5 years.

Angioimmunoblastic T-cell lymphoma: This lymphoma tends to occur in the lymph nodes. Patients usually have fever, weight loss, and skin rashes and often develop infections. This lymphoma progresses rapidly, with some patients getting better with cortisone-like drugs (corticosteroids) such as prednisone and/or chemotherapy. But it's not clear that anyone with this lymphoma can be cured.

Extranodal natural killer/T-cell lymphoma, nasal type: This type often involves the upper airway passages, such as the nose and upper throat, but it also invades the skin and digestive tract. All ages can be affected. If the lymphoma is localized to the nasal passages, it can be cured by chemotherapy and radiotherapy. But if it is widespread, then only a few patients are cured by very aggressive chemotherapy.

Enteropathy type T-cell lymphoma: This lymphoma occurs in people with sensitivity to gluten, the main protein in wheat flour. The disease, called gluten-sensitive enteropathy, can progress to this lymphoma, which typically invades the walls of the intestines. Once it occurs, outlook is poor because of damage to the intestines.

Subcutaneous panniculitis-like T-cell lymphoma: This lymphoma invades the deepest layers of the skin, where it causes nodules to form. These are often slow growing at first and can be treated with radiation therapy. In time, they begin to grow faster. Chemotherapy can sometimes control the growth, but after a while it no longer works. This lymphoma usually cannot be cured.

Anaplastic large T/null-cell lymphoma: About 2% of lymphomas are this type. The cells are large. It is more common in young people and usually starts in lymph nodes, but can also spread to skin. There is also a form that begins in the skin. Although this type of lymphoma appears to be a fast growing, treatment with chemotherapy often works well. Many patients with this lymphoma are cured.

Unspecified: This group has no other name. Most patients with this form are in their 60s. The lymphoma tends to be widespread and grows quickly. Cells can be small or large. Few patients survive 5 years.

CAUSES, RISK FACTORS, AND PREVENTION

What Are the Risk Factors for Non-Hodgkin Lymphoma?

A risk factor is anything that increases a person's chance of getting a disease. Risk factors can be classified as genetic (inherited), lifestyle-related, or environmental. It is important to note here that having one or more risk factors does not mean that a person will develop this type of cancer. While no specific risk factor has been identified for this disease, age seems to be the greatest factor in acquiring this disease, with most cases occurring among those in their 60s

Genetic Risk Factors

Several genetic diseases can cause children to be born with an abnormal or deficient immune system. In addition to developing serious infections due to reduced immune defenses, they also have an increased risk of developing non-Hodgkin lymphoma during childhood or as young adults.

Although these congenital immune deficiency diseases can be passed on to children, people with non-Hodgkin lymphoma who do not have these inherited diseases do not pass an increased risk of lymphoma to their children.

Lifestyle-Related Risk Factors

Examples of lifestyle-related risk factors for some cancers include exposing skin to strong sunlight, a diet high in fat and low in fruits and vegetables, and habits such as smoking and excessive drinking of alcohol. With the exception of being obese, which may increase your risk of non-Hodgkin lymphoma, lifestyle-related factors such as those noted above do not strongly affect a person's risk of developing non-Hodgkin lymphoma

Environmental Risk Factors

Environmental risk factors are influences in our surroundings, such as radiation, chemicals, and infections.

Radiation: Survivors of atomic bombs and nuclear reactor accidents have an increased risk of developing several types of cancer, including leukemia, thyroid cancer, and non-Hodgkin lymphoma. Patients treated with radiation therapy for some other cancers have a slightly increased risk of developing non-Hodgkin lymphoma later in life. This risk is greater for patients treated with both radiation therapy and chemotherapy.

Chemicals: Some studies have suggested that chemicals such as benzene and certain herbicides and insecticides (weed- and insect-killing substances) are associated with an increased risk of non-Hodgkin lymphoma. Recent studies have found that this is not certain, and research to clarify this issue is still in progress.

Some chemotherapy drugs used to treat other cancers can increase the risk of developing leukemia or non-Hodgkin lymphoma many years later; however, a direct cause and effect relationship has not yet been definitely established. For example, patients who have been treated for Hodgkin disease have an increased risk of later developing non-Hodgkin lymphoma. This may be related to the disease itself or may be an effect of the treatment.

Immune deficiency: Patients with transplanted organs (kidney, heart, liver) and some other conditions like rheumatoid arthritis are treated with drugs that interfere with their immune system to

prevent it from attacking the new organs. This effect on the immune system carries a significant risk to the patient of developing non-Hodgkin lymphoma. The exact risk depends on which drugs and at what doses they are used.

Infections: Infection with human immunodeficiency virus (HIV), also known as the AIDS virus, is an increasingly common cause of immune system deficiency. HIV infection is a risk factor for developing certain types of non-Hodgkin lymphoma.

Infection with the human T-cell leukemia/lymphoma virus (HTLV-1) increases a person's risk of developing certain types of T-cell non-Hodgkin lymphoma. This virus is most common in some parts of Japan and in the Caribbean region. In some areas of Japan, it is responsible for about half of the non-Hodgkin lymphoma cases. In the United States, it causes less than 1% of lymphomas.
HTLV-1 belongs to the same family of viruses as HIV. Like HIV, it spreads through sexual intercourse and contaminated blood and can be passed to children through breast milk.

In areas of Africa where Burkitt lymphoma is common, infection with the parasite that causes malaria and with the Epstein-Barr virus (EBV) are important risk factors for this disease. EBV is also associated with lymphomas in developed countries, particularly in patients infected with HIV.

Scientists have recently found that a type of bacteria, *Helicobacter pylori,* known to cause stomach ulcers, can also cause some lymphomas of the stomach. The body's immune reaction to this infection increases the risk of non-Hodgkin lymphoma. The most important consequence of this recent discovery is that antibiotics can be helpful in treating some patients who have already developed lymphomas of the stomach.

Do We Know What Causes Non-Hodgkin Lymphoma?

Although researchers have found that non-Hodgkin lymphoma *may* be associated with a number of risk factors, most patients with non-Hodgkin lymphoma do not have any specific risk factors, and the causes of their cancers remain unknown.

Scientists have recently made great progress in understanding how certain changes in DNA can cause normal lymphocytes to become lymphoma cells. DNA is what carries the instructions for nearly everything our cells do. We resemble our parents because they are the source of our DNA. But DNA affects more than our outward appearance. Some genes (parts of our DNA) contain instructions for controlling when cells grow and divide.

Certain genes that speed up cell division are called **oncogenes**. Others that slow down cell division or cause cells to die at the right time are called **tumor suppressor genes**. We know that cancers can be caused by DNA mutations that turn on oncogenes or turn off tumor suppressor genes.

Some people with certain types of cancer have DNA mutations they inherited from a parent, which increased their risk for the disease. But non-Hodgkin lymphoma is not one of the cancer types often caused by these inherited mutations.

DNA mutations related to non-Hodgkin lymphoma are usually acquired after birth, rather than being inherited. Acquired mutations may result from exposure to radiation or cancer-causing chemicals, but often these mutations occur for no apparent reason. They seem to happen more often as we age, and lymphomas for the most part are a cancer of older people.

Every time a cell prepares to divide into 2 new cells, it must duplicate its DNA. This process is not perfect and sometimes copying errors occur. Fortunately, cells have repair enzymes that proofread DNA. But some errors may slip past, especially if the cells are growing rapidly.

Translocations are another type of DNA abnormality that can cause non-Hodgkin lymphoma to develop. Human DNA is packaged in 23 pairs of chromosomes. A translocation means that DNA from one chromosome breaks off and becomes attached to a different chromosome. When this happens, oncogenes can be turned on or tumor suppressor genes can be turned off. This often occurs in cases of non-Hodgkin lymphoma. Some lymphomas classified in the REAL/WHO system are characterized by specific chromosomal defects that may lead to the development of lymphoma.

Scientists are learning much about the exact genes involved in this process and how they cause lymphoma and other cancers. This information is already being used to develop new and more accurate tests for detecting and classifying certain types of non-Hodgkin lymphoma. Hopefully, these discoveries will soon be applied to developing new treatments.

Even though researchers have found many of the key DNA changes that cause lymphoma and are beginning to understand how these changes develop in people with certain risk factors, they still do not know why most lymphomas develop in people with no apparent risk factors.

The immune system seems to play an important role in many cases of lymphoma. People with immune deficiencies (due to inherited conditions, drug treatment, organ transplantation, or HIV infection) have a chance of developing lymphoma that is many times greater than a person without an immune deficiency.

Can Non-Hodgkin Lymphoma Be Prevented?

Since most people with non-Hodgkin lymphoma have no specific risk factors, and there is no way to prevent their lymphomas from developing. For now, the only chance for trying to prevent non-Hodgkin lymphoma is by preventing the known risk factors, such as, acquired immune deficiency syndrome (AIDS).

The most preventable cause of immune deficiency is not becoming exposed to the human immunodeficiency virus (HIV) infection. HIV is spread among adults mostly through unprotected sex and sharing of contaminated needles by injection drug users. Preventing the spread of HIV would prevent many deaths from infections and non-Hodgkin lymphoma. Treating HIV with three or more anti-HIV drugs also seems to lower the chance of developing non-Hodgkin lymphoma.

Preventing the spread of the human T-cell leukemia/lymphoma virus (HTLV-1) could have a great impact on non-Hodgkin lymphoma prevention in areas of the world where this virus is common, such as Japan and the Caribbean region. Compared to worldwide statistics, the virus is rare in the United States but seems to be increasing in some areas. The same strategies used to prevent HIV spread could also help control HTLV-1.

The recent discovery of the connection between *Helicobacter pylori* infection and primary gastric lymphomas offers a potential opportunity for prevention, but the benefit of this strategy has not been proven yet. Most people with *H. pylori* infection have no symptoms, and some have only mild heartburn. Finding the best way to detect and treat this infection in people without symptoms will require more research.

Treatment of cancers with radiation and chemotherapy and the use of immune system-suppressing drugs to avoid rejection of transplanted organs also cause some non-Hodgkin lymphomas. Doctors are studying how to treat cancer and organ transplant patients in ways that do not increase the risk of

lymphoma as much. At the present time, however, the life-threatening nature of the diseases requiring these treatments still usually outweighs the risk of developing non-Hodgkin lymphoma several years later.

EARLY DETECTION, DIAGNOSIS, AND STAGING

Can Non-Hodgkin Lymphoma Be Found Early?

At this time, no special tests are available that can find non-Hodgkin lymphoma early. The best strategy for early diagnosis is prompt attention to the signs and symptoms of this disease, which are discussed in the next section.

How Is Non-Hodgkin Lymphoma Diagnosed?

If signs or symptoms suggest that a patient may have non-Hodgkin lymphoma, exams and tests are performed to be certain if this disease is present and, if so, to determine the exact type of lymphoma.

Signs and Symptoms of Non-Hodgkin Lymphoma

Non-Hodgkin lymphoma may cause many different signs and symptoms, depending on its location in the body.

Non-Hodgkin lymphoma can involve easily seen or felt lymph nodes close to the surface of the body (such as on the sides of the neck, in the groin or underarm areas, or above the collar bone). These are often found by the patient, a family member, or a health care professional.

When the lymphoid tissue inside the abdomen is involved, the abdomen can become swollen. This may be due to either large collections of fluid or a tumor. When lymphoma causes swelling near the intestines, the passage of feces may be blocked, which may lead to nausea or vomiting. The pressure or blockage can also cause discomfort or abdominal pain.

When lymphoma starts in the thymus or lymph nodes in the chest, it may irritate or compress the nearby trachea (windpipe), which can cause coughing or trouble breathing.

The superior vena cava (SVC) is the large vein that carries blood from the head and arms back to the heart. It passes near the thymus and lymph nodes inside the chest. Growth of lymphoma may push on this vein. This causes swelling of the head and arms known as **SVC syndrome**. This can be life threatening. Patients with SVC syndrome need to be treated as soon as possible.

Lymphomas of the stomach often cause pain in the stomach, nausea, and reduced appetite.

Lymphomas of the brain, called **primary brain lymphomas**, can cause headache, trouble thinking and moving parts of the body, personality changes, and, sometimes, seizures.

Lymphomas of the skin can be seen and felt. They often appear as itchy, red to purple lumps or nodules under the skin. In addition to symptoms and signs resulting from local effects of cancer growth, non-Hodgkin lymphoma can produce generalized symptoms, such as:

- unexplained weight loss
- fever
- profuse sweating (enough to soak clothing), particularly at night
- severe itchiness

Oncologists sometimes call these generalized effects **B symptoms**. The presence of B symptoms is associated with a poor outlook and is related to the presence of more cancer cells in some patients.

The diagnosis of lymphoma may be delayed because enlarged lymph nodes are more often caused by infections than by non-Hodgkin lymphoma. Because of this, doctors often wait a few weeks to see if they remain large. Sometimes they prescribe antibiotics to see if they cause the nodes to shrink.

If the node continues to grow, either a small piece of the node or, more commonly, the entire node should be removed for viewing under the microscope and for other lab tests. This procedure is called a biopsy.

An immediate biopsy may be needed if the size, texture, or location of the node or the presence of other symptoms strongly suggests cancer is present. But there is no evidence that a delay in diagnosis of a few weeks is harmful in most instances. The exception to this would be a very rapidly growing lymphoma.

TYPES OF BIOPSIES USED IN DIAGNOSIS OF NON-HODGKIN LYMPHOMA

A biopsy is the only way to diagnose non-Hodgkin lymphoma. There are several biopsy procedures, and the doctor's choice is based on the unique aspects of each person's situation.

Excisional or incisional biopsy: In this procedure, a surgeon cuts through the skin to remove either the entire node (excisional biopsy) or a small part of a large tumor (incisional biopsy). If the node is near the skin surface, this is a simple operation that can be done with local anesthesia (numbing medication). But if the node is inside the chest or abdomen, general anesthesia is used (the patient is asleep). This method almost always provides enough tissue to diagnose the exact type of non-Hodgkin lymphoma. It is preferred, if it can be done without too much discomfort to the patient.

Fine needle aspiration (FNA) biopsy: FNA uses a very thin needle and a syringe to withdraw a small amount of tissue from the tumor mass. The doctor can aim the needle while feeling an enlarged node near the surface of the body. If the tumor is deep inside the body, the doctor can guide the needle while viewing a computed tomography (CT) scan (see discussion of imaging tests later in this section).

The main advantage of FNA is that it does not require surgery. The disadvantage is that in some cases the thin needle cannot remove enough tissue for a definite diagnosis of non-Hodgkin lymphoma. However, advances in performing lab tests and the growing experience of many doctors with FNA have improved the accuracy of this procedure. FNA is also very useful in diagnosing cancers that spread to nodes from other organs and in identifying nodes swollen by infection that don't need to be removed.

Other Types of Biopsies

These procedures may be done to diagnose lymphoma, but they are more often done to help stage (determine the extent of) a lymphoma that has already been diagnosed.

Bone marrow aspiration and biopsy: These procedures are usually done at the same time. In bone marrow aspiration, a needle and syringe are used to remove small amounts of bone marrow. For

bone marrow biopsy, a larger needle is used to remove a cylinder of bone and marrow, about 1/16-inch across and 1-inch long. Both samples are usually taken from marrow at the back of the pelvic bone after numbing the area with local anesthesia. These tests can be used for the initial diagnosis and for staging (to see how far the cancer has spread).

Lumbar puncture (spinal tap): During a lumbar puncture, a thin needle is inserted between the bones in the lower spine (below the level of the spinal cord) to withdraw some cerebrospinal fluid (CSF) to be examined for lymphoma cells.

LABORATORY TESTS USED TO DIAGNOSE AND CLASSIFY NON-HODGKIN LYMPHOMA

All biopsy specimens and fluids are examined by a pathologist. The pathologist looks at the size and shape of the cells and how the cells are arranged in the lymph node to determine whether a lymphoma is present and if so, what type it is.

The many specific types of lymphomas are sometimes grouped together into low-grade, intermediate-grade, or high-grade categories. High-grade lymphomas grow more rapidly and spread through the body quickly. Without treatment, most patients with these lymphomas would live only a short time. The term "aggressive" is also sometimes used to describe high-grade lymphomas. Most high-grade lymphomas respond well to chemotherapy, and many can be cured.

Pathologists can often tell which kind of lymphoma a patient has by examining the specimen microscopically, but sometimes this exam may not provide a definite answer and other lab tests are needed.

Immunohistochemistry: In this test, a part of the biopsy sample is treated with special laboratory antibodies that attach to specific molecules on the cell surface. These antibodies cause color changes, which can be seen under a microscope. This test may be helpful in distinguishing different types of non-Hodgkin lymphoma from one another and also from other diseases.

Flow cytometry: Some specific molecules on the surface of lymphoma cells can be detected using fluorescent antibodies. The cells being examined by this test are treated with the antibodies and passed in front of a laser beam. Each antibody sticks only to certain types of cells. If the sample contains those cells, the laser light will cause them to give off light of a different color, which is measured exactly and analyzed by a computer. This test can look at many more cells than immunohistochemistry.

Flow cytometry can help determine whether lymph node swelling is due to non-Hodgkin lymphoma, some other cancer, or a noncancerous disease. It has also become very useful in helping doctors determine the exact type of non-Hodgkin lymphoma so that they can select the best treatment.

Cytogenetics: This technique involves using a microscope to examine cells to see if the chromosomes have any translocations (where part of one chromosome has broken off and is now attached to another chromosome), as happens in certain types of lymphoma. In addition to translocations, some lymphoma cells may have too many chromosomes.

Molecular genetic studies: Molecular tests of lymphoma cell DNA can detect translocations that are not visible under a microscope in cytogenetic tests. These tests can also detect certain genes that have been "turned on" and are contributing to the lymphoma cells abnormal growth. In the future, as researchers learn more about lymphomas, these may become the most useful tests for determining what kind of lymphoma is present.

IMAGING STUDIES USED TO DIAGNOSE AND STAGE NON-HODGKIN LYMPHOMA

Imaging tests are used to find and look at tumors inside the body. These tests are an important part of staging.

Chest x-ray: An x-ray of the chest is often done to look for enlarged lymph nodes in this area.

Computed tomography (CT, CAT) scan: The CT scan is an x-ray procedure that produces detailed cross-sectional images of your body. Instead of taking one picture, as does a conventional x-ray, a CT scanner takes many pictures. A computer then combines these pictures into an image of a slice of your body. A CT is useful for looking for lymphoma in the abdomen, pelvis, chest, head, and neck.

A newer kind of CT, known as a **spiral CT**, uses a rapid scanner that takes quicker images. This reduces the chances that body movement caused by the patient taking breaths will distort the images and therefore, can provide greater detail. This type of CT scan is still relatively new and is not yet available in all areas.

CT scans can also be used to precisely guide a biopsy needle into an enlarged lymph node deep in the body. For this procedure, called a **CT-guided needle biopsy**, the patient remains on the CT scanning table while a radiologist advances a biopsy needle toward the mass

Magnetic resonance imaging (MRI) scan: MRI scans use radio waves and strong magnets instead of x-rays. The energy from the radio waves is absorbed and then released in a pattern formed by the type of tissue and by certain diseases. A computer translates the pattern of radio waves given off by the tissues into a very detailed image of parts of the body. Not only does this produce cross-sectional slices of the body like a CT scanner, it can also produce slices that are parallel with the length of your body.

MRI scans are helpful in examining the brain and spinal cord.

Positron emission tomography (PET) scan: PET scans use glucose that contains a slightly radioactive atom. The glucose solution is injected into a vein and travels throughout the body. Cancer cells absorb high amounts of the radioactive sugar because of their high rate of metabolism. A special camera can then detect the radioactivity.

PET is useful to look for lymphoma throughout your body. A PET scan can be more helpful than several different x-rays because it scans your whole body. It can also tell if an enlarged lymph node is a lymphoma or is benign.

PET is also used after treatment in helping decide whether an enlarged lymph node still appears to be a lymphoma or is merely scar tissue. Although this test is relatively new, it is becoming widely used to examine people with lymphomas.

Gallium scan: During this procedure, the radiologist injects slightly radioactive gallium into a vein. It is attracted to areas of lymphatics in the body. A special camera can then detect the radioactivity, showing the location of the gallium. These tests can find tumors that might be non-Hodgkin lymphoma in bones and other organs.

The gallium scan will not detect most slow-growing lymphomas but will recognize most fast-growing (aggressive) lymphomas. It was used before PET scans were available and can still be useful in finding lymphoma deposits that the PET scan may miss. It is also useful in separating infections from lymphomas when the diagnosis is not clear.

Bone scan: For bone scans, a different radioactive substance is used. After it is injected, it travels to areas of the bone that are damaged. Lymphoma in bone often causes bone damage, and a bone scan will find it. But a bone scan will also pick up non-cancerous problems, such as arthritis and fractures. This test is not generally used in the early staging process for non-Hodgkin lymphoma.

Ultrasound: Ultrasound uses sound waves and their echoes to produce a picture of internal organs or masses. A small microphone-like instrument called a transducer emits sound waves. These waves are transmitted into the area of the body being studied and echo back. The echoes are picked up by the transducer and converted by a computer into an image that is displayed on a computer screen.

Sometimes an ultrasound is used to find masses in the abdomen. It can also detect kidneys that have become swollen because the outflow of urine has been blocked by enlarged lymph nodes.

How Is Non-Hodgkin Lymphoma Staged?

Once non-Hodgkin lymphoma is diagnosed, tests are done to determine the stage (extent of spread) of the disease. The treatment and prognosis (the outlook for chances of survival) for a patient with non-Hodgkin lymphoma depend on both the exact type and the stage of the lymphoma. This disease tends to be widespread, although the less aggressive types may be localized.

Tests used to gather information for staging include:

- physical examination
- blood tests
- imaging tests, including a chest x-ray, CT or MRI scan of the chest/abdomen/pelvis, and PET scan
- bone marrow aspiration and biopsy (often but not always done)
- lumbar puncture (spinal tap - this is not often done)

The staging system most often used to describe the spread of non-Hodgkin lymphoma in adults is called the **Ann Arbor staging system**. The stages are described by Roman numerals I through IV. Lymphomas that affect organs outside of the lymph system ("extranodal' organs) have "E" added to their stage (for example, stage IIIE).

Stage I: Either of the following means the disease is a stage I:

- The lymphoma is in a lymph node or nodes in only 1 region, such as the neck, groin, underarm, and so on.
- The cancer is found only in 1 area of a single organ outside of the lymph system (IE).

Stage II: Either of the following means the disease is a stage II:

- The lymphoma is in 2 groups of lymph nodes on the same side of (above or below) the diaphragm (the breathing muscle that aids breathing and separates the chest and abdomen). For example, this might include nodes in the underarm and neck area but not the combination of underarm and groin nodes.

- The cancer extends locally from the lymph node(s) into nearby tissue (IIE).

Stage III: Either of the following means the disease is a stage III:

- The lymphoma is found in lymph node areas on both sides of (above and below) the diaphragm.
- The cancer may also have extended into an area or organ next to the lymph node (IIIE), into the spleen (IIIS), or both (IIISE).

Stage IV: Any of the following means the disease is a stage IV:

- The lymphoma has spread to more than 1 spot in an organ or to 2 or more organs outside of the lymph system. Cancer cells may or may not be found in nearby lymph nodes.

- Cancer has spread to only 1 organ outside of the lymph system, but lymph nodes far away from that organ are involved.

- The lymphoma has spread to the brain or spinal cord, liver, or bone marrow.

The letter "B" is added (stage IIIB, for example) if any B symptoms are present:

- unexplained weight loss (more than 10% of weight) l soaking night sweats
- unexplained high fever For patients without these symptoms, the letter "A" is added to their stage.

International Prognostic Index (IPI)

This index was developed to help predict how rapidly the lymphoma would grow and how well patients would respond to treatment (or whether they would need treatment at all). Although the REAL/WHO classifications give us some idea of this, many times people with so-called low-grade lymphomas have a very fast growing disease that does not respond to treatment, while patients with high-grade lymphomas may respond very well to treatment.

The index depends on 5 factors:

- age
- stage of the lymphoma
- whether or not it is in organs outside the lymph system
- performance status (PS) - how well the person can complete normal daily activities
- blood (serum) level of lactate dehydrogenase (LDH) - this level goes up in the presence of fast growing tumors

Good prognostic factors	Poor prognostic factors
Age 60 or below	Age above 60
Stage I or II	Stage III or IV
No lymphoma outside of lymph nodes	Lymphoma present outside of lymph nodes
PS: Able to function normally	PS: Needs a lot of help with daily activities
Serum LDH is normal	Serum LDH is elevated

For each poor prognostic factor, 1 point is assigned. The index divides people with lymphomas into 4 categories. The low category (0 or 1 point) means the person with lymphoma has mostly good factors (is young, has stage I disease, can still work, and so on). The highest category indicates mostly or all unfavorable factors (high stage, high LDH, bedridden, and so on). No matter what the type of lymphoma, over 75% of people in the lowest group will live longer than 5 years, whereas only 30% of people in the highest group live 5 years.

This prognostic index is important because it allows doctors to plan treatment better than they could from just the pathology report and staging information. This has become more important as new, more effective treatments have been developed that sometimes have more side effects. The index tells us whether these treatments are needed. It also provides information to patients about the outlook for their future.

TREATING NON-HODGKIN TYPE LYMPHOMAS

How Is Non-Hodgkin Lymphoma Treated?

This information represents the views of the doctors and nurses serving on the American Cancer Society's Cancer Information Database Editorial Board. These views are based on their interpretation of non-Hodgkin lymphoma treatment studies published in medical journals, as well as their own professional experience.

In recent years, much progress has been made in treating non-Hodgkin lymphoma. The treatment options for people with lymphoma depend on the kind of lymphoma and its stage, as well as the other prognostic indices of the lymphoma. Of course, no two patients are exactly alike, and standard options are often tailored to each patient's unique situation.

It is important to understand all treatment options. It is often a good idea to seek a second opinion. This can provide additional information and help you feel more confident about the treatment plan that is chosen. Several different types of treatment can be used against non-Hodgkin lymphoma.

Surgery

Surgery is often used to obtain a tissue sample to diagnose and classify a lymphoma, but it is rarely used as a treatment option.

It is sometimes used to treat lymphomas that start in certain organs outside of the lymph system, such as the thyroid or stomach, and that have not spread beyond these organs. For treating lymphoma that is completely confined to one area, radiation therapy is usually preferred over surgery.

Radiation Therapy

Radiation therapy uses high-energy rays to kill cancer cells. Radiation focused on a cancer from a source outside the body is called **external beam radiatio**n. This is the type of radiation therapy most often used to treat non-Hodgkin lymphoma. Radiation might be used as the main (primary) treatment of early (stage I or II) non-Hodgkin lymphomas. More often, it is used along with chemotherapy. But it can be used also for localized tumors because non-Hodgkin lymphoma responds very well to radiation.

Radiation therapy can also be used to ease symptoms caused by lymphoma involving internal organs, such as the brain or spinal cord, or when it is causing pain because it is pressing on nerves.

Side effects of radiation therapy may include mild skin problems or fatigue.

- Radiation of the abdomen may cause upset stomach and diarrhea. Often these effects go away after a short while.
- Chest radiation therapy may cause lung damage and lead to breathing difficulty. Lung cancer can also occur after lung radiation, particularly in smokers, though it is not common.
- Side effects of brain radiation therapy usually become most serious 1 or 2 years after treatment and may include headaches and difficulty with thinking.

Radiation may also make the side effects of chemotherapy worse.

Chemotherapy

Chemotherapy uses anticancer drugs that are injected into a vein or a muscle or taken by mouth. These drugs enter the bloodstream and reach all areas of the body, making this treatment very useful for lymphoma. Depending on the type and the stage of the lymphoma, chemotherapy may be used alone or in combination with radiation therapy. In some cases, chemotherapy is given by injection into the spinal fluid (intrathecal injection) to treat lymphoma cells on the surface of the brain and spinal cord.

Many drugs are useful in the treatment of patients with lymphoma. Often, several drugs are combined. The treatments all have different schedules, but they are usually repeated several times in cycles given 3 or 4 weeks apart. Most chemotherapy treatments are given on an outpatient basis (in the doctor's office or clinic or hospital outpatient department) but some require hospital admission.

Sometimes a patient may take one chemotherapy combination for several cycles and later be switched to a different one if the first combination doesn't seem to be working. This is usually determined after retesting (usually by CT scan) or by physical exam (for example, if an enlarged lymph node has not shrunk).

Chemotherapy drugs are intended to kill lymphoma cells, but they can also damage normal cells. For this reason, some side effects occur. These side effects depend on the type and dose of drugs given and the length of time they are taken. As a result, a patient may have:

- hair loss
- mouth sores
- increased chance of infections (due to low white blood cell counts)
- easy bruising or bleeding after minor cuts or injuries (due to low platelet counts)
- fatigue (due to low red blood cell counts)
- loss of appetite
- nausea and vomiting

These side effects are usually temporary and go away after treatment is finished.

Tumor lysis syndrome is a side effect of the rapid breakdown of cells during very effective chemotherapy for some bulky lymphomas. When the lymphoma cells are killed, they break open and release their contents into the bloodstream, which may affect the kidneys, heart, and nervous system. This condition can be prevented by giving extra fluids and certain drugs, such as sodium bicarbonate and allopurinol, which help the body dispose of these substances.

Organs that could be directly damaged by chemotherapy drugs include the kidneys, liver, testes, ovaries, brain, heart, and lungs. With careful monitoring, such side effects are rare. If serious side effects occur, the chemotherapy may have to be reduced or stopped, at least temporarily. Careful monitoring and adjustment of drug doses are important because some side effects to organs are permanent.

One of the most serious late complications of successful chemotherapy is the possibility of developing leukemia. This affects a small percentage of lymphoma patients.

Biological Therapy (Immunotherapy)

Biological therapies use substances naturally produced by the immune system. These substances may kill lymphoma cells, slow their growth, or activate the patient's own immune system to more effectively fight the lymphoma.

Interferon: Interferon is a hormone-like protein produced by white blood cells to help the immune system fight infections. Some studies have suggested that giving man-made interferon can cause some types of non-Hodgkin lymphomas to shrink or stop growing.

Side effects of this treatment include moderate to severe fatigue, fever, chills, headaches, muscle and joint aches, and mood changes. It is still not clear if interferon is the best treatment for some non-Hodgkin lymphomas patients or if it should be given to some patients in addition to chemotherapy.

Monoclonal antibodies: Antibodies are normally produced by the immune system to help fight infections. Similar antibodies, called monoclonal antibodies, can be made in the laboratory. Instead of attacking germs as usual antibodies do, some monoclonal antibodies are designed to attack lymphoma cells.

After years of research, several monoclonal antibodies are now being used as treatments for lymphoma. In fact, more monoclonal antibodies are available to treat lymphoma than any other type of cancer.

The first monoclonal antibody approved by the FDA to treat any cancer was rituximab (Rituxan). This antibody recognizes and attaches to a substance called CD20 that is found on the surface of some types of lymphoma cells. This attachment seems to cause the lymphoma cell to die. Patients usually receive 4 intravenous infusions over a period of about 3 weeks. The treatments can be given in the doctor's office or clinic. Common side effects are usually mild but may include chills, fever, nausea, rashes, fatigue, and headaches.

Newer forms of monoclonal antibodies similar to rituximab but with radioactive molecules attached to them have also been developed for use in lymphomas. The first to be approved by the FDA was ibritumomab tiuxetan (Zevalin), which is an antibody that has radioactive yttrium attached to it. It is used in patients with follicular lymphoma that has returned after treatment and is also being studied in other types of lymphoma. The second drug approved was tositumomab (Bexxar), which is an antibody with radioactive iodine attached. It is also used against follicular lymphoma after initial therapies no longer work. Both these drugs are being used for lymphomas that have not responded to other treatments. Their one disadvantage is they cannot be used along with chemotherapy because they lower blood counts.

Another man-made molecule approved by the FDA is called denileukin diftitox (Ontak). It is used to treat T-cell skin lymphomas. It is made by combining interleukin-2 (a protein that attaches to some types of lymphocytes) and diphtheria toxin, which kills cells.

Alemtuzumab (Campath) is an antibody that is useful in chronic lymphocytic leukemia (CLL) and even T-cell leukemias of the skin.

Other monoclonal antibodies to treat lymphomas are also being developed.

Bone Marrow or Peripheral Blood Stem Cell Transplantation (SCT)

Stem cell transplantation is used to treat lymphoma patients when standard treatment has failed. Although only a small number of patients with NHL are treated with this therapy, this number is growing. In 2002, approximately 4,300 non-Hodgkin lymphoma patients in the US received a stem cell transplant.

SCT allows doctors to use very high doses of chemotherapy to try to wipe out the lymphoma. Such high doses would normally cause permanently damage the bone marrow, which would halt the production of blood cells. This could be life threatening.

Stem cells (that form the blood cells) are the earliest form of bone marrow cells. Once they are produced in the bone marrow, they are released into the blood and develop into normal blood cells such as red blood cells, white blood cells, and platelets. Stem cells are given to patients after they have had high-dose chemotherapy to help repopulate the bone marrow. This treatment can be used for some patients who are in remission or if they have a relapse during or after treatment.

Blood-forming stem cells can be taken from several bone marrow aspirates, or they can be removed from the peripheral blood by a method known as apheresis. Recent studies have shown that there may be an advantage to using stem cells obtained by apheresis instead of bone marrow aspiration. This has become the usual way that doctors obtain stem cells. Regardless of where the stem cells are taken from (blood or bone marrow), there are 2 main types of SCT - allogeneic and autologous.

In an **allogeneic stem cell transplan**t, the blood-forming stem cells come from a donor whose cells are almost identical with those of the patient. The donor is often a brother or sister, or it can be a matched, unrelated donor. Allogeneic transplantation has limited usefulness, however, because of the need for a matched donor. Another drawback is that side effects of this treatment are too severe for most people over 55 years old. About one fourth of all transplants for lymphoma are this kind.

In an **autologous stem cell transplan**t, a patient's own blood-forming stem cells are removed from his or her bone marrow or bloodstream before treatment. With some types of lymphoma that tend to spread to the bone marrow or blood, an autologous transplant may not be possible because it may be hard to get stem cells that do not have lymphoma cells present. Even after purging (treating the stem cells in the lab to kill or remove lymphoma cells), returning some lymphoma cells with the stem cell transplantation is possible.

In either case, blood-forming stem cells collected from the donor or the patient are carefully frozen and stored. The patient then receives high-dose chemotherapy and sometimes whole body radiation treatment as well. This destroys remaining cancer cells, but it also kills all or most normal cells in the bone marrow. After therapy, the frozen stem cells are thawed and returned to the body like a blood transfusion.

Bone marrow transplantation is very expensive (more than $100,000) and can require a lengthy hospital stay. Because some insurance companies view this procedure in certain cases as experimental, they may not pay for it.

Side effects from a stem cell transplant are generally divided into early and long-term effects. The early complications and side effects are basically the same as those caused by any other type of high-dose chemotherapy. They are caused by damage to the bone marrow and other rapidly growing tissues of the body.

Complications and side effects that can persist for a long time or not occur until years after the transplant include:

- Radiation damage to the lungs, causing shortness of breath
- Graft-versus-host disease, which occurs only in allogeneic (donor) transplants (see below)
- Damage to the ovaries in women that can cause infertility and premature menopausal symptoms
- Infertility in male patients
- Damage to the thyroid gland that can cause problems with metabolism
- Cataracts (damage to the lens of the eye that can affect vision)
- Bone damage called aseptic necrosis. If damage is severe, the patient will need to have part of the affected bone and the joint replaced.
- Development of leukemia years later is also a possible complication of this treatment

Graft-versus-host disease: This is the major complication of allogeneic (donor) stem cell transplants. It occurs because the immune system of the patient is taken over by that of the donor. The donor immune system then begins reacting against the patient's body. The most disabling symptoms are severe skin rashes with itching and severe diarrhea. The liver and lungs may also be damaged. The patient may also become easily fatigued and develop muscle aching. Sometimes the graft-versus-host disease becomes chronic and disabling and, if it is severe enough, can be fatal. Usually drugs can control graft-versus-host disease.

On the positive side, the graft-versus-host disease also leads to graft-versus-lymphoma activity. Lymphoma cells remaining after the chemotherapy and radiation therapy are often killed by immune reactions of the donor cells. Mild graft-versus-host disease can be a good thing.

Nonmyeloablative transplants: This is a special kind of transplant that takes advantage of the donor cells' immune response to kill the lymphoma. Only low doses of chemotherapy (usually a drug called fludarabine, which lowers a patient's immunity) are given. Then stem cells from a matched donor are given. Over time the donor cells take over the bone marrow and develop an immune response to the lymphoma cells and destroy them.

The problem with nonmyeloablative transplants is the graft-versus-host disease, which damages the patient. Researchers are looking for ways to eliminate the graft-versus-host response while keeping the graft-versus-lymphoma effect. One advantage of this kind of transplant, even though it is allogeneic (from another donor, not the patient), is that older patients tolerate it without life-threatening toxic effects seen with the other transplants.

Clinical Trials

The purpose of clinical trials: Studies of promising new or experimental treatments in patients are known as clinical trials. A clinical trial is only done when there is some reason to believe that the treatment being studied may be valuable to the patient. Treatments used in clinical trials are often found to have real benefits.

Types of clinical trials: There are 3 phases of clinical trials in which a treatment is studied before it is eligible for approval by the FDA (Food and Drug Administration).

Phase I clinical trials: The purpose of a phase I study is to find the best way to give a new treatment and find out how much of it can be given safely. Doctors watch patients carefully for any harmful side effects. The treatment has been well tested in laboratory and animal studies, but the side effects in patients are not completely known. Doctors conducting the clinical trial start by giving very low doses of the drug to the first patients and increasing the dose for later groups of patients until side effects appear. Although doctors are hoping to help patients, the main purpose of a phase I study is to test the safety of the drug.

Phase II clinical trials: These studies are designed to see if the drug works. Patients are given the highest dose that doesn't cause severe side effects (determined from the phase I study) and closely observed for an effect on the cancer. The doctors also look for side effects.

Phase III clinical trials: Phase III studies involve large numbers of patients. Some clinical trials enroll thousands of patients. One group (the control group) receives the standard (most accepted) treatment. The other group(s) receives the new treatment. All patients in phase III studies are closely watched. The study will be stopped if the side effects of the new treatment are too severe or if one group has had much better results than the others.

TREATMENT OF SPECIFIC LYMPHOMAS

Treatment usually depends both on the type of lymphoma and on the extent of the disease in the body.

B-CELL LYMPHOMA TREATMENTS

Diffuse large B-cell lymphoma: This lymphoma can be cured in around 40% of patients. The cure rate is much higher if the International Prognostic Index is low and lower if the index is high.

The main treatment is chemotherapy, usually with a regimen of 4 drugs known as CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone).

If the lymphoma is localized to 1 or 2 lymph node groups on the same side of the abdomen (that is, if it is stage I or II), radiation therapy to the lymph node areas may be added to the chemotherapy. The usual chemotherapy regimen is given anywhere from 3 to 8 months depending on the size of the lymph nodes and whether the lymphoma is growing into nearby organs.

For stage III or IV lymphoma, chemotherapy is the main treatment. Once again, the usual regimen is CHOP. Many doctors are now adding rituximab (Rituxan) to the chemotherapy. Studies have shown that this increases the chance for a complete remission of the lymphoma. Another approach is shortening the interval between chemotherapy treatments from 3 weeks to 2 weeks. This requires the use of drugs to boost the white count---either G-CSF (Neupogen or Neulasta) or GM-CSF (Leukine).

If the lymphoma relapses after treatment or is refractory (doesn't respond well to primary treatment), doctors will suggest another chemotherapy regimen. If the lymphoma shrinks with this, a stem cell transplant is often suggested, because otherwise the lymphoma will usually grow back. Stem cell transplants are not effective unless the lymphoma responds to chemotherapy. As of yet, it is not clear if they are better than standard treatment as the initial treatment.

New techniques for studying the gene composition of large cell lymphomas have shown there may be 2 types. One responds well to usual treatment and the other doesn't. Clinical trials are now in progress to find out how best to treat the type that doesn't respond well.

Follicular lymphoma: This lymphoma has not been shown to be curable by any of the standard treatments. Although some new, more aggressive treatments seem to be very effective, it still isn't clear if they are better than standard treatment.

If the lymphoma is localized to 1 or 2 lymph node groups on the same side of the abdomen (stage I or II), it can be treated with radiation therapy to the lymph node areas. Chemotherapy is not usually recommended if the lymphoma is localized.

If the lymphoma is not localized (stage III or IV), then chemotherapy can be given. Radiotherapy can also be given to any large areas of lymphoma to reduce symptoms even if it is not stage I or II. Another option is observation with no treatment. This is reasonable if the lymphoma isn't very large and isn't causing symptoms, harming vital organs, or growing fast. While some patients are uncomfortable with this approach, it's important to remember that because follicular lymphoma isn't curable, the point of therapy is to control the disease for as long as possible while causing the fewest side effects.

The usual chemotherapy regimens consist of a single drug such as chlorambucil (Leukeran) or fludarabine (Fludara). Some doctors prefer combinations of cyclophosphamide (Cytoxan), vincristine (Oncovin), and prednisone. Other choices for treatment are rituximab (either alone or combined with chemotherapy) or interferon (either alone or combined with chemotherapy). The newer monoclonal antibodies, Zevalin and Bexxar, are also possible treatment options when other treatments are no longer working.

Sometimes patients with follicular lymphoma relapse with a large diffuse B-cell lymphoma. If this happens, then the treatment becomes the same as for that disease. If the relapse remains a follicular lymphoma, other chemotherapy drugs can be given. If the lymphoma responds to a new chemotherapy, stem cell transplant can be considered. This may help some patients, but it is best done in a clinical trial. A nonmyeloablative transplant is another option.

Chronic lymphocytic leukemia/small lymphocytic lymphoma: Treatment options for people with CLL vary greatly, depending on the disease stage and if the leukemia is causing any symptoms. Perhaps the most important factor is determining the risk group. Although the staging system has been traditionally used, testing for cellular and chromosome changes may be more useful. Even more important will be the tests for Zap-70 and CD38. These will eventually be available but for now we will use the standard classifications.

*Low risk-CLL***:** The prognosis for this group is very good, with an average survival of 20-25 years. The usual approach is to give no immediate treatment. Careful and frequent follow-up exams are recommended. Treatment should be considered if there are signs that the leukemia is progressing or if the patient later develops bothersome symptoms. When indicated, initial treatment is usually chemotherapy, as described in the next section.

*Intermediate- and high-risk CLL***:** Patients with intermediate- and high-risk CLL who do not have any symptoms may not need treatment right away. They can be observed for signs of progression and onset of new symptoms. The people in this category live for an average of 8-10 years.

The usual treatment is chemotherapy with chlorambucil. Cyclophosphamide may be substituted if chlorambucil causes side effects. Steroids such as prednisone may also be used. Combinations of drugs may also be also used. Some doctors combine cyclophosphamide with doxorubicin and other drugs such as vincristine and prednisone.

Fludarabine is a newer chemotherapy drug that has proven very useful in CLL. Oncologists usually

reserve fludarabine for CLL that has recurred (come back) after treatment with other drugs. Recently, however, many have started to use fludarabine as the first treatment, particularly in younger people. Other drugs that work similarly to fludarabine are pentostatin and cladribine (2-CdA). Giving rituximab (Rituxan) along with fludarabine may be even more effective.

When to use alemtuzumab is still unclear. Because it is a new drug, it is usually used after the older drugs have failed. But with more experience, doctors are beginning to study its use earlier in the course of CLL.

If the only problem is an enlarged spleen or swollen lymph nodes in one region of the body, localized treatment with low-dose radiation therapy is often used. Splenectomy (surgery to remove the spleen) is another option if enlargement of this organ causes symptoms.

If very high numbers of leukemia cells are interfering with normal circulation, leukapheresis is used before chemotherapy. This is a procedure in which the blood is passed through a special machine that removes white blood cells (including leukemia cells) and returns the rest of the blood cells and plasma to the patient. The benefit of this treatment is immediate but temporary. Leukapheresis is useful because chemotherapy may not affect the number of cells until a few days after the first dose.
As mentioned previously, stem cell transplantation may be another treatment option for certain patients, but its usefulness is not yet proven.

*Treatment of complications of CLL***:** CLL can cause serious problems with other blood components. It can also (rarely) transform into another, more aggressive type of cancer. Treatment of CLL itself may also lead to the development of another cancer.

Sometimes CLL alters a patient's immune system in a way that causes it to attack his or her own red blood cells (auto-immune hemolytic anemia) or blood platelets (immune-mediated thrombocytopenia). These conditions are treated with corticosteroid drugs such as prednisone, which is taken by mouth.

One of the most serious complications of CLL is a change (transformation) of the leukemia to a high-grade or aggressive type of non-Hodgkin lymphoma called large cell lymphoma. This is known as Richter syndrome or Richter transformation. If this occurs, patients receive treatment for lymphoma. See our document on "Non-Hodgkin Lymphoma" for more information on lymphoma treatment.
Patients with CLL rarely will have their leukemia transform into the acute form of lymphocytic leukemia. If this happens, then the patient will be treated with a chemotherapy regimen that is used for patients with acute lymphocytic leukemia (ALL).

Mantle cell lymphoma: Although not a rapidly growing lymphoma, this disease can be fatal and often requires intensive treatment. All stages are treated in a similar way.

Chemotherapy is the usual treatment, but no specific chemotherapy regimen has proved better than others. Rituximab is sometimes added to the chemotherapy. Many clinical trials that use high-dose chemotherapy and stem cell transplantation are underway.

Another treatment has included Zevalin. This is given in high doses and is followed by stem cell transplantation. Because there is no curative or generally accepted treatment for this lymphoma, patients should consider entering a clinical trial.

Extranodal marginal zone B-cell lymphomas - mucosa-associated lymphoid tissue (MALT) lymphomas: The most common of these, gastric lymphoma, is thought to occur as a result of an infection with *H. pylor*i. Because of this, therapy for gastric lymphomas is different than for the other lymphomas in this group.

Treatment of early stage gastric MALT lymphomas (stages I and II) consists of antibiotics directed against *H. pylori* along with drugs that block acid secretion by the stomach. Usually the drugs are given for 10 to 14 days. Examination of the stomach using a flexible tube with a viewing lens (gastroscopy) is then repeated at certain intervals to see if the *H. pylori* is gone and the lymphoma has decreased in size.

Radiation therapy to the stomach or chemotherapy may be used for stages II through IV. They are also given for early stage disease if the symptoms are so severe that they need to be relieved before the antibiotics take effect, which can take several weeks to months. The drugs used are the same as those used for follicular lymphoma. Single agents such as chlorambucil or fludarabine or combinations such as cyclophosphamide, vincristine, and prednisone are used.

Local radiation and single-agent chemotherapy as outlined above are the treatments for MALT lymphomas that arise in sites other than the stomach.

Nodal marginal zone B-cell lymphoma: This is generally a low-grade lymphoma. It is treated like follicular lymphoma with either observation or low-intensity chemotherapy. It can also transform into a high-grade large cell lymphoma, which requires more aggressive chemotherapy such as CHOP.

Splenic marginal zone B-cell lymphoma: This is also a low-grade lymphoma and is treated with either observation or low-intensity chemotherapy like follicular lymphoma.

Because the lymphoma invades and enlarges the spleen, an organ in the left upper part of the abdomen, doctors may decide to surgically remove it. This alone can lead to a long-term remission of the disease. Radiation therapy is an alternative to surgery.

This lymphoma can transform into a large-cell aggressive lymphoma, which requires more intensive chemotherapy.

Primary mediastinal B-cell lymphoma: This is treated like localized diffuse large B-cell lymphoma. The main treatment is radiation to the chest mass along with about 6 courses of CHOP chemotherapy.

Burkitt lymphoma: This is a very fast growing lymphoma that must be treated intensely. Most regimens for this disease include high doses of cyclophosphamide (Cytoxan), doxorubicin (Adriamycin), cytarabine (Cytosar), and methotrexate, along with standard doses of vincristine (Oncovin). Prednisone or dexamethasone is also used. Finally, because this lymphoma tends to invade the spinal fluid, chemotherapy with methotrexate is given into the spinal fluid. About half of all patients are cured.

Lymphoplasmocytic lymphoma (Waldenstrom macroglobulinemia): The main treatment for this lymphoma is chemotherapy or rituximab.

Hairy cell leukemia: This is also a slow growing lymphoma that invades the spleen and lymph nodes as well as the blood. The drugs used to treat it are called pentostatin and 2-CdA. Both are equally effective. They are given intravenously for either a few months (pentostatin) or a week (2-CdA). Most patients go into remission. Only a small percentage relapse, and those that do usually can be treated successfully again. Sometimes the disease is resistant to these drugs. Rituximab has been used to treat these patients with success. Removing the spleen with surgery can also help.

T-CELL LYMPHOMA TREATMENTS

Precursor T-lymphoblastic lymphoma/leukemia: This disease can occur as leukemia in both children and adults.

It is called a lymphoma if there are tumor masses and the number of lymphoma cells in the bone marrow is less than 25%. This is a fast growing disease and is treated with intensive chemotherapy.

Many drugs are used. These include cyclophosphamide (Cytoxan), doxorubicin (Adriamycin), vincristine (Oncovin), L-asparaginase, methotrexate, prednisone, and, sometimes, cytosine arabinoside (ara-C, Cytosar). Chemotherapy with methotrexate is also given into the spinal fluid. Some doctors suggest high-dose chemotherapy followed by an autologous stem cell transplant after a patient goes into remission.

Peripheral T-cell lymphomas:

Cutaneous T-cell lymphomas (mycosis fungoides, Sezary syndrome): The treatment of these lymphomas depends on how advanced they are. Early disease with only patches or plaques (raised patches) of lymphoma is treated with the following skin-directed treatments:

- **Chemotherapy solutions or ointments** can be applied directly to the whole body surface except uninvolved face, hands, and genitals. The drugs used are either nitrogen mustard or BCNU. Sometimes steroid creams can help. The nitrogen mustard can cause redness and itching.
- **PUVA (psoralen ultraviolet A) light treatment** involves receiving psoralen, a light-sensitizing drug that is taken by mouth, followed by exposing the skin to a special ultraviolet light. This is done 3 times a week until the lesions regress and then less often. Sometimes interferon therapy is added.
- **Electron beam therapy** is a type of external radiation. It is different from standard radiation therapy because the beam is made of electrons and does not penetrate but only treats the skin. This can be aimed at specific lesions or the whole skin. The major side effect is moderate sunburn.
- **Bexarotene (Targretin),** a new topical skin gel, contains a vitamin A-like compound that can be useful in some instances. More advanced disease that is either forming tumors or is invading the whole skin surface is treated with:
- **Electron beam therapy to the whole skin**
- **Electron beam therapy combined with PUVA**
- **Photopheresis** is a treatment like PUVA except that instead of the skin being treated, the blood is treated. First the patient receives psoralen. Then blood is removed through a vein in the arm and circulated through an apheresis machine, where the white blood cells are separated out. These are treated with the special ultraviolet light and are returned to the body through another vein along with the red blood cells.

If the skin lymphoma has spread to lymph nodes or other organs, chemotherapy is usually needed. Drugs used include doxorubicin, cyclophosphamide, methotrexate, bleomycin, and prednisone (alone or in combination). Nucleoside analogs (pentostatin, 2-CdA, or fludarabine) and interferon are sometimes used. Biological therapies using newer man-made molecules such as denileukin diftitox (Ontak) or the monoclonal antibody alemtuzumab (Campath) are other treatment options. In this situation, a clinical trial may be the best option.

Angioimmunoblastic T-cell lymphoma: This type is often treated with corticosteroids (such as prednisone or dexamethasone) alone. This treatment can reduce fever and stop the weight loss.

The effect is temporary, however. Usually some form of chemotherapy is needed. But even chemotherapy is not completely successful, and remissions are usually short.

Extranodal natural killer / T-cell lymphoma, nasal type: Because this lymphoma is often confined to the nasal passages, it can be treated with radiation therapy. However, this is usually not enough, and chemotherapy is often added. A typical chemotherapy regimen is CHOP. If the lymphoma has spread, the chemotherapy is more intense. Multiple drugs are used at high doses, and stem cell transplantation may be added.

Enteropathy type T-cell lymphoma: The only effective treatment is prevention. This lymphoma develops from hypersensitivity to gluten. If the symptoms of this hypersensitivity are recognized early, then a gluten-free diet will help prevent the lymphoma from developing. Otherwise, there is no accepted treatment, although a clinical trial of chemotherapy may be suggested.

Subcutaneous panniculitis-like T-cell lymphoma: This type of lymphoma responds poorly to chemotherapy. Radiation therapy is useful to relieve symptoms.

Anaplastic large T / null-cell lymphoma: This lymphoma is treated like diffuse B-cell lymphoma with CHOP or similar regimens. Response rates are high, and results are excellent.

Unspecified: These lymphomas are treated the same way as diffuse large B-cell lymphomas. Chemotherapy with CHOP or other combinations is used. The outlook is not as good as in diffuse B-cell lymphoma. Stem cell transplants may be recommended as part of the treatment.

Primary central nervous system (CNS) lymphoma: This is a special class of lymphoma because it begins in the brain or spinal cord**.** This type often develops in people with immune system problems caused by AIDS or from drugs given to prevent rejection of transplanted organs.

Most patients are treated with chemotherapy and radiation. High doses of methotrexate have been shown to be effective. Often other drugs are added, but doctors aren't sure which drugs are the best ones to add. This is still being studied. Radiation is also given, but some doctors are trying to avoid it, especially in older patients, because it often causes mental changes. Another problem that affects a patient's outlook aside from the tumor, is the patient's general health.

Treatment of HIV-Associated Lymphoma

Although people with HIV and lymphoma often have aggressive or highly aggressive lymphoma their outlook has improved considerably. First, it appears that they are getting less aggressive lymphomas and secondly, they are better able to tolerate chemotherapy.

Most experts believe that the prognosis of the person with HIV-associated lymphoma relates more to the HIV infection than to the lymphoma. Because modern anti-HIV therapy is controlling the immune deficiency in patients with AIDS, the outlook for those patients who develop lymphoma has improved considerably. Also, it appears that fewer AIDS patients are developing lymphoma with the advent of modern therapies.

What If the Lymphoma Doesn't Respond or Comes Back After Treatment?

Lymphomas tend to come back in the same part of the body they started. For example, if the lymphoma began in lymph nodes in the abdomen, this is the most likely place it will recur. If the bone marrow was involved, it will most likely return there. Usually, the lymphoma will respond to new kinds of chemotherapy. Another option is the use of high-dose chemotherapy with stem cell transplantation.

After more than one chemotherapy treatment has failed, the lymphoma is much less likely to respond to additional or new chemotherapy. If the lymphoma does respond, the response may be short lived. Over time, chemotherapy provides less benefit, although immunotherapy and other new approaches to treatment available through clinical trials may be effective.

What's New in Non-Hodgkin Lymphoma Research and Treatment?

Genetics: Scientists are making great progress in understanding how changes in DNA can cause normal lymphocytes to develop into lymphoma cells. Greater understanding of the genes involved in certain translocations that often occur in lymphoma is providing insight into why these cells may grow too rapidly, live too long, and not develop into mature cells that take part in normal immune reactions.

Once this is understood, then drugs may be developed that block this process. An effective drug has already been developed for people with chronic myelogenous leukemia (CML) that blocks the defect produced by translocation in that disease. Research is in progress that is taking a similar approach to lymphoma treatment.

Progress in understanding DNA changes in lymphoma has already provided improved and highly sensitive tests for detecting this disease. Such tests can identify lymphoma cells based on their gene translocations or rearrangements. The polymerase chain reaction (PCR) test can detect one cell from certain types of lymphoma among a million normal cells. It is useful in determining how completely the lymphoma has been destroyed by treatment and whether a relapse is likely.

One of the more important breakthroughs in recent years has been the development of DNA microarrays. These are tests of a tumor's DNA that can spot the abnormal genes in the tumor and also tell how the cancer will respond to chemotherapy. This may lead to a new classification of these diseases. The usefulness and reliability of these tests is now being studied.

Chemotherapy: Many clinical trials are currently in progress to study new chemotherapy drugs. Others are studying ways to use drugs already known to be effective by combining them in new ways or using different doses or different sequences of drugs.

Chemotherapy treatment for some lymphomas is sometimes limited by resistant populations of lymphoma cells. Lymphoma cells can overcome the effect of chemotherapy in several ways. Certain drugs used in chemotherapy work by blocking certain steps in DNA metabolism. Lymphoma cells can sometimes develop resistance to these drugs by producing some of the enzymes that speed up these pathways in metabolism. Another way in which lymphoma cells can become resistant to chemotherapy is by turning on a "pump" in their outer membranes that removes the drug from the cell.

Clinical trials are now in progress to evaluate new drugs designed to interfere with these resistant mechanisms in order to enhance the effectiveness of currently existing chemotherapy.

Biological therapy: Lymphoma cells contain certain chemicals on their surface. Specially manufactured antibodies that recognize these substances can be targeted to destroy the lymphoma cells while causing little damage to normal body tissues. This treatment strategy has already proven effective. Several such drugs, including rituximab, are already available.

Because of the success of rituximab and its radioactive counterparts, new monoclonal antibodies are being developed. Their use combined with chemotherapy is also being tested in clinical trials.

Bone marrow and peripheral blood stem cell transplantation: Researchers continue to improve bone marrow and peripheral blood stem cell transplantation methods, including new ways to harvest these cells before transplantation.

Autologous transplantation has the risk of reintroducing lymphoma cells back into the patient after treatment. Researchers are testing new and improved ways to remove the last traces of lymphoma from these stem cells before they are returned to the patient. Some of the new monoclonal antibodies developed for treating lymphoma may be also used to remove these remaining cells.

Much research is focusing on eliminating graft-versus-host disease in allogeneic (donor) transplants. This work revolves around altering the transplanted T-cells so that they won't react with the recipient's normal cells but still kill the lymphoma cells.

Vaccines: Doctors have always known that it was possible for people with cancer to develop antibodies to their cancer. In rare instances, these people's immune systems have rejected their cancers, and they have been cured. Scientists are now developing ways of encouraging this immune reaction by the use of vaccines.

The difference from the usual use of vaccines in children is that the object there is to prevent an infectious disease from ever taking hold. With cancer vaccines, the goal is to create an immune reaction in patients who have very early disease or in patients whose disease is in remission. So far, there have been a few successes with this approach, and it is a major area of research in lymphoma treatment. These are still being tested in clinical trials.

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