



Non-Hodgkin Lymphoma

What is cancer?

The body is made up of trillions of living cells. Normal body cells grow, divide, and die in an orderly fashion. During the early years of a person's life, normal cells divide faster to allow the person to grow. After the person becomes an adult, most cells divide only to replace worn-out or dying cells or to repair injuries.

Cancer begins when cells in a part of the body start to grow out of control. There are many kinds of cancer, but they all start because of out-of-control growth of abnormal cells.

Cancer cell growth is different from normal cell growth. Instead of dying, cancer cells continue to grow and form new, abnormal cells. Cancer cells can also invade (grow into) other tissues, something that normal cells cannot do. Growing out of control and invading other tissues are what makes a cell a cancer cell.

Cells become cancer cells because of damage to DNA. DNA is in every cell and directs all its actions. In a normal cell, when DNA gets damaged the cell either repairs the damage or the cell dies. In cancer cells, the damaged DNA is not repaired, but the cell doesn't die like it should. Instead, this cell goes on making new cells that the body does not need. These new cells will all have the same damaged DNA as the first cell does.

People can inherit damaged DNA, but most DNA damage is caused by mistakes that happen while the normal cell is reproducing or by something in our environment. Sometimes the cause of the DNA damage is something obvious, like cigarette smoking. But often no clear cause is found.

In most cases the cancer cells form a tumor. Some cancers, like leukemia, rarely form tumors. Instead, these cancer cells involve the blood and blood-forming organs and circulate through other tissues where they grow.

Cancer cells often travel to other parts of the body, where they begin to grow and form new tumors that replace normal tissue. This process is called *metastasis*. It happens when the cancer cells get into the bloodstream or lymph vessels of our body.

No matter where a cancer may spread, it is always named for the place where it started. For example, breast cancer that has spread to the liver is still called breast cancer, not liver cancer. Likewise, prostate cancer that has spread to the bone is metastatic prostate cancer, not bone cancer.

Different types of cancer can behave very differently. For example, lung cancer and breast cancer are very different diseases. They grow at different rates and respond to different treatments. That is why people with cancer need treatment that is aimed at their particular kind of cancer.

Not all tumors are cancerous. Tumors that aren't cancer are called *benign*. Benign tumors can cause problems – they can grow very large and press on healthy organs and tissues. But they cannot grow into (invade) other tissues. Because they can't invade, they also can't spread to other parts of the body (metastasize). These tumors are almost never life threatening.

What is non-Hodgkin lymphoma?

Non-Hodgkin lymphoma (also known as non-Hodgkin's lymphoma, NHL, or sometimes just lymphoma) is a cancer that starts in cells called lymphocytes, which are part of the body's immune system. Lymphocytes are in the lymph nodes and other lymphoid tissues (such as the spleen and bone marrow). These will be described in more detail below.

Some other types of cancer – lung or colon cancers, for example – can spread to lymph tissue such as the lymph nodes. But cancers that start in these places and then spread to the lymph tissue are not lymphomas.

There are 2 main types of lymphomas.

- Hodgkin lymphoma (also known as Hodgkin's lymphoma, Hodgkin disease, or Hodgkin's disease), which is named after Dr. Thomas Hodgkin, who first described it
- Non-Hodgkin lymphoma

These 2 types of lymphomas behave, spread, and respond to treatment differently.

Doctors can usually tell the difference between them by looking at the cancer cells under a microscope. In some cases, sensitive lab tests may be needed to tell them apart.

Hodgkin disease is discussed in a separate American Cancer Society document. We also have other documents that focus on non-Hodgkin lymphoma in children and lymphoma of the skin.

The rest of this document focuses only on non-Hodgkin lymphoma in adults.

The lymph system and lymphoid tissue

To know what lymphoma is, it helps to understand the body's lymph system.

The lymph system (also known as the lymphatic system) is composed mainly of lymphoid tissue, lymph vessels, and a clear fluid called lymph. Lymphoid tissue includes the lymph nodes and related organs that are part of the body's immune and blood-forming systems, such as the spleen and bone marrow.

Lymphocytes

Lymphoid tissue is made up of several types of immune system cells that help the body fight infections. Most of the cells in lymphoid tissue are lymphocytes, a type of white blood cell. The 2 main types of lymphocytes are *B lymphocytes* (B cells) and *T lymphocytes* (T cells). Normal B cells and T cells do different jobs within the immune system.

B lymphocytes: B cells normally help protect the body against germs (bacteria or viruses) by making proteins called antibodies. The antibodies attach to the germs, marking them for destruction by other immune system cells. Antibodies also attract certain blood proteins that can kill bacteria.

T lymphocytes: There are several types of T cells, each with a special job. Some T cells can directly destroy cells infected with viruses, fungi, or certain kinds of bacteria. T cells can also release substances that attract other types of white blood cells, which then digest the infected cells. Some types of T cells play a role in either boosting or slowing the activity of other immune system cells.

Both types of lymphocytes can develop into lymphoma cells, but B-cell lymphomas are much more common in the United States than T-cell lymphomas. Different types of lymphoma can develop from each type of lymphocyte, based on how mature the cells are when they become cancerous and other factors.

Treatment for each lymphoma depends on which type it is, so determining the exact type of lymphoma is important.

Organs that have lymphoid tissue

Lymphoid tissue is found in many places throughout the body. Because lymphoid tissue is in many parts of the body, lymphomas can start almost anywhere. The major sites of lymphoid tissue are:

Lymph nodes: Lymph nodes are bean-sized organs found throughout the body, including inside the chest, abdomen, and pelvis. They can sometimes be felt under the skin in the neck, under the arms, and in the groin. Lymph nodes are made up mainly of lymphocytes.

The lymph nodes in the body are connected by a system of lymph vessels. These vessels are like veins, except that instead of carrying blood, they carry lymph and lymphocytes.

Lymph nodes get bigger when they fight infection. Lymph nodes that grow in reaction to infection are called *reactive nodes* or *hyperplastic nodes* and are often tender to the touch. An enlarged lymph node is not always a sign of a serious problem. People with sore throats or colds often feel enlarged lymph nodes in the neck. But a large lymph node

is also the most common sign of lymphoma. Lymph node enlargement is discussed more in the section, "How is non-Hodgkin lymphoma diagnosed?"

Spleen: The spleen is an organ 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 makes lymphocytes and other immune system cells to help fight infection. It also stores healthy blood cells and filters out damaged blood cells, bacteria, and cell waste.

Thymus: The thymus is a small organ behind the upper part of the breastbone and in front of the heart. Before birth, the thymus plays a vital role in development of T lymphocytes. The thymus shrinks and becomes less important over the first 20 years of life. Despite this, it continues to play a role in immune system function.

Adenoids and tonsils: These are collections of lymphoid tissue at the back of the throat. They help make 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.

Digestive tract: The stomach and intestines as well as many other organs also have lymphoid tissue.

Bone marrow: The bone marrow (the soft inner part of certain bones) makes red blood cells, blood platelets, and white blood cells. Red blood cells carry oxygen from the lungs to the rest of the body. Platelets plug up small holes in blood vessels caused by cuts or scrapes. White blood cells' main job is fighting infections. The 2 main types of white blood cells are granulocytes and lymphocytes. Bone marrow lymphocytes are primarily B cells. Lymphomas sometimes start from bone marrow lymphocytes.

Types of non-Hodgkin lymphoma

Classifying non-Hodgkin lymphoma can be quite confusing (even for doctors) because there are so many types and because several different systems have been used. The most recent system is the *World Health Organization (WHO)* classification. The WHO system groups lymphomas based on how they look under a microscope, the chromosome features of the lymphoma cells, and the presence of certain proteins on the surface of the cells. (Older systems classified lymphomas only by how they looked under a microscope.)

The more common types of lymphoma are listed below according to whether they are B-cell or T-cell lymphomas. Some rarer forms of non-Hodgkin lymphoma are not discussed here.

B-cell lymphomas

B-cell lymphomas make up most (about 85%) of non-Hodgkin lymphomas in the United States.

Diffuse large B-cell lymphoma

This is the most common type of non-Hodgkin lymphoma in the United States, accounting for about 1 out of every 3 cases. The cells are fairly large when seen using a microscope.

Diffuse large B-cell lymphoma (DLBCL) can affect any age group but occurs mostly in older people (the average age is mid-60s). It usually starts as a quickly growing mass in a lymph node deep inside the body, such as in the chest or abdomen or in a lymph node that you can feel, such as in the neck or armpit. It can also start in other areas such as the intestines, bone, or even the brain or spinal cord.

About 1 in 3 of these lymphomas is confined to one part of the body (localized) when it is found. Lymphomas are easier to treat when they are localized than when they have spread to other parts of the body.

Genetic tests have shown that there are different subtypes of DLBCL, even though they look the same under the microscope. These subtypes seem to have different outlooks (prognoses) and responses to treatment.

DLBCL is a fast growing lymphoma, but it often responds well to treatment. Overall, about 3 out of 4 people will have no signs of disease after the initial treatment, and about half of all people with this lymphoma are cured with therapy.

Primary mediastinal B-cell lymphoma: This is a subtype of DLBCL in which the lymphoma cells are large but there is a lot of fibrosis (scar-like tissue) in the background. It accounts for about 2% of all lymphomas. About 2 out of 3 people with this lymphoma are women. Most are young – in their 30s.

This lymphoma starts in the mediastinum (the area around the heart and behind the breastbone). It usually is localized when it is found. It can cause trouble breathing because it often presses on the windpipe (trachea) leading into the lungs. It can also block the superior vena cava (the large vein that returns blood to the heart from the arms and head). This can make the arms and face swell.

This is a fast-growing lymphoma, but it usually responds well to treatment. About half of patients can be cured.

Follicular lymphoma

About 1 out of 5 lymphomas in the United States is follicular lymphoma. The term follicular means that the cells tend to grow in a circular pattern in lymph nodes.

The average age for people with this lymphoma is about 60. It is rare in very young people. Most of the time, this lymphoma occurs in many lymph node sites in the body, as well as in the bone marrow.

Follicular lymphomas are often slow-growing and respond well to treatment, but they are hard to cure. The 5-year survival rate (the percentage of people surviving *at least* 5 years) is around 70%, but the stage (extent) of the lymphoma and other factors can affect this.

These lymphomas may not require treatment when they are first diagnosed. Instead, treatment may be delayed until the lymphoma is causing problems. Over time, about 1 in 3 follicular lymphomas transforms (changes) into a fast-growing diffuse B-cell lymphoma.

Chronic lymphocytic leukemia /small lymphocytic lymphoma

These are closely related diseases. In fact, many doctors consider them different versions of the same disease. The same type of cell (known as a small lymphocyte) is seen in both chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL). The only difference is where the cancer cells are found. In CLL most of the cancer cells are in the blood and bone marrow. In SLL, the cancer cells are mainly in the lymph nodes and spleen. SLL accounts for about 5% to 10% of all lymphomas.

Both CLL and SLL are slow-growing diseases, although CLL, which is much more common, tends to grow slower. CLL and SLL are treated the same way. They are usually not curable with standard treatments, but depending on the stage and growth rate of the disease, most patients live longer than 10 years. Sometimes, these slow-growing lymphomas transform into a more aggressive type of lymphoma.

For more detailed information, see our document, *Leukemia -- Chronic Lymphocytic*.

Mantle cell lymphoma

Only about 5% of lymphomas are this type. The cells are small to medium in size.

Men are affected most often. The average age of patients is in the early 60s. The lymphoma is usually widespread when it is diagnosed, in the lymph nodes, bone marrow, and often the spleen.

This usually isn't a very fast-growing lymphoma, but it is hard to treat. Newer, more aggressive treatments may be more effective than those used in the past, and may offer a better chance for long-term survival for patients now being diagnosed.

Marginal zone B-cell lymphomas

Marginal zone lymphomas account for about 5% to 10% of lymphomas. The cells in these lymphomas look small under the microscope. There are 3 main types of marginal zone lymphomas.

Extranodal marginal zone B-cell lymphomas, also known as mucosa-associated lymphoid tissue (MALT) lymphomas: These lymphomas start in places other than the lymph nodes (hence the name extranodal) and are the most common type. Most MALT lymphomas start in the stomach and are thought to be related to an infection by the bacteria *Helicobacter pylori*, which is also the cause of stomach ulcers. Other possible sites of MALT lymphomas include the lung, skin, thyroid, salivary glands, and tissues surrounding the eye. Usually it is confined to the area where it begins and is not

widespread. Many of these other MALT lymphomas have also been linked to infections with bacteria or viruses.

The average age of patients with MALT lymphoma is about 60. It is a slow-growing lymphoma and is often curable in its early stages. Doctors often use antibiotics as the first treatment for MALT lymphoma of the stomach, because treating the *Helicobacter pylori* infection often cures the lymphoma.

Nodal marginal zone B-cell lymphoma: This is a rare disease, found mainly in older women. It usually stays in the lymph nodes, although lymphoma cells can also sometimes be found in the bone marrow.

This tends to be a slow-growing lymphoma (although not usually as slow as MALT lymphoma), and many patients are cured if they are diagnosed when the disease is in the early stages.

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

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

Burkitt lymphoma

This type makes up about 1% to 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 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 and is related to infection with the Epstein-Barr virus (which can also cause infectious mononucleosis or “mono”). In the more common types seen in the United States, the lymphoma usually starts in the abdomen, where it forms a large tumor mass. It can also start in the ovaries, testicles, or other organs, and can spread to the brain and spinal fluid. The type seen in the United States is usually not linked to Epstein-Barr viral infection.

Close to 90% of patients are male, and the average age is about 30. Although this is a fast-growing lymphoma, more than half of patients can be cured by intensive chemotherapy.

Lymphoplasmacytic lymphoma (Waldenstrom macroglobulinemia)

This type is not common, accounting for 1% to 2% of lymphomas. The lymphoma cells are small and found mainly in the bone marrow, lymph nodes, and spleen.

Most of the time the lymphoma cells make an antibody called immunoglobulin M (IgM), which is a very large protein. This antibody circulates in the blood in large amounts, and causes the liquid part of the blood to thicken, like syrup. This can lead to decreased blood flow to many organs, which can cause problems with vision (because of poor circulation in blood vessels in the back of the eyes) and neurological problems (such as headache, dizziness, and confusion) caused by poor blood flow within the brain. Other symptoms can include feeling tired and weak, and a tendency to bleed easily.

This lymphoma is slow growing. Although it isn't usually considered to be curable, treatment can be very helpful, and most patients live longer than 5 years.

For more information, see our document, *Waldenstrom Macroglobulinemia*.

Hairy cell leukemia

Despite the name, this is sometimes considered to be a type of lymphoma. Hairy cell leukemia (HCL) is rare – about 700 people in the United States are diagnosed with it each year. The cells are small B lymphocytes with projections coming off them that give them a "hairy" appearance. They are typically found in the bone marrow and spleen and in the blood.

Men are more likely to get HCL than women, and the average age is around 50.

Hairy cell leukemia is slow-growing, and some patients may never need treatment. An enlarging spleen or dropping blood cell counts (due to cancer cells invading the bone marrow) are the usual reasons to begin treatment. If treatment is needed, it is usually very effective.

Hairy cell leukemia is also described in our document, *Leukemia--Chronic Lymphocytic*

Primary central nervous system (CNS) lymphoma

This lymphoma usually involves the brain (called primary brain lymphoma), but it may also be found in the spinal cord and in tissues around the spinal cord and the eye. Over time, it tends to become widespread in the central nervous system.

Primary CNS lymphoma is rare overall, but it is more common in people with immune system problems, such as those infected with HIV, the virus that causes AIDS. Most people develop headaches and confusion. They can also have vision problems, paralysis of some facial muscles, and even seizures in some cases.

The outlook for people with this condition has always been thought to be fairly poor, but some people can live at least 5 years with today's treatments.

Lymphoma of the eye (primary intraocular lymphoma), which is related to primary CNS lymphoma, is discussed in our document, *Eye Cancer (Melanoma and Lymphoma)*.

T-cell lymphomas

T-cell lymphomas make up less than 15% of non-Hodgkin lymphomas in the United States. There are many types of T-cell lymphoma, but they are all fairly rare.

Precursor T-lymphoblastic lymphoma/leukemia

This disease accounts for about 1% of all lymphomas. It can be considered either a lymphoma or leukemia, depending on how much of the bone marrow is involved (leukemias have more bone marrow involvement). The cancer cells are small-to-medium sized, immature T-cells.

This lymphoma often starts in the thymus (where many T cells are made) and can develop into a large tumor in the mediastinum (the area around the heart and behind the breast bone). This can cause trouble breathing if it presses on the windpipe (trachea) leading into the lungs. It can 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.

Patients are most often young adults, with males being affected more often than females.

This 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.

Often, the lymphoma form of this disease is treated in the same way as the leukemia form. For more information, see our document *Leukemia - Acute Lymphocytic (Adults)*.

Peripheral T-cell lymphomas

These types of lymphomas develop from more mature forms of T cells. They are rare, accounting for only a small portion of all lymphomas.

Cutaneous T-cell lymphomas (mycosis fungoides, Sezary syndrome, and others):

These lymphomas start in the skin. Skin lymphomas account for about 5% of all lymphomas. They are described in our document, *Lymphoma of the Skin*.

Angioimmunoblastic T-cell lymphoma: This lymphoma accounts for about 3% of all lymphomas. It tends to occur in the lymph nodes and may affect the spleen or liver. Patients usually have fever, weight loss, and skin rashes and often develop infections. This lymphoma often progresses quickly. Treatment is often effective at first, but the lymphoma tends to come back.

Extranodal natural killer/T-cell lymphoma, nasal type: This rare type often involves the upper airway passages, such as the nose and upper throat, but it can also invade the skin and digestive tract. It is much more common in parts of Asia and South America.

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 (celiac sprue), can progress to lymphoma, which typically invades the walls

of the intestines. If the symptoms of enteropathy are recognized early, then a gluten-free diet may help prevent the lymphoma from developing.

Anaplastic large cell lymphoma: About 2% of lymphomas are of this type. It is more common in young people (including children), but it does occur in people in their 50s and 60s. It usually starts in lymph nodes and can also spread to skin. This type of lymphoma tends to be fast-growing, but many people with this lymphoma are cured with aggressive chemotherapy. A related form of this lymphoma, which affects only the skin, is described in our document, *Lymphoma of the Skin*.

Peripheral T-cell lymphoma, unspecified: This name is given to T-cell lymphomas that don't readily fit into any of the groups above. They make up about half of all T-cell lymphomas. The tumor cells can be small or large. Most people diagnosed with this disease are in their 60s. As a group, these lymphomas tend to be widespread and grow quickly. Some cases respond well to chemotherapy, but long-term survival is not common.

What are the key statistics about non-Hodgkin lymphoma?

Non-Hodgkin lymphoma (NHL) is one of the most common cancers in the United States, accounting for about 4% of all cancers. The American Cancer Society's most recent estimates for non-Hodgkin's lymphoma are for 2012:

- About 70,130 people (38,160 males and 31,970 females) will be diagnosed with NHL. This includes both adults and children.
- About 18,940 people will die from this cancer (10,320 males and 8,620 females).

The average American's risk of developing NHL during his or her lifetime is about 1 in 50. Each person's risk may be affected by certain risk factors (listed in the next section).

The number of people getting NHL has been fairly steady for more than a decade.

Although some types of NHL are among the more common childhood cancers, more than 95% of cases occur in adults. The types of NHL seen in children are often very different from those seen in adults. For more information, see our document, *Non-Hodgkin Lymphoma in Children*.

While NHL can occur at any age, about half of patients are older than 65. The risk of developing NHL increases throughout life. The aging of the American population is likely to lead to an increase in NHL cases during the coming years.

Survival rates vary widely based on the type of lymphoma and stage (extent) of disease at the time of diagnosis. However, the overall 5-year relative survival rate for people with NHL is 67%, and the 10-year relative survival rate is 55%. (More detailed information about the prognosis for some types of lymphoma can be found in the section, "What is non-Hodgkin lymphoma?")

The 5-year survival rate refers to the percentage of patients who live *at least* 5 years after their cancer is diagnosed. Although many of these patients live much longer than 5 years after diagnosis, doctors use 5-year rates as a standard way of discussing prognosis. Five-year *relative* survival rates assume that some people will die of other causes and compare the observed survival with that expected for people without the cancer. This is a better way to see the impact of cancer on survival. Because 5-year survival rates are based on patients first diagnosed and treated more than 5 years ago, the outlook for newly diagnosed patients may be better.

What are the risk factors for non-Hodgkin lymphoma?

A risk factor is something that affects your chance of getting a disease such as cancer. Different cancers have different risk factors. Some risk factors, like smoking, can be controlled. Others, like a person's age or family history, can't be changed.

But risk factors don't tell us everything. Having a risk factor, or even many risk factors, does not mean that you will get the disease. And many people who get the disease may have few or no known risk factors. Even if a person with non-Hodgkin lymphoma has a risk factor, it is often very hard to know how much that risk factor may have contributed to the lymphoma.

Researchers have found several factors that may affect a person's chance of getting non-Hodgkin lymphoma. There are many types of lymphoma, and some of these factors have been linked only to certain types.

Age

Getting older is a strong risk factor for lymphoma overall, with most cases occurring in people in their 60s or older. But some types of lymphoma are more common in younger people.

Gender

Overall, the risk of non-Hodgkin lymphoma is higher in men than in women, but there are certain types of non-Hodgkin lymphoma that are more common in women. The reasons for this are not known.

Race, ethnicity, and geography

In the United States, whites are more likely than African Americans and Asian Americans to develop non-Hodgkin lymphoma.

Worldwide, non-Hodgkin lymphoma is more common in developed countries, with the United States and Europe having the highest rates. Some types of lymphoma that have

been linked to specific infections (described further on) are more common in certain parts of the world.

Exposure to certain chemicals

Some studies have suggested that chemicals such as benzene and certain herbicides and insecticides (weed- and insect-killing substances) may be linked with an increased risk of non-Hodgkin lymphoma. Research to clarify these possible links is still in progress.

Some chemotherapy drugs used to treat other cancers may increase the risk of developing non-Hodgkin lymphoma many years later. For example, patients who have been treated for Hodgkin disease have an increased risk of later developing non-Hodgkin lymphoma. But it's not totally clear if this is related to the disease itself or if it is an effect of the treatment.

Radiation exposure

Studies of survivors of atomic bombs and nuclear reactor accidents have shown they 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, such as Hodgkin disease, 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.

Immune system deficiency

People with weakened immune systems have an increased risk for non-Hodgkin lymphoma. For example, people who receive organ transplants (kidney, heart, liver) are treated with drugs that suppress their immune system to prevent it from attacking the new organ. These people have a higher risk of developing non-Hodgkin lymphoma.

The human immunodeficiency virus (HIV) can also weaken the immune system, and people infected with HIV are at increased risk of non-Hodgkin lymphoma.

Some genetic (inherited) syndromes can cause children to be born with a deficient immune system. Along with an increased risk of serious infections, these children also have a higher risk of developing non-Hodgkin lymphoma. These inherited immune deficiency diseases can be passed on to children, but people with non-Hodgkin lymphoma who do not have these inherited diseases do not pass an increased risk of lymphoma on to their children.

Autoimmune diseases

Some autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus (SLE, or lupus), celiac sprue (gluten-sensitive enteropathy), and others have been linked with an increased rate of non-Hodgkin lymphoma.

In autoimmune diseases, the immune system sees the body's own tissues as foreign and attacks them, as it would a germ. Lymphocytes (the cells from which lymphomas start) are part of the body's immune system. The overactive immune system in autoimmune diseases may cause lymphocytes to grow and divide more often than normal. This may increase the risk of them developing into lymphoma cells.

Certain infections

Some types of infections may raise the risk of non-Hodgkin lymphoma in different ways.

Infections that directly transform lymphocytes

Some viruses can directly affect the DNA of lymphocytes, helping to transform them into cancer cells. The human T-cell leukemia/lymphoma virus (HTLV-1) and the Epstein-Barr virus (EBV) seem to work in this way.

Infection with HTLV-1 increases a person's risk of developing certain types of T-cell lymphoma. This virus is most common in some parts of Japan and in the Caribbean region, but is found throughout the world. In the United States, it causes less than 1% of lymphomas. HTLV-1 spreads through sex and contaminated blood and can be passed to children through breast milk from an infected mother.

In areas of Africa where Burkitt lymphoma is common, infection with the Epstein-Barr virus (EBV) is an important risk factor for lymphoma. In developed countries such as the United States, EBV is more often linked with lymphomas in patients infected with HIV, the virus that causes AIDS. It has also been linked with developing nasal T-cell lymphoma and post-transplant lymphoma.

Human herpes virus 8 (HHV8) can also infect lymphocytes, leading to a rare type of lymphoma called *primary effusion lymphoma*. This lymphoma is most often seen in patients who are infected with HIV. HHV8 infection is also linked to another cancer, Kaposi sarcoma. For this reason, another name for this virus is *Kaposi sarcoma-associated herpes virus* (KSHV).

Infections that weaken the immune system

Infection with human immunodeficiency virus (HIV), also known as the AIDS virus, commonly causes immune system deficiency. HIV infection is a risk factor for developing certain types of non-Hodgkin lymphoma, such as Burkitt lymphoma and diffuse large B-cell lymphoma.

Infections that cause chronic immune stimulation

Some long-term infections may increase the risk of lymphoma by forcing a person's immune system to be on constant alert. As more lymphocytes are made to fight the infection, there is a greater chance that genetic mistakes can occur, which might eventually lead to lymphoma.

Helicobacter pylori, a type of bacteria known to cause stomach ulcers, has also been linked to mucosa-associated lymphoid tissue (MALT) lymphoma of the stomach. The body's immune reaction to this infection increases the risk of lymphoma. The importance of this is that antibiotics can help treat some patients who have already developed lymphomas of the stomach due to *H. pylori*.

The hepatitis C virus (HCV) can also cause long-term infections. Recent reports have found that infection with HCV seems to be a risk factor for developing certain types of lymphoma.

Body weight and diet

Some studies have suggested that being overweight or obese may increase your risk of non-Hodgkin lymphoma. Other studies have suggested that a diet high in fat and meats may raise your risk. More research is needed to confirm these findings. In any event, maintaining a healthy weight and eating a healthy diet have many known health benefits outside of the possible effect on lymphoma risk.

Do we know what causes non-Hodgkin lymphoma?

Researchers have found that non-Hodgkin lymphoma is linked with a number of risk factors, but the causes of most lymphomas are unknown. This is complicated by the fact that lymphomas are actually a diverse group of cancers.

Still, scientists have made a lot of progress in understanding how certain changes in DNA can cause normal lymphocytes to become lymphoma cells. Normal human cells grow and function mainly based on the information contained in each cell's chromosomes. Human DNA is packaged in 23 pairs of chromosomes, which are long molecules of DNA in each cell. DNA is the chemical that makes up our genes – the instructions for how our cells function. We look like our parents because they are the source of our DNA. But DNA affects more than how we look.

Some genes contain instructions for controlling when cells grow and divide. Certain genes that speed up cell division or help cells live longer are called *oncogenes*. Others that slow down cell division or cause cells to die at the right time are called *tumor suppressor genes*.

Each time a cell prepares to divide into 2 new cells, it must make a new copy of the DNA in its chromosomes. This process is not perfect, and errors can occur that may affect genes within the DNA. Cancers can be caused by DNA mutations (changes) that turn on oncogenes or turn off tumor suppressor genes.

Some people inherit DNA mutations from a parent that increase their risk for some types of cancer. But non-Hodgkin lymphoma is not one of the cancer types often caused by these inherited mutations. In other words, there is no increased risk of lymphoma in the children of patients with lymphoma.

DNA changes related to non-Hodgkin lymphoma are usually acquired after birth, rather than being inherited. Acquired changes may result from exposure to radiation, cancer-causing chemicals, or infections, but often these changes 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.

Translocations are a type of DNA change that can cause non-Hodgkin lymphoma to develop. 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. Some lymphomas tend to have specific chromosome defects. For example, most cases of follicular lymphoma have a translocation between chromosomes 14 and 18, which turns on the *bcl-2* oncogene. This stops the cell from dying at the right time, and this can lead to lymphoma.

Scientists are learning much about the exact gene changes involved in lymphoma. This information is being used to develop more accurate tests to detect and classify certain types of lymphoma. Hopefully, these discoveries can be used to develop new treatments as well.

Researchers are beginning to understand how these gene changes develop in people with certain risk factors, but they still do not know why most lymphomas develop in people with no apparent risk factors.

Lymphocytes (the cells from which lymphomas start) are immune system cells, so it's not surprising that changes in the immune system seem to play an important role in many cases of lymphoma.

- People with immune deficiencies (due to inherited conditions, drug treatment, organ transplants, or HIV infection) have a much higher chance of developing lymphoma than people without an immune deficiency.
- People with certain autoimmune diseases (where the immune system constantly attacks a certain part of the body) have an increased risk of getting lymphoma.
- People with certain chronic infections are also at increased risk, probably because the immune system is constantly making new lymphocytes to fight the infection, which increases the chances for mistakes in their DNA.

Can non-Hodgkin lymphoma be prevented?

Most people with non-Hodgkin lymphoma have no risk factors that can be changed, so there is no way to protect against these lymphomas. For now, the best way to reduce the risk for non-Hodgkin lymphoma is to try to prevent known risk factors such as immune deficiency.

Infection with the human immunodeficiency virus (HIV) is a preventable cause of immune deficiency. HIV is spread among adults mostly through unprotected sex and by injection drug users sharing contaminated needles. Blood transfusions are now an

extremely rare source of HIV infection. Curbing the spread of HIV would prevent many deaths from non-Hodgkin lymphoma. Treating HIV with anti-HIV drugs also lowers 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 in areas of the world where this virus is common, such as Japan and the Caribbean region. 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.

Helicobacter pylori infection has been linked to some lymphomas of the stomach. Treating *H. pylori* infections with antibiotics and antacids may lower this risk, 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. More research is needed to find the best way to detect and treat this infection in people without symptoms.

Another risk factor for non-Hodgkin lymphoma is infection with the Epstein-Barr virus (the cause of infectious mononucleosis, or mono), but there is no known way of preventing this infection.

Some lymphomas are caused by treatment of cancers with radiation and chemotherapy or by the use of immune-suppressing drugs to avoid rejection of transplanted organs. Doctors are trying to find better ways to treat cancer and organ transplant patients without increasing the risk of lymphoma as much. But for now, the benefits of these treatments still usually outweigh the small risk of developing lymphoma many years later.

Some studies have suggested that being overweight or obese may increase your risk of non-Hodgkin lymphoma. Other studies have suggested that a diet high in fat and meats may raise your risk. Maintaining a healthy weight and eating a healthy diet may help protect against lymphoma, although more research is needed to confirm this.

Can non-Hodgkin lymphoma be found early?

At this time, there are no widely recommended screening tests for this cancer. (Screening is testing for cancer in people without any symptoms.) Still, in some cases lymphoma can be found early.

The best way to find this cancer early is prompt attention to the signs and symptoms of this disease, which are discussed in the section, "How is non-Hodgkin lymphoma diagnosed?"

Careful, regular medical checkups are important for people with known risk factors for non-Hodgkin lymphoma (such as HIV infections, organ transplants, autoimmune disease, or prior cancer treatment). These people do not commonly develop lymphoma, but they and their doctors should be aware of possible symptoms and signs of lymphoma.

How is non-Hodgkin lymphoma diagnosed?

Most people with non-Hodgkin lymphoma see their doctor because they have felt a lump that hasn't gone away, they develop some of the other symptoms listed below, or they just don't feel well and go in for a checkup.

If signs or symptoms suggest that a person may have non-Hodgkin lymphoma, exams and tests are done to find out for certain if they do 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 where it is in the body. In some cases it may not cause any symptoms until it grows quite large. Common symptoms include:

- Enlarged lymph nodes
- Swollen abdomen (belly)
- Feeling full after only a small amount of food
- Chest pain or pressure
- Shortness of breath or cough
- Fever
- Weight loss
- Night sweats
- Fatigue

Swollen lymph nodes

Non-Hodgkin lymphoma can cause lymph nodes to become enlarged. When this occurs in 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), they may be seen or felt as lumps under the skin. These are often found by the patient, a family member, or a health care professional. Although enlarged lymph nodes are a common symptom of lymphoma, they are much more often caused by infections.

Lymphoma in the abdomen

Lymphomas in the abdomen may cause it to become swollen and tender. This may be because of lymph nodes in the abdomen enlarging, but can also be caused by the buildup of large amounts of fluid.

Lymphoma can cause the spleen to become enlarged and press on the stomach. This can cause a person to feel full after eating only a small amount of food.

When lymphoma is in the intestines or causes swelling near the intestines, bowel movements may be blocked, which may lead to abdominal pain, nausea, or vomiting. Lymphoma in the intestines can also cause holes to develop in the intestine wall (called *perforations*). This allows the contents of the intestines to leak out into the abdominal cavity, leading to serious infection and severe pain with nausea and vomiting.

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

Lymphoma in the chest

When lymphoma starts in the thymus or lymph nodes in the chest, it may press on the nearby trachea (windpipe), which can cause coughing or trouble breathing. Lymphomas in this area can also cause a feeling of chest pain or pressure.

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. Lymphomas in this area may push on the SVC, which can cause the blood to back up in the veins. This can lead to swelling (and sometimes a bluish-red color) in the head, arms, and upper chest. It can also cause trouble breathing and a change in consciousness if it affects the brain. This condition, known as *SVC syndrome*, can be life-threatening, and requires treatment right away.

Lymphoma affecting the brain

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

Other types of lymphoma can spread to the area around the brain and spinal cord. This can cause problems such as double vision, facial numbness, and trouble speaking.

Lymphoma in the skin

Lymphomas of the skin may be seen or felt. They often appear as extremely itchy, red or purple lumps or nodules under the skin. (For more details, see the separate document *Lymphoma of the Skin*.)

General symptoms

Along with causing symptoms and signs in the part of the body where it starts, non-Hodgkin lymphoma can also cause general symptoms, such as:

- Unexplained weight loss

- Fever
- Drenching night sweats (enough to soak clothing and sheets)

When talking about lymphoma, doctors call these *B symptoms*. The presence of B symptoms is often found in more rapidly growing lymphomas. These symptoms are important not only in helping diagnose non-Hodgkin lymphoma, but also in determining the stage and prognosis (outlook) if lymphoma is found (see "How is non-Hodgkin lymphoma staged?").

Other symptoms can be caused by low blood counts. Blood counts can become low when lymphoma spreads to the bone marrow and crowds out the normal, healthy cells that make new blood cells. This can lead to problems like:

- Severe or frequent infections (from low white blood cell counts)
- Easy bruising or bleeding (from low blood platelet counts)
- Fatigue (from low red blood cell counts [anemia])

Anemia can also occur if the lymphoma cells cause the body to destroy red blood cells (this is called *hemolytic anemia*).

Medical history and physical exam

If the symptoms suggest you might have non-Hodgkin lymphoma, your doctor will want to get a thorough medical history, including information about your symptoms, possible risk factors, family history, and other medical conditions.

Next, the doctor will examine you, paying special attention to the lymph nodes and other areas of the body that might be involved, including the spleen and liver. Because infections are the most common cause of enlarged lymph nodes, the doctor will look for an infection in the part of the body near the swollen lymph nodes.

If the doctor suspects that non-Hodgkin lymphoma might be causing the symptoms, he or she will recommend a biopsy of the area.

Biopsy

Many of the symptoms of non-Hodgkin lymphoma are not specific enough to say for certain if they are being caused by cancer. Most of these symptoms can also be caused by non-cancerous problems, like infections, or by other kinds of cancers.

For example, enlarged lymph nodes are more often caused by infections than by non-Hodgkin lymphoma. Because of this, doctors often prescribe antibiotics and wait a few weeks to see if the nodes shrink.

If the nodes stay the same or continue to grow, the doctor may then advise a biopsy. Either a small piece of a node or, more commonly, the entire node is removed for viewing under the microscope and for other lab tests.

A biopsy may be needed right away if the size, texture, or location of the node or the presence of other symptoms strongly suggests cancer. But a delay in diagnosis of a few weeks is not likely to be harmful unless it is a very rapidly growing lymphoma.

Types of biopsies used to diagnose non-Hodgkin lymphoma

A biopsy is the only way to diagnose non-Hodgkin lymphoma. There are several types of biopsies. Doctors choose which one to use based on the unique aspects of each person's situation.

Excisional or incisional biopsy: This is the most common type of biopsy if lymphoma is suspected. 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 often be done with local anesthesia (numbing medicine). But if the node is inside the chest or abdomen, the patient is sedated or given general anesthesia (where he or she is in a deep sleep).

This method almost always provides enough of a sample 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) or core needle biopsy: In an FNA biopsy, the doctor uses a very thin, hollow needle attached to a syringe to withdraw (aspirate) a small amount of tissue from an enlarged lymph node or a tumor mass. For a core needle biopsy, the doctor uses a larger needle to remove a slightly larger piece of tissue.

For an enlarged node near the surface of the body, the doctor can aim the needle while feeling the node. If the tumor is deep inside the body, the doctor can guide the needle using a computed tomography (CT) scan or ultrasound (see descriptions of imaging tests later in this section).

A needle biopsy does not require surgery, but in some cases it may not remove enough of a sample to make a definite diagnosis. Most doctors do not use needle biopsies to diagnose lymphoma. But if the doctor suspects that your lymph node swelling is caused by an infection or by the spread of cancer from another organ (such as the breast, lungs, or thyroid), a needle biopsy may be the first type of biopsy done. An excisional biopsy may still be needed to diagnose and classify lymphoma, even after a needle biopsy has been done.

Once lymphoma has been diagnosed, needle biopsies are sometimes used to check areas in other parts of the body that might be lymphoma spreading or coming back after treatment.

Other types of biopsies

These procedures are not normally done to diagnose lymphoma, but they may be done to help determine the stage (extent) of a lymphoma that has already been diagnosed.

Bone marrow aspiration and biopsy: These procedures are often done after lymphoma has been diagnosed to help determine if it has reached the bone marrow. The two tests are often done at the same time. The samples are usually taken from the back of the pelvic (hip) bone, although in some cases they may be taken from the sternum (breast bone) or other bones.

In bone marrow *aspiration*, you lie on a table (either on your side or on your belly). After cleaning the skin over the hip, the doctor numbs the area and the surface of the bone with local anesthetic, which may cause a brief stinging or burning sensation. A thin, hollow needle is then inserted into the bone and a syringe is used to suck out a small amount of liquid bone marrow (about 1 teaspoon). Even with the anesthetic, most patients still have some brief pain when the marrow is removed.

A bone marrow *biopsy* is usually done just after the aspiration. A small piece of bone and marrow is removed with a slightly larger needle that is twisted as it is pushed down into the bone. The biopsy may also cause some brief pain. Once the biopsy is done, pressure will be applied to the site to help stop any bleeding.

Lumbar puncture (spinal tap): This test looks for lymphoma cells in the cerebrospinal fluid (CSF), which is the liquid that bathes the brain and spinal cord.

For this test, the patient may lie on their side or sit up. The doctor first numbs an area in the lower part of the back over the spine. A small, hollow needle is then placed between the bones of the spine to withdraw some of the fluid.

Most people with lymphoma will not need this test. But doctors may order it for certain types of lymphoma or if a person has symptoms that suggest the lymphoma may have reached the brain.

Pleural or peritoneal fluid sampling: Spread of lymphoma to the chest or abdomen can cause fluid to build up. Pleural fluid (inside the chest) or peritoneal fluid (inside the abdomen) can be removed by placing a hollow needle through the skin into the chest or abdomen. The doctor uses a local anesthetic to numb the skin before inserting the needle. The fluid is then withdrawn and looked at under the microscope to check for lymphoma cells. When this procedure is used to remove fluid from the area around the lung, it is called a *thoracentesis*. When it is used to collect fluid from inside the abdomen, it is known as a *paracentesis*.

Lab tests on biopsy samples to diagnose and classify lymphoma

All biopsy samples and fluids are looked at under a microscope by a pathologist (a doctor with special training in recognizing cancer cells), who studies the size and shape of the cells and how they are arranged. This may reveal not only if the person has a lymphoma, but also what type of lymphoma it is. Because diagnosing lymphoma can be tricky, it helps if the pathologist specializes in diseases of the blood.

Pathologists can sometimes tell which kind of lymphoma a patient has by looking at the cells, but usually other types of tests are needed to confirm the diagnosis.

Immunohistochemistry

In this test, a part of the biopsy sample is treated with special antibodies (man-made versions of immune system proteins) that attach only 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 lymphoma from one another and from other diseases.

Flow cytometry

Like immunohistochemistry, this test looks for certain substances on the outside surface of cells that help identify what types of cells they are. But this test can look at many more cells than immunohistochemistry.

For this test, a sample of cells is treated with special antibodies that stick to the cells only if certain substances are present on their surfaces. The cells are then passed in front of a laser beam. If the cells now have antibodies attached to them, the laser will cause them to give off light, which can be measured and analyzed by a computer. Groups of cells can be separated and counted by these methods.

This is the most commonly used test for *immunophenotyping* (classifying lymphoma cells according to the substances [antigens] on their surfaces). Different types of lymphocytes have different antigens on their surface. These antigens may also change as each cell matures.

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

Cytogenetics

This technique allows doctors to evaluate the chromosomes (long strands of DNA) in the lymphoma cells. The cells are looked at under a microscope 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. Some lymphoma cells may have too many chromosomes, too few chromosomes, or other chromosome abnormalities. These changes can help identify the type of lymphoma.

Cytogenetic testing usually takes about 2 to 3 weeks because the lymphoma cells must grow in lab dishes for a couple of weeks before their chromosomes are ready to be viewed under the microscope.

Molecular genetic tests

These tests look more closely at lymphoma cell DNA. They can detect most changes that are visible under a microscope in cytogenetic tests, as well as others that can't be seen.

Fluorescent in situ hybridization (FISH): FISH is similar to cytogenetic testing. It uses special fluorescent dyes that only attach to specific parts of chromosomes. FISH can find most chromosome changes (such as translocations) that can be seen under a microscope in standard cytogenetic tests, as well as some changes too small to be seen with usual cytogenetic testing.

FISH can be used to look for specific changes in chromosomes. It can be used on regular blood or bone marrow samples. It is very accurate and can usually provide results within a couple of days, which is why this test is now used in many medical centers.

Polymerase chain reaction (PCR): PCR is a very sensitive DNA test that can also find some chromosome changes too small to be seen under a microscope, even if very few lymphoma cells are present in a sample.

These tests can also detect certain genes that have been "turned on" and are contributing to the lymphoma cells' abnormal growth. As researchers learn more about lymphomas, these may become even more important.

Blood tests

Blood tests measure the amounts of certain types of cells and chemicals in the blood. They are not used to diagnose lymphoma, but they can sometimes help determine how advanced the lymphoma is.

In patients already known to have lymphoma, low blood cell counts can mean that the lymphoma is growing in the bone marrow and affecting new blood cell formation. Results of another blood test that measures levels of lactate dehydrogenase (LDH) will often be abnormally high in the blood of patients with fast-growing lymphomas.

Other blood tests can help detect liver or kidney problems caused by the spread of lymphoma or that are the side effects of certain chemotherapy drugs. Blood tests can also help determine if treatment is needed to correct low or high blood levels of certain minerals. Tests may also be done to make sure blood is clotting properly.

For some types of lymphoma, your doctor may also advise other blood tests to see if you have been infected with certain viruses, such as the hepatitis B virus (HBV), hepatitis C virus (HCV), or human immunodeficiency virus (HIV). Infections with these viruses may affect your treatment.

Imaging tests

Imaging tests use x-rays, sound waves, magnetic fields, or radioactive particles to produce pictures of the inside of the body. These tests may be done for a number of

reasons, including to help find a suspicious area that might be cancerous, to learn how far a cancer may have spread, and to help determine if treatment has been effective.

Chest x-ray

X-rays of the chest may be done to look for enlarged lymph nodes in this area.

Computed tomography (CT) scan

The CT scan is an x-ray test that produces detailed, cross-sectional images of your body. Unlike a regular x-ray, CT scans can show the detail in soft tissues (such as internal organs). This scan can help tell if any lymph nodes or organs in your body are enlarged.

CT scans are useful for looking for lymphoma in the abdomen, pelvis, chest, head, and neck.

Instead of taking one picture, as does a regular x-ray, a CT scanner takes many pictures as it rotates around you. A computer then combines these pictures into detailed images of the part of your body that is being studied.

Before the scan, you may be asked to drink a contrast solution and/or get an intravenous (IV) injection of a contrast dye that helps better outline abnormal areas in the body. You may need an IV line through which the contrast dye is injected. The injection can cause some flushing (a feeling of warmth, especially in the face). Some people are allergic and get hives or, rarely, more serious reactions like trouble breathing and low blood pressure. Be sure to tell the doctor if you have any allergies or have ever had a reaction to any contrast material used for x-rays.

CT scans take longer than regular x-rays. You need to lie still on a table while they are being done. During the test, the table slides in and out of the scanner, a ring-shaped machine that completely surrounds the table. You might feel a bit confined by the ring you have to lay in when the pictures are being taken. Many medical centers now use *spiral CT* (also known as helical CT), which completes the scan more quickly and also yields more detailed pictures.

In some cases, CT can be used to guide a biopsy needle into a suspicious area. For this procedure, called a *CT-guided needle biopsy*, you remain on the CT scanning table while a radiologist moves a biopsy needle through the skin and toward the location of the mass. CT scans are repeated until the needle is within the mass. A biopsy sample is then removed to be looked at under a microscope.

Magnetic resonance imaging (MRI) scan

This test is not used as often as CT scans for lymphoma, but if your doctor is concerned about spread to the spinal cord or brain, MRI is very useful for looking at these areas.

Like CT scans, MRI scans provide detailed images of soft tissues in the body. But MRI scans use radio waves and strong magnets instead of x-rays. The energy from the radio

waves is absorbed by the body and then released in a pattern formed by the type of body tissue and by certain diseases. A computer translates the pattern into a very detailed image of parts of the body.

A contrast material called gadolinium may be injected into a vein before the scan to better see details. This material does not often cause allergic reactions, but be sure to let the doctor know if you have had a problem with it in the past. This material should be used with caution (if at all) in people on dialysis (for kidney failure).

MRI scans take longer than CT scans – often up to an hour. You may have to lie inside a narrow tube, which is confining and can be distressing to some people. Newer, more open MRI machines may be another option. The MRI machine makes loud buzzing and clicking noises that you may find disturbing. Some places provide headphones or earplugs to help block this noise out.

Ultrasound

Ultrasound uses sound waves and their echoes to produce a picture of internal organs or masses. For this test, a small, microphone-like instrument called a transducer is placed on the skin (which is first lubricated with a gel). It emits sound waves and picks up the echoes as they bounce off the organs. The echoes are converted by a computer into a black and white image that is displayed on a computer screen.

Ultrasound can be used to look at lymph nodes near the surface of the body or to look inside your abdomen for enlarged lymph nodes or organs such as the liver and spleen. It can also detect kidneys that have become swollen because the outflow of urine has been blocked by enlarged lymph nodes. (It can't be used to look at organs or lymph nodes in the chest because the ribs block the sound waves.)

This is an easy test to have done, and it uses no radiation. For most ultrasounds, you simply lie on a table, and a technician moves the transducer over the part of your body being looked at.

Positron emission tomography (PET) scan

For a PET scan, a form of radioactive sugar (known as fluorodeoxyglucose or FDG) is injected into the blood. Because cancer cells in the body grow rapidly, they absorb large amounts of the radioactive sugar. After about an hour, you will be moved onto a table in the PET scanner. You lie on the table for about 30 minutes while a special camera creates a picture of areas of radioactivity in the body. The picture is not finely detailed like a CT or MRI scan, but it can provide helpful information about your whole body.

PET scans can help tell if an enlarged lymph node contains lymphoma or is benign. It can also help spot small areas that might be lymphoma, even if the area looks normal on a CT scan.

PET scans can be used to tell if a lymphoma is responding to treatment. Some doctors will repeat the PET scan after 1 or 2 courses of chemotherapy. If the chemotherapy is

working, the lymph nodes will no longer take up the radioactive sugar. PET scans can also be used after treatment in helping decide whether an enlarged lymph node still contains lymphoma or is merely scar tissue.

Often, for patients with lymphoma, a machine that combines the PET scan with a CT scan (PET/CT scan) is used. This allows the doctor to compare areas of higher radioactivity on the PET scan with the more detailed appearance of that area on the CT.

Gallium scan

For this test, a solution containing slightly radioactive gallium is injected into a vein. It is attracted to lymph tissue in the body. A few days later a special camera is used to detect the radioactivity, showing the location of the gallium. The gallium scan will not detect most slow-growing lymphomas but will find many fast-growing (aggressive) lymphomas.

This test is not used as much now as in the past, as many doctors may do a PET scan instead. It can still sometimes be useful in finding areas of lymphoma that the PET scan may miss. It can also help distinguish an infection from a lymphoma when the diagnosis is not clear.

Bone scan

For bone scans, a radioactive substance called technetium is used. After it is injected into a vein, it travels to damaged areas of the bone. Lymphoma often causes bone damage, and a bone scan will find it. But a bone scan may also pick up non-cancerous problems, such as arthritis and fractures.

This test is not usually done unless a person is having bone pain or has lab test results that suggest the lymphoma may have reached the bones.

Tests of heart and lung function

These tests are not used to help diagnose non-Hodgkin lymphoma, but they may be done if you are going to get certain chemotherapy drugs commonly used to treat lymphoma that may affect the heart or the lungs.

- Your heart function may be checked with an echocardiogram (an ultrasound of the heart) or a MUGA scan.
- Your lung function may be checked with pulmonary function tests, in which you breathe into a tube connected to a machine.

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 (outlook) for a patient with non-Hodgkin lymphoma depend on both the exact type and the stage of the lymphoma.

Tests used to gather information for staging include:

- Physical exam
- Biopsies of enlarged lymph nodes or other abnormal areas
- Blood tests
- Imaging tests, such as CT scans
- Bone marrow aspiration and biopsy (often but not always done)
- Lumbar puncture (spinal tap – this may not need to be done)

These tests are described in the section, "How is non-Hodgkin lymphoma diagnosed?"

Ann Arbor staging system

A staging system is a way for members of the cancer care team to summarize the extent of a cancer's spread. The staging system most often used to describe the extent of non-Hodgkin lymphoma in adults is called the Ann Arbor staging system.

The stages are described by Roman numerals I through IV (1-4). Lymphomas that affect an organ outside of the lymph system (an extranodal organ) have E added to their stage (for example, stage IIE), while those affecting the spleen have an S added.

Stage I

Either of the following means the disease is stage I:

- The lymphoma is in only 1 lymph node area or lymphoid organ such as the thymus (I).
- 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 stage II:

- The lymphoma is in 2 or more groups of lymph nodes on the same side of (above or below) the diaphragm (the thin band of muscle that 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 (II).
- The lymphoma extends from a single group of lymph node(s) into a nearby organ (IIE). It may also affect other groups of lymph nodes on the same side of the diaphragm.

Stage III

Either of the following means the disease is stage III:

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

Stage IV

Either of the following means the disease is stage IV:

- The lymphoma has spread outside of the lymph system into an organ that is not right next to an involved node.
- The lymphoma has spread to the bone marrow, liver, brain or spinal cord, or the pleura (thin lining of the lungs).

Other modifiers may also be used to describe the lymphoma stage:

Bulky disease

This term is used to describe tumors in the chest that are at least one-third as wide as the chest, or tumors in other areas that are at least 10 centimeters (about 4 inches) across. It is usually designated by adding the letter X to the stage. Bulky disease may require more intensive treatment.

A vs. B

Each stage may also be assigned an A or B. The letter B is added (stage IIIB, for example) if a person has any of the B symptoms listed below:

- Loss of more than 10% of body weight over the previous 6 months (without dieting)
- Unexplained fever of at least 101.5°F
- Drenching night sweats

These symptoms usually mean the disease is more advanced. If a person has any of these, then more intensive treatment is usually recommended. If no B symptoms are present, the letter A is added to the stage.

Small lymphocytic lymphoma (SLL) /chronic lymphocytic leukemia (CLL)

The Ann Arbor system is most often used to stage this lymphoma if it is only in lymph nodes. But if the disease is affecting the blood or bone marrow, it is often staged using

the systems for CLL. These systems are described in our document on CLL, in the section, "How is chronic lymphocytic leukemia staged?"

Factors that affect prognosis (outlook) for non-Hodgkin lymphoma

The type and stage of the lymphoma provide useful information about a person's prognosis (outlook), but for some types of lymphomas the stage is not too helpful on its own. In these cases, other factors can give doctors a better idea about a person's prognosis.

International Prognostic Index

The International Prognostic Index (IPI) was first developed to help doctors determine the outlook for people with fast-growing lymphomas. However, it has proven useful for most other lymphomas as well (other than slow-growing follicular lymphomas, which are discussed below). The index depends on 5 factors:

- The patient's age
- The stage of the lymphoma
- Whether or not it is in organs outside the lymph system
- Performance status (PS) – how well a person can complete normal daily activities
- The blood (serum) level of lactate dehydrogenase (LDH), which goes up with the amount of lymphoma in the body

Good prognostic factors

Age 60 or below

Stage I or II

No lymphoma outside of lymph nodes, or lymphoma in only 1 area outside of lymph nodes

PS: Able to function normally

Serum LDH is normal

Poor prognostic factors

Age above 60

Stage III or IV

Lymphoma is in more than 1 organ of the body outside of lymph nodes

PS: Needs a lot of help with daily activities

Serum LDH is high

Each poor prognostic factor is assigned 1 point. People with no poor prognostic factors would have a score of 0, while those with all of the poor prognostic factors would have a score of 5. The index divides people with lymphomas into 4 risk groups:

- Low (0 or 1 poor prognostic factors)

- Low intermediate (2 poor prognostic factors)
- High intermediate (3 poor prognostic factors)
- High (4 or 5 poor prognostic factors)

In the studies used to develop the index, about 75% of people in the lowest risk group lived at least 5 years, whereas only about 30% of people in the highest risk group lived at least 5 years. These numbers show the difference the index scores can make, but the IPI was devised in the early 1990s. Newer treatments have been developed since then, so current survival rates are likely to be higher.

Revised International Prognostic Index

A more recent version of the IPI is based on people with fast-growing lymphomas who have received more modern treatment, including a newer drug called rituximab (Rituxan), which is described in the "Immunotherapy" section. The revised IPI uses the same factors but divides patients into only 3 risk groups:

- Very good (no poor prognostic factors)
- Good (1 or 2 poor prognostic factors)
- Poor (3 or more poor prognostic factors)

In the study used to develop this index, about 95% of people in the very good risk group lived at least 4 years, whereas only about 55% of people in the poor risk group lived at least 4 years.

The IPI allows doctors to plan treatment better than they could just based on the type and stage of the lymphoma. This has become more important as new, more effective treatments have been developed that sometimes have more side effects. The index helps doctors figure out whether these treatments are needed.

Follicular Lymphoma International Prognostic Index

The IPI is useful for most lymphomas, but it is not as helpful for follicular lymphomas, which tend to be slower growing. Doctors have developed the Follicular Lymphoma International Prognostic Index (FLIPI) specifically for this type of lymphoma. It uses slightly different prognostic factors than the IPI.

Good prognostic factors	Poor prognostic factors
Age 60 or below	Age above 60
Stage I or II	Stage III or IV
Blood hemoglobin 12 g/dL or above	Blood hemoglobin level below 12 g/dL
4 or fewer lymph node areas affected	More than 4 lymph node areas affected

Serum LDH is normal	Serum LDH is high
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Patients are assigned a point for each poor prognostic factor. People without any poor prognostic factors would have a score of 0, while those with all poor prognostic factors would have a score of 5. The index then divides people with follicular lymphoma into 3 groups:

- Low risk: no or 1 poor prognostic factor(s)
- Intermediate risk: 2 poor prognostic factors
- High risk: 3 or more poor prognostic factors

The study used to develop the FLIPI produced the following survival rates:

Risk group	5-year survival rate	10-year survival rate
Low-risk	91%	71%
Intermediate-risk	78%	51%
High-risk	53%	36%

These rates reflect the number of people who lived for *at least* 5 or 10 years after being diagnosed – many people lived longer than this. The rates were based on people diagnosed with follicular lymphoma in the 1980s and 1990s. Newer treatments have been developed since then, so current survival rates are likely to be higher.

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 studies published in medical journals, as well as their own professional experience.

The treatment information in this document is not official policy of the Society and is not intended as medical advice to replace the expertise and judgment of your cancer care team. It is intended to help you and your family make informed decisions, together with your doctor.

Your doctor may have reasons for suggesting a treatment plan different from these general treatment options. Don't hesitate to ask him or her questions about your treatment options.

General treatment information

Once non-Hodgkin lymphoma has been diagnosed and staged, your cancer care team will discuss treatment options with you. Several different types of treatment can be used against non-Hodgkin lymphoma. The treatment options depend on the type of lymphoma

and its stage (extent), as well as the other prognostic factors. Of course, no 2 patients are exactly alike, and standard options are often tailored to each patient's situation.

Based on your treatment options, you may have different types of doctors on your treatment team. These doctors may include:

- A hematologist: a doctor who treats disorders of the blood, including lymphomas.
- A medical oncologist: a doctor who treats cancer with medicines.
- A radiation oncologist: a doctor who treats cancer with radiation therapy.

Many other specialists may be involved in your care as well, including nurse practitioners, nurses, nutrition specialists, social workers, and other health professionals.

It is important to discuss all of your treatment options as well as their possible side effects with your doctors to help make the decision that best fits your needs. In choosing a treatment plan, consider your health and the type and stage of the lymphoma. Be sure that you understand all the risks and side effects of the various treatments before making a decision.

If time permits, it is often a good idea to seek a second opinion. Getting a second opinion can give you more information and help you feel confident about the treatment plan that you choose. Your doctor should be willing to help you find another cancer doctor who can give you a second opinion.

The next few sections describe the types of treatment used for non-Hodgkin lymphoma. This is followed by a discussion of the typical treatment options based on the type of lymphoma, as well as the stage and other prognostic factors when these are important.

Surgery for non-Hodgkin lymphoma

Surgery is often used to obtain a biopsy sample to diagnose and classify a lymphoma, but it is rarely used as a form of treatment.

In rare cases surgery may be used to treat lymphomas that start in the spleen or in certain organs outside of the lymph system, such as the thyroid or stomach, and that have not spread beyond these organs. But for treating lymphoma that is completely confined to one area, radiation therapy is usually preferred over surgery.

Radiation therapy for non-Hodgkin lymphoma

Radiation therapy uses high-energy rays to kill cancer cells.

When radiation is used to treat non-Hodgkin lymphoma, it is most often done with a carefully focused beam of radiation, delivered from a machine outside the body. This is known as *external beam radiation*. The treatment is much like getting an x-ray, but the radiation is more intense. The procedure itself is painless. Before the treatments start, the radiation team takes careful measurements to determine the correct angles for aiming the radiation beams and the proper dose. Each treatment lasts only a few minutes, although

the setup time – getting you into place for treatment – usually takes longer. Most often, radiation treatments are given 5 days a week for several weeks.

Radiation can also be given in the form of a drug in some cases (see the section, "Immunotherapy" for more details).

Radiation might be used as the main treatment for some types of lymphoma if they are found early (stage I or II), because these tumors respond very well to radiation. For more advanced lymphomas and for some lymphomas that are more aggressive, radiation is sometimes used along with chemotherapy.

People who are getting a stem cell transplant may get radiation to the whole body along with high-dose chemotherapy, to try to kill lymphoma cells throughout the body. For more information, see the section, "High-dose chemotherapy and stem cell transplant."

Radiation therapy can also be used to ease (palliate) symptoms caused by lymphoma that has spread to internal organs, such as the brain or spinal cord, or when a tumor is causing pain because it is pressing on nerves.

Possible side effects

The side effects of radiation therapy depend on where the radiation is aimed. Some people have skin changes similar to sunburn, which slowly fades away. Other possible short-term side effects include fatigue, dry mouth, nausea, or diarrhea. Radiation given to several areas, especially after chemotherapy, can lower blood cell counts.

Radiation of the abdomen may cause nausea, vomiting, or diarrhea. Radiation to the head and neck area can lead to mouth sores and trouble swallowing. Often these effects go away a short while after treatment is finished.

Possible long-term side effects of radiation therapy can be more serious.

- Chest radiation therapy may cause lung damage and lead to trouble breathing. It can also affect the heart, making you more likely to have a heart attack later on.
- Radiation to the neck can lead to thyroid problems later in life. This can lead to fatigue and weight gain. Treatment with pills containing thyroid hormone can help with this. Radiation to the neck may also increase the risk of stroke many years later.
- Side effects of brain radiation therapy usually become most serious 1 or 2 years after treatment and may include headaches and problems such as memory loss, personality changes, and trouble concentrating.
- Other types of cancer can form in the area that received radiation. For example, radiation to the chest may increase the risk of lung cancer (especially in smokers) and of breast cancer. This happens rarely.

Radiation may also make the side effects of chemotherapy worse.

Chemotherapy for non-Hodgkin lymphoma

Chemotherapy (chemo) is the use of anti-cancer drugs that are usually injected into a vein or taken by mouth. These drugs enter the bloodstream and reach almost all areas of the body, making this treatment very useful for lymphoma. In some cases where the lymphoma may have reached the brain or spinal cord, chemotherapy may also be given into the cerebrospinal fluid. This is called *intrathecal* chemo.

Depending on the type and the stage of the lymphoma, chemotherapy may be used alone or combined with radiation therapy.

Doctors give chemo in cycles, in which a period of treatment is followed by a rest period to allow the body time to recover. Each chemo cycle generally lasts for several weeks. Most chemo treatments are given on an outpatient basis (in the doctor's office or clinic or hospital outpatient department) but some may require a hospital stay.

Many chemo drugs are useful in treating lymphoma patients. Often, several drugs are combined. The number of drugs, their doses, and the length of treatment depend on the type and stage of the lymphoma. Some of the drugs commonly used to treat lymphoma include:

- Cyclophosphamide (Cytosan[®])
- Vincristine (Oncovin[®])
- Doxorubicin (Adriamycin[®])
- Prednisone
- Fludarabine (Fludara[®])
- Cytarabine (ara-C)
- Chlorambucil
- Mitoxantrone
- Methotrexate
- Etoposide (VP-16)
- Dexamethasone (Decadron[®])
- Cisplatin
- Carboplatin
- Ifosfamide (Ifos[®])
- Bleomycin
- Bendamustine (Treanda[®])
- Gemcitabine
- Pralatrexate (Folotyn[®])

One of the most common combination of drugs is called CHOP. This includes the drugs cyclophosphamide, doxorubicin (which has a chemical name beginning with H), vincristine (Oncovin) and prednisone. Another common combination leaves out doxorubicin and is called CVP.

Sometimes a patient may get one chemo combination for several cycles and later switch to a different one if the first combination doesn't seem to be working.

Possible side effects

Chemo drugs attack cells that are dividing quickly, which is why they work against lymphoma cells. But other cells in the body, such as those in the bone marrow, the lining of the mouth and intestines, and the hair follicles, also divide quickly. These cells are also likely to be affected by chemotherapy, which can lead to certain side effects.

The side effects of chemo depend on the type and dose of drugs given and the length of time they are taken. These side effects can include:

- Hair loss
- Mouth sores
- Loss of appetite
- Nausea and vomiting
- Diarrhea
- Increased chance of infections (from low white blood cell counts)
- Easy bruising or bleeding (from low blood platelet counts)
- Fatigue (from low red blood cell counts)

These side effects are usually short-term and go away after treatment is finished. If serious side effects occur, the chemotherapy may have to be reduced or delayed.

There are often ways to lessen these side effects. For example, drugs are usually given to help prevent or reduce nausea and vomiting.

Infections can be very serious in people getting chemo. Drugs known as growth factors (G-CSF or GM-CSF, for example) are sometimes given to help the white blood cells recover from the effects of chemo and thus reduce the chance of infection. Antibiotics may also be given at the earliest sign of an infection, such as a fever.

If your white blood cell counts are very low during treatment, you can help reduce your risk of infection by carefully limiting your exposure to germs. During this time, your doctor may advise you to:

- Wash your hands often.
- Avoid fresh, uncooked fruits and vegetables and other foods that might carry germs.
- Avoid fresh flowers and plants because they may carry mold.
- Make sure other people wash their hands before they touch you.
- Avoid large crowds and people who are sick (wearing a surgical mask offers some protection in these situations).

If your platelet counts are very low, you may be given drugs or platelet transfusions to help protect against bleeding. Fatigue caused by anemia (very low red blood cell counts) can be treated with drugs or with red blood cell transfusions.

Certain drugs have specific possible side effects. For example, drugs such as doxorubicin can damage the heart. Your doctor may order a test of heart function (like a MUGA scan or echocardiogram) before starting you on one of these drugs. Bleomycin can damage lungs. Doctors often test lung function before starting someone on this drug.

Other drugs can sometimes damage the kidneys, liver, testicles, ovaries, brain, or nerves in the hands or feet. Your doctor or nurse can tell you about the possible side effects of specific drugs you may be getting.

If serious side effects occur, chemotherapy may have to be reduced or stopped, at least for a short time. Careful monitoring and adjustment of drug doses are important because some side effects can be permanent.

Chemotherapy can also cause side effects that might not occur until years after treatment. For example, in rare cases, people may develop leukemia several years later.

Tumor lysis syndrome is a possible side effect of chemo in patients who had large numbers of lymphoma cells in the body before treatment. It occurs most often with the first cycle of chemo. When the cells are killed, they break open and release their contents into the bloodstream. This can overwhelm the kidneys, which cannot get rid of all of these substances at once. This can lead to the buildup of excess amounts of certain minerals in the blood and even kidney failure. The excess minerals can lead to problems with the heart and nervous system. Doctors work to prevent these problems by giving the patient extra fluids and certain drugs, such as sodium bicarbonate, allopurinol, and rasburicase.

Other drugs used to treat lymphoma

As researchers have learned more about the changes in cells that cause cancer, they have been able to develop newer drugs that specifically target these changes. These drugs are often referred to as *targeted therapy*. These drugs work differently from standard chemotherapy drugs and often have different (and less severe) side effects.

Bortezomib (Velcade[®]) is a type of drug known as a proteasome inhibitor. It is most often used to treat other cancers of lymphocytes. But it can also be used to treat some lymphomas, usually after other treatments have been tried. Bortezomib is given as an infusion into a vein (IV) or an injection under the skin (sub-Q), typically twice a week for 2 weeks, followed by a rest period. Side effects can be similar to those of standard chemo drugs, including low blood counts, nausea, loss of appetite, and nerve damage.

Romidepsin (Istodax[®]) is in a class of drugs called histone deacetylase (HDAC) inhibitors. It is used to treat some T-cell lymphomas, usually after at least one other treatment has been tried. This drug is given as an IV infusion, usually once a week. Side effects tend to be mild, but can include lowered blood cell counts and effects on the rhythm of the heart.

Immunotherapy for non-Hodgkin lymphoma

Immunotherapy is treatment that either boosts the patient's own immune system or uses man-made versions of the normal parts of the immune system. These treatments may kill lymphoma cells or slow their growth.

Monoclonal antibodies

Antibodies are proteins made by the body's immune system to help fight infections. Man-made versions, called monoclonal antibodies, can be designed to attack a specific target, such as a substance on the surface of lymphocytes (the cells in which lymphomas start).

Several monoclonal antibodies are now being used to treat lymphoma.

Rituximab (Rituxan[®]): This is an antibody that attaches to a substance called CD20 found on some types of lymphoma cells. This attachment seems to cause the lymphoma cell to die. The treatments are given as intravenous (IV) infusions in the doctor's office or clinic.

When it is used by itself to treat lymphoma, it is given weekly for 4 to 8 weeks. When it is combined with chemotherapy, it is most often given on the first day of each chemo cycle. For some lymphomas, it may be given after chemo as *maintenance* therapy. In that case it is given weekly for 4 weeks in a row, every 6 months for up to 2 years.

Common side effects are usually mild but may include chills, fever, nausea, rashes, fatigue, and headaches. Rarely, more severe side effects occur during infusions, such as trouble breathing and low blood pressure. Even if these symptoms occur during the first rituximab infusion, it is very unusual for them to recur with later doses. This drug may also increase a person's risk of certain infections for up to 6 months after the drug is stopped.

Rituximab can cause hepatitis B infections that were dormant (inactive) to become active again, sometimes leading to severe liver problems or even death. For that reason, your doctor may check your blood for signs of an old hepatitis infection before starting this drug.

Ibritumomab (Zevalin[®]) and tositumomab (Bexxar[®]): These drugs are monoclonal antibodies aimed at CD20 (like rituximab) that have radioactive molecules attached to them. The antibodies bring radiation directly to the lymphoma cells, which may help them work better. These drugs are given as intravenous (IV) infusions. Side effects are similar to those seen with rituximab, although low blood cell counts are seen more often with these drugs.

These drugs are not used as often as rituximab, in part because they are somewhat harder for doctors to give (because of the radiation dosing involved). They cannot be used with chemotherapy because they also lower blood counts, which may raise the risk of infections, bleeding, or other problems. At this time these drugs are most often used if chemotherapy and/or rituximab are no longer working.

Alemtuzumab (Campath®): This antibody is directed at the CD52 antigen. It is useful in some cases of chronic lymphocytic leukemia (CLL) and also some types of peripheral T-cell lymphomas. It is given by infusion into a vein (IV), usually 3 times a week for up to 12 weeks. The most common side effects are fever, chills, nausea, and rashes. It can also cause very low white blood cell counts, which increases the risk for serious infections. Antibiotic and antiviral medicines are given to help protect against them, but severe and even life-threatening infections can still occur.

Ofatumumab (Arzerra®): Ofatumumab is another antibody that targets the CD20 antigen. It is approved to treat chronic lymphocytic leukemia and is used mainly when other treatments such as chemotherapy, rituximab, and alemtuzumab are no longer working. It is being studied for use in treating other lymphomas. Side effects are similar to those that are seen with rituximab.

Brentuximab vedotin (Adcetris™): This drug is an anti-CD30 antibody attached to a chemotherapy drug. Some lymphoma cells have the CD30 molecule on their surface. The antibody acts like a homing signal, bringing the chemo drug to the lymphoma cells, where it enters the cells and causes them to die when they try to divide into new cells.

Brentuximab can be used to treat anaplastic large cell lymphoma (ALCL) that has come back after other treatments. It is given as an infusion into a vein (IV) every 3 weeks. Common side effects include nerve damage (neuropathy), low blood counts, fatigue, fever, nausea and vomiting, infections, diarrhea, and cough.

Interferon

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

Common side effects of this treatment include fatigue, fever, chills, headaches, muscle and joint aches, and mood changes. Because of these side effects, interferon is not used very often. It may be given to some patients in addition to chemotherapy.

Immunomodulating agents

These drugs are thought to work against certain cancers by affecting parts of a person's immune system, although exactly how they work is not clear. They are sometimes used to help treat certain types of lymphoma, usually after other treatments have been tried.

Thalidomide (Thalomid®): The main use of this drug is to treat another cancer of the lymphocytes known as multiple myeloma, but it may also be used to treat some types of lymphoma.

Side effects of thalidomide include drowsiness, fatigue, severe constipation, low white blood cell counts (with an increased risk of infection), and neuropathy (painful nerve damage). The neuropathy can be severe, and may not go away after the drug is stopped. There is also an increased risk of serious blood clots (that start in the leg and can travel to

the lungs). Because thalidomide causes severe birth defects if taken during pregnancy, this drug should not be used by women who are or may become pregnant.

Lenalidomide (Revlimid®): This is a newer drug that is similar to thalidomide. It may be used to treat some types of lymphoma.

The most common side effects of lenalidomide are low platelet counts (with an increased risk of bleeding) and low white blood cell counts (with an increased risk of infection). It can also cause painful nerve damage. The risk of blood clots is not as high as that seen with thalidomide, but it is still increased. Like thalidomide, access to lenalidomide is tightly controlled out of concern about possible serious birth defects.

High-dose chemotherapy and stem cell transplant for non-Hodgkin lymphoma

Stem cell transplants are sometimes used to treat lymphoma patients who are in remission or who have a relapse during or after treatment. Although only a small number of patients with lymphoma are treated with this therapy, this number is growing.

Stem cell transplants allow doctors to use higher doses of chemotherapy (and sometimes radiation) than would normally be tolerated. High-dose chemotherapy destroys the bone marrow, which prevents new blood cells from being formed. This could lead to life-threatening infections, bleeding, and other problems due to low blood cell counts.

Doctors try to get around this problem by giving an infusion of blood-forming stem cells after the high-dose treatment. Stem cells are very primitive cells that can create new blood cells.

Blood-forming stem cells used for a stem cell transplant can come from:

- The blood (for a peripheral blood stem cell transplant, or PBSCT)
- The bone marrow (for a bone marrow transplant, or BMT)
- Umbilical cord blood (for a cord blood transplant)

Most stem cell transplants are now PBSCTs.

Types of transplants

There are 2 main types of stem cell transplants. The blood-forming stem cells come from different sources.

Autologous stem cell transplant

In an autologous stem cell transplant, the patient's own stem cells are removed from his or her bone marrow or peripheral blood. They are collected on several occasions in the weeks before treatment. The cells are frozen and stored while the person gets treatment (high-dose chemotherapy and/or radiation) and are then reinfused into the patient's blood.

This is the most common type of transplant used to treat lymphoma, but it generally isn't an option if the lymphoma has spread to the bone marrow or blood. If that occurs, it may be hard to get a stem cell sample that is free of lymphoma cells. Even after purging (treating the stem cells in the lab to kill or remove lymphoma cells), it's possible to return some lymphoma cells with the stem cell transplant.

Allogeneic stem cell transplant

In an allogeneic stem cell transplant, the stem cells come from someone else. The donor's tissue type (also known as the HLA type) needs to match the patient's tissue type as closely as possible to help prevent the risk of major problems with the transplant. Usually this donor is a brother or sister if they have the same tissue type as the patient. If there are no siblings with a good match, the cells may come from an HLA-matched, unrelated donor – a stranger who has volunteered to donate their cells.

The stem cells for an allogeneic SCT are usually collected from a donor's bone marrow or peripheral (circulating) blood on several occasions. In some cases, the source of the stem cells may be blood collected from an umbilical cord attached to the placenta after a baby is born (which is rich in stem cells). Regardless of the source, the stem cells are then frozen and stored until they are needed for the transplant.

The use of allogeneic transplants is limited in treating lymphoma because they can have severe side effects that make them hard to tolerate, especially for patients who are older or who have other medical problems. It can also be hard to find a matched donor. About 1 out of 4 transplants for lymphoma is of this kind.

Non-myeloablative transplant (mini-transplant): This is a type of allogeneic transplant in which lower doses of chemotherapy and radiation are used than in a standard SCT. These lower doses do not completely destroy the cells in the bone marrow. When the donor stem cells are given, they enter the body and establish a new immune system, which sees the lymphoma cells as foreign and attacks them (a "graft-versus-lymphoma" effect).

Doctors have learned that if they use small doses of certain chemotherapy drugs and low doses of total body radiation, an allogeneic transplant can still sometimes work with less serious side effects.

This type of transplant may be an option for some patients who couldn't tolerate a regular allogeneic transplant because it is too toxic. In fact, a patient can receive a non-myeloablative transplant as an outpatient.

The major side effect is graft-versus-host disease, which can be serious (this is discussed later in this section).

Doctors aren't yet sure exactly how effective these types of transplants are for patients with lymphoma, but studies are now being done to find out.

The transplant procedure

The patient getting the stem cell transplant may be admitted to the stem cell transplant unit of the hospital or receive treatment as an outpatient depending on a number of factors.

If treated as an inpatient, the patient is usually admitted to the hospital on the day before the high-dose chemo begins. He or she will usually stay in the hospital until after the chemo and the stem cells have been given, and until the stem cells have started making new blood cells again (see below).

If this is done as an outpatient procedure, patients and their families must be able to spot complications that would require their doctor's attention. Unless they live close to the transplant center, they will be asked to stay in a nearby hotel.

Treatment starts with high-dose chemo and may include high-dose whole body radiation. The chemo and radiation treatments are meant to destroy any remaining cancer cells. They also kill the normal cells of the bone marrow and the immune system. Once treatment is complete, the new stem cells (autologous or allogeneic) are given through a vein (infused), just like a blood transfusion. The stem cells then migrate to the bone marrow.

In an allogeneic SCT, the person getting the transplant may be given drugs to keep the new immune system from attacking the body (known as *graft-versus-host disease*). For the next several weeks the patient will likely have very low blood cell counts, so they are given as much supportive therapy as needed. This may include antibiotics, red blood cell or platelet transfusions, other medicines, and help with nutrition.

Usually around 2 to 3 weeks after the stem cells have been infused, they begin making new white blood cells. This is later followed by the new platelet production and new red blood cell production. Because of the high risk of serious infections right after treatment, patients remain in protective isolation (where exposure to germs is kept to a minimum) until a measure of their white blood cells – the absolute neutrophil count (ANC) – rises above 500. They can usually leave the hospital when their ANC nears 1,000.

Patients then typically make regular visits to the outpatient transplant clinic for about 6 months, after which time their care is continued by their regular doctors. At this point, they may only come back to the clinic for regular exams or if they have symptoms that should be checked by their doctor.

Practical points

Bone marrow or peripheral blood SCT is a complex treatment that can cause life-threatening side effects. If the doctors think a patient might benefit from a transplant, it should be done at a hospital where the staff has experience with the procedure and with managing the recovery phase. Some stem cell transplant programs may not have experience in certain types of transplants, especially transplants from unrelated donors.

SCT is very expensive (often costing well over \$100,000) and often requires a long hospital stay. Autologous transplant is considered a standard treatment for lymphoma under certain conditions, so most medical insurance will cover the cost. Still, some insurance companies may view other types of SCT as an experimental treatment, and they may not pay for those procedures. Even if the transplant is covered by your insurance, your co-pays or other costs could easily amount to tens of thousands of dollars. Find out what your insurer will cover before deciding on a transplant so you will have an idea of what you might have to pay.

Possible side effects

Side effects from a stem cell transplant are generally divided into early and long-term effects.

Early or short-term effects: The early complications and side effects are basically the same as those caused by any other type of high-dose chemotherapy (see the "Chemotherapy" section of this document), and can be severe. They are caused by damage to the bone marrow and other quickly growing tissues of the body and can include:

- Low blood cell counts (with fatigue and increased risks of infection and bleeding)
- Nausea and vomiting
- Loss of appetite
- Diarrhea
- Mouth sores
- Hair loss

One of the most common and serious short-term effects is the increased risk for infection. Antibiotics are often given to try to keep this from happening. Other side effects, like low red blood cell and platelet counts, may require blood product transfusions or other treatments.

Long-term side effects: Some complications and side effects can persist for a long time or may not occur until months or years after the transplant. These include:

- Graft-versus-host disease (GVHD), which occurs only in allogeneic transplants (see below)
- Infertility and premature menopausal symptoms in female patients (caused by damage to the ovaries)
- 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)

- Damage to the lungs, causing shortness of breath
- Bone damage called aseptic necrosis (if damage is severe, the patient may need to have part of the affected bone and the joint replaced)
- Possible development of leukemia several years later

Graft-versus-host disease (GVHD): This is one of the most serious complications 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 may recognize the patient's own body tissues as foreign and may react against them.

Symptoms can include severe skin rashes, itching, mouth sores (which can affect eating), nausea, and severe diarrhea. Liver damage may cause yellowing of the skin and eyes (jaundice). The lungs may also be damaged. The patient may also become easily fatigued and develop muscle aches.

GVHD is often described as either acute or chronic, based on how soon after the transplant it begins. Sometimes GVHD can become disabling, and if it is severe enough, it can be life-threatening. Usually, immune-suppressing drugs can be used to help control GVHD, although they may have their own side effects.

On the positive side, the graft-versus-host disease also leads to "graft-versus-lymphoma" activity. Any lymphoma cells remaining after the chemotherapy and radiation therapy are often killed by donor immune cells since the lymphoma cells are seen as foreign by the donor's immune system as well. Mild graft-versus-host disease can be a good thing.

For more information on these procedures, see our document, *Stem Cell Transplant (Peripheral Blood, Bone Marrow, and Cord Blood Transplants)*.

Clinical trials for non-Hodgkin lymphoma

You may have had to make a lot of decisions since you've been told you have cancer. One of the most important decisions you will make is choosing which treatment is best for you. You may have heard about clinical trials being done for your type of cancer. Or maybe someone on your health care team has mentioned a clinical trial to you.

Clinical trials are carefully controlled research studies that are done with patients who volunteer for them. They are done to get a closer look at promising new treatments or procedures.

If you would like to take part in a clinical trial, you should start by asking your doctor if your clinic or hospital conducts clinical trials. You can also call our clinical trials matching service for a list of clinical trials that meet your medical needs. You can reach this service at 1-800-303-5691 or on our Web site at www.cancer.org/clinicaltrials. You can also get a list of current clinical trials by calling the National Cancer Institute's Cancer Information Service toll-free at 1-800-4-CANCER (1-800-422-6237) or by visiting the NCI clinical trials Web site at www.cancer.gov/clinicaltrials.

There are requirements you must meet to take part in any clinical trial. If you do qualify for a clinical trial, it is up to you whether or not to enter (enroll in) it.

Clinical trials are one way to get state-of-the-art cancer treatment. Sometimes they may be the only way to get access to some newer treatments. They are also the only way for doctors to learn better methods to treat cancer. Still, they are not right for everyone.

You can get a lot more information on clinical trials in our document called *Clinical Trials: What You Need to Know*. You can read it on our Web site or call our toll-free number and have it sent to you.

Complementary and alternative therapies for non-Hodgkin lymphoma

When you have cancer you are likely to hear about ways to treat your cancer or relieve symptoms that your doctor hasn't mentioned. Everyone from friends and family to Internet groups and Web sites may offer ideas for what might help you. These methods can include vitamins, herbs, and special diets, or other methods such as acupuncture or massage, to name a few.

What exactly are complementary and alternative therapies?

Not everyone uses these terms the same way, and they are used to refer to many different methods, so it can be confusing. We use *complementary* to refer to treatments that are used *along with* your regular medical care. *Alternative* treatments are used *instead of* a doctor's medical treatment.

Complementary methods: Most complementary treatment methods are not offered as cures for cancer. Mainly, they are used to help you feel better. Some methods that are used along with regular treatment are meditation to reduce stress, acupuncture to help relieve pain, or peppermint tea to relieve nausea. Some complementary methods are known to help, while others have not been tested. Some have been proven not to be helpful, and a few have even been found harmful.

Alternative treatments: Alternative treatments may be offered as cancer cures. These treatments have not been proven safe and effective in clinical trials. Some of these methods may pose danger, or have life-threatening side effects. But the biggest danger in most cases is that you may lose the chance to be helped by standard medical treatment. Delays or interruptions in your medical treatments may give the cancer more time to grow and make it less likely that treatment will help.

Finding out more

It is easy to see why people with cancer think about alternative methods. You want to do all you can to fight the cancer, and the idea of a treatment with few or no side effects sounds great. Sometimes medical treatments like chemotherapy can be hard to take, or

they may no longer be working. But the truth is that most of these alternative methods have not been tested and proven to work in treating cancer.

As you consider your options, here are 3 important steps you can take:

- Look for "red flags" that suggest fraud. Does the method promise to cure all or most cancers? Are you told not to have regular medical treatments? Is the treatment a "secret" that requires you to visit certain providers or travel to another country?
- Talk to your doctor or nurse about any method you are thinking about using.
- Contact us at 1-800-227-2345 to learn more about complementary and alternative methods in general and to find out about the specific methods you are looking at.

The choice is yours

Decisions about how to treat or manage your cancer are always yours to make. If you want to use a non-standard treatment, learn all you can about the method and talk to your doctor about it. With good information and the support of your health care team, you may be able to safely use the methods that can help you while avoiding those that could be harmful.

Treating specific lymphomas

Treatment usually depends both on the type of lymphoma and on the extent of the disease in the body. Other factors may be important as well.

B-Cell lymphomas

Diffuse large B-cell lymphoma

In most cases, the treatment for diffuse large B-cell lymphoma (DLBCL) is chemotherapy, usually with a regimen of 4 drugs known as CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), plus the monoclonal antibody rituximab (Rituxan). This regimen, known as R-CHOP, is usually given for about 6 months.

If the lymphoma is stage I or II (that is, if it is localized to 1 or 2 lymph node groups on the same side of the diaphragm), radiation therapy to the lymph node areas may be added to treatment with R-CHOP. If radiation is given, then the treatment time with R-CHOP may be shortened to about 2 to 3 months. Sometimes if the lymphoma mass is large, radiation may be added after a full course of treatment (about 6 months) with R-CHOP.

For stage III or IV lymphomas, most doctors will give R-CHOP for about 6 months as first-line treatment, although some doctors may prefer to give other chemotherapy regimens. People with lymphoma in certain locations (such as the sinuses or testicles) are often given chemotherapy to the brain and spinal cord as well.

Some studies have suggested that for younger patients with a high International Prognostic Index (IPI) score, high-dose chemotherapy followed by an autologous stem

cell transplant may be better than chemotherapy alone. But it is not yet clear if transplants are better as the initial treatment. Most doctors feel that if a transplant is done as part of the first treatment, it should be done in a clinical trial.

If the lymphoma doesn't go away completely with treatment or if it recurs (comes back) after treatment, doctors will usually suggest another chemotherapy regimen. Several different regimens are being used, and they may or may not include rituximab. If the lymphoma shrinks with this treatment, a stem cell transplant is often suggested if possible, as it offers the best chance of curing the lymphoma. Stem cell transplants are not effective unless the lymphoma responds to chemotherapy. Unfortunately, not everyone is a good candidate for a stem cell transplant. Clinical trials of new treatments may be another good option for some people.

DLBCL can be cured in about half of all patients, but the stage of the disease and the IPI score can have a large effect on this. Patients with lower disease stages have better survival rates, as do patients with lower IPI scores.

Primary mediastinal B-cell lymphoma: This lymphoma is treated like a localized diffuse large B-cell lymphoma. The main treatment is usually about 6 courses of CHOP chemotherapy plus rituximab (R-CHOP). A PET/CT scan is typically done after the chemo to see if there is any tumor remaining in the chest. If no active lymphoma is seen on the PET/CT, the patient may be observed without further treatment. If the PET/CT scan is positive (shows possible active lymphoma), radiation may be needed. Often, the doctor will order a biopsy of the chest tumor to confirm that lymphoma is still present before starting radiation.

Follicular lymphoma

This type of lymphoma is often slow growing and responds well to treatment, but it is very hard to cure. It is common for this lymphoma to come back after treatment, although it can take years to do so. It is not always clear if treating the lymphoma right away is helpful. Because of this, some doctors recommend no treatment until the lymphoma has begun to cause problems other than mildly swollen lymph nodes. Some patients may never need treatment at all. In those that do, treatment is needed after an average of about 3 years.

If treatment is needed and the lymphoma is localized to 1 lymph node group or to 2 nearby groups on the same side of the diaphragm (stage I or early stage II), it can often be treated with only radiation therapy to the lymph node areas.

Regardless of the stage of the lymphoma, there are usually several treatment options. Many doctors will first try rituximab (Rituxan) combined with chemotherapy, using either a single chemo drug (such as bendamustine or fludarabine) or a combination of drugs, such as the CHOP or CVP regimens. Rituximab alone or chemotherapy alone (either one or several drugs) may also be used. Large areas of lymphoma may also be treated with radiation to reduce symptoms, even if it is not stage I or II.

The radioactive monoclonal antibodies, ibritumomab (Zevalin) and tositumomab (Bexxar) are also possible treatment options, although they are more often used as

second-line treatments than in newly-diagnosed patients. They are usually given alone, but in some cases chemotherapy may be given first.

For patients who may not be able to tolerate more intensive chemotherapy regimens, rituximab alone, milder chemotherapy drugs (such as chlorambucil or cyclophosphamide), or both may be good options.

If the lymphoma shrinks or goes away with the initial treatment, doctors may advise either close follow-up or further treatment. This might include either rituximab for up to 2 years or treatment with a radioactive antibody. Further treatment may lower the chance that the lymphoma will come back later and may help some patients live longer, but it can also have side effects.

If follicular lymphoma doesn't go away after initial treatment or if it comes back later, other treatment approaches such as using different chemo drugs, monoclonal antibodies, or some combination of these can be tried. If the lymphoma responds to this treatment, a stem cell transplant may be an option.

In some cases, follicular lymphoma can change (transform) into or return as a diffuse large B-cell lymphoma. When this happens, the treatment is the same as for this more aggressive disease.

Chronic lymphocytic leukemia/small lymphocytic lymphoma

Like follicular lymphoma, these types of lymphoma are often slow growing, but they are very hard to cure. The treatment of chronic lymphocytic leukemia (CLL) is described in detail our document, *Leukemia -- Chronic Lymphocytic*.

Treatment for both CLL and small lymphocytic lymphoma (SLL) is generally similar to that for follicular lymphoma. When the lymphoma is only in one lymph node or lymph node area (Ann Arbor stage I), it may be treated with radiation treatment alone. Often, disease that isn't causing any problems or growing quickly can be watched closely without treatment for a time. When treatment is needed, chemotherapy, with or without rituximab, is the usual first-line treatment. Treatment depends on the age and health of the patient, as well as on whether the cancer cells have certain chromosome changes.

Other monoclonal antibodies are most often used as second-line treatment if the disease doesn't respond or comes back after initial treatment.

Mantle cell lymphoma

This type of lymphoma is very hard to cure. It has often spread widely when it is first found, and although it doesn't usually grow as quickly as some fast-growing lymphomas, it often doesn't respond as well to treatment, either. Because current treatments for this type of lymphoma are very unlikely to cure it, patients might want to consider entering a clinical trial.

Early stage lymphomas (stages I or II), which are extremely rare, can sometimes be treated with radiation therapy. Otherwise, chemotherapy plus rituximab is the usual treatment. When possible, the chemo treatment is intense, using combinations of drugs

that may be changed during treatment. Less intense chemo regimens may be used for people who are older or who have other health issues. No specific regimen is clearly better than others, although there are reports that higher doses of chemo may be more effective. For those whose lymphoma responds well to initial treatment, a stem cell transplant may be a good option.

For mantle cell lymphomas that don't respond or that come back after initial treatment, chemo with drugs such as fludarabine, cladribine, or pentostatin may be used, sometimes along with other chemo drugs or with rituximab. Newer drugs such as bortezomib (Velcade) and lenalidomide (Revlimid) have also helped some patients who did not respond to other treatment. The exact role of these drugs in treating mantle cell lymphoma is still being worked out in clinical trials.

Extranodal marginal zone B-cell lymphoma – mucosa-associated lymphoid tissue (MALT) lymphoma

The most common type, gastric (stomach) lymphoma, is thought to occur as a result of a chronic infection with the bacterium, *H. pylori*. Because of this, treatment for gastric lymphomas is different from treatment for the other lymphomas in this group.

For early-stage gastric MALT lymphomas (stages I and II) in people who test positive for *H. pylori*, treatment often consists of antibiotics, along with proton pump inhibitors, which are drugs that block acid secretion by the stomach. Usually the drugs are given for 10 to 14 days. This may be repeated after a couple of weeks. Examination of the stomach lining using gastroscopy (where a flexible tube with a viewing lens is passed down the throat) is then repeated at certain intervals to see if the *H. pylori* is gone and if the lymphoma has decreased in size. About 2 out of 3 of these lymphomas go away completely with antibiotic treatment, but it can sometimes take several months to be effective. In cases where symptoms need to be relieved before the antibiotics take effect or where antibiotics don't shrink the lymphoma, radiation therapy to the area is often the preferred treatment. The monoclonal antibody rituximab may be another option.

For early stage gastric MALT lymphomas (stages I and II) in people who test negative for *H. pylori*, treatment is usually either radiation therapy to the stomach or rituximab.

For more advanced (stage III or IV) gastric MALT lymphomas, which are rare, treatment is often similar to that for follicular lymphoma (see above). Lymphomas that are not growing quickly may be followed without treatment right away. If the lymphoma is large, is causing symptoms, or is growing, radiation therapy to the stomach or chemotherapy may be used. The drugs used are the same as those used for follicular lymphoma, and may include single agents such as chlorambucil or fludarabine or combinations such as CVP, often along with rituximab.

For MALT lymphomas that start in sites other than the stomach (non-gastric lymphomas), treatment depends on the site of the lymphoma and how extensive it is. Early stage lymphomas can often be treated with local radiation. In certain sites (such as the lungs, breast, or thyroid), surgery may be an option. For more advanced disease (stage III or IV), treatment is generally the same as for follicular lymphoma (see above).

Nodal marginal zone B-cell lymphoma

This rare type of lymphoma is generally slow growing. It is usually treated like follicular lymphoma (see above) with either close follow-up or low-intensity chemotherapy. It can also change into a fast-growing large cell lymphoma, which would require more aggressive chemotherapy.

Splenic marginal zone B-cell lymphoma

This is also a slow-growing lymphoma. If it is not causing symptoms, it is often watched closely without treating it right away. If the spleen is enlarged, doctors may decide to surgically remove it, especially if the patient has symptoms. This alone can sometimes lead to a long-term remission of the disease. Treatment with rituximab may be another option. Patients who have chronic hepatitis C virus infection may also benefit from treatment with anti-viral drugs.

If the disease is more advanced or progresses, it is usually treated in the same way as a follicular lymphoma, which might include chemotherapy or other options.

In some cases this lymphoma can transform into an aggressive large-cell lymphoma, which requires more intensive chemotherapy.

Burkitt lymphoma

This is a very fast-growing lymphoma that usually must be treated in the hospital with intensive chemotherapy. Most regimens for this disease include at least 5 chemotherapy drugs. Many regimens also include a steroid drug such as prednisone or dexamethasone. Rituximab may also be added. Because this lymphoma tends to invade the spinal fluid, chemotherapy with methotrexate is given into the spinal fluid (this is called *intrathecal therapy*). Some examples of chemo regimens used for this lymphoma include hyper-CVAD, CODOX-M, and EPOCH.

An important part of the initial treatment of this disease is making sure these patients get plenty of fluids and drugs like allopurinol to help prevent tumor lysis syndrome (described in the "Chemotherapy" section).

More than half of all patients with Burkitt lymphoma can be cured with modern treatments.

Lymphoplasmacytic lymphoma (Waldenstrom macroglobulinemia)

The main treatment for this lymphoma is usually chemotherapy or rituximab. For more detailed information see our document, *Waldenstrom Macroglobulinemia*.

Hairy cell leukemia

This is a slow-growing lymphoma that tends to invade the spleen and lymph nodes as well as the blood. Patients without symptoms often don't need to be treated right away, but they do need to have careful follow-up exams. These are done every few months to check for disease progression and the appearance of symptoms. Some patients with hairy cell leukemia (HCL) live for many years without having any symptoms or treatment.

Treatment may be advised for HCL patients with low blood cell counts, recurrent infections, or an enlarged spleen or lymph nodes. Treatment is most often with chemo drugs such as cladribine (2-CdA) or pentostatin. Up to 80% to 90% of patients respond to these drugs, and the responses last more than 5 years in most patients. Even if HCL recurs, many patients will respond to a second treatment with these drugs.

Giving rituximab after these drugs may get rid of any remaining disease in people who haven't fully responded. Because this is a fairly rare disease, too few people have been treated with rituximab to know if it will make a difference.

In rare cases, HCL may not respond to chemotherapy. Rituximab or interferon-alfa, a type of immunotherapy, may be helpful. If a patient is uncomfortable because of an enlarged spleen, removing the spleen by surgery (splenectomy) can often help relieve pain or other symptoms.

T-cell lymphomas

Precursor T-lymphoblastic lymphoma/leukemia

This disease can occur in both children and adults. The treatment for the lymphoma form of this disease is similar to that used for the leukemia form, which is discussed in more detail in our documents, *Leukemia--Acute Lymphocytic (Adults)* and *Childhood Leukemia*.

It is called a lymphoma if there are tumor masses and if lymphoma cells make up less than 25% of the bone marrow. This is a fast-growing disease that is treated with intensive chemotherapy when possible.

Combinations of many drugs are used. These can include cyclophosphamide, doxorubicin (Adriamycin), vincristine, L-asparaginase, methotrexate, prednisone, and, sometimes, cytarabine (ara-C). Because of the risk of spread to the brain and spinal cord, chemotherapy with methotrexate is also given into the spinal fluid. Some doctors suggest maintenance chemotherapy for up to 2 years after the initial treatment to reduce the risk of recurrence. High-dose chemotherapy followed by a stem cell transplant may be another option.

An important part of the initial treatment of this disease is making sure patients get plenty of fluids and drugs like allopurinol, as they are at risk for tumor lysis syndrome (described in the "Chemotherapy" section).

Although this lymphoma is fast-growing, if it hasn't spread to the bone marrow when it is first diagnosed, the chance of cure with chemotherapy is quite good. But once it has spread to the bone marrow, only about 40% to 50% of patients can be cured.

Cutaneous T-cell lymphomas (mycosis fungoides, Sezary syndrome, and others)

Treatment of these skin lymphomas is discussed in our document, *Lymphoma of the Skin*.

Angioimmunoblastic T-cell lymphoma

This fast-growing lymphoma is often first treated with steroids (such as prednisone or dexamethasone) alone. This treatment can reduce fever and weight loss, but the effect is often temporary, and usually chemotherapy is needed. Several chemo drugs are often used. If the lymphoma is only in one area, radiation therapy may be used as well.

Chemo rarely produces long-term remissions, so a stem cell transplant is often suggested after initial chemotherapy if a person can tolerate it.

Extranodal natural killer/T-cell lymphoma, nasal type

This rare lymphoma is often confined to the nasal passages. If there are no poor risk factors, radiation therapy alone may be an option. Otherwise, this lymphoma is usually treated with radiation therapy plus chemotherapy, using a regimen such as CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone). Chemotherapy may be given into the spinal fluid as well.

If the lymphoma has spread or is outside the nasal passages, the chemotherapy regimen may be more intense. Several drugs are used at high doses, and a stem cell transplant may be done if possible.

Enteropathy type T-cell lymphoma

This lymphoma develops from hypersensitivity to gluten, and is almost always in the intestines. It is very hard to treat. Chemotherapy using several drugs is usually the first treatment. If the lymphoma is only in one area, radiation therapy may be used as well. A stem cell transplant may be an option if the lymphoma responds to chemo.

Anaplastic large cell lymphoma

This fast-growing lymphoma mainly affects lymph nodes and is treated with CHOP or similar chemotherapy regimens. In some cases, doctors may recommend radiation therapy as well.

This lymphoma often responds well to treatment, and long-term survival is common, especially if the lymphoma cells stain positive for the ALK protein. If the cells lack the ALK protein or if the lymphoma returns after initial treatment, an autologous stem cell transplant may be an option. Another option for lymphomas that no longer respond to initial treatment is the monoclonal antibody brentuximab vedotin (Adcetris).

Peripheral T-cell lymphoma, unspecified

These lymphomas are generally treated the same way as diffuse large B-cell lymphomas. Chemotherapy with CHOP or other drug combinations is used. For early-stage disease, radiation therapy may be added. Stem cell transplants may be recommended as part of the treatment when possible.

If other treatments are no longer working, newer chemo drugs such as pralatrexate (Folotyn), targeted drugs such as bortezomib (Velcade) or romidepsin (Istodax), or immunotherapy drugs such as alemtuzumab (Campath) and denileukin diftitox (Ontak) may be tried.

The outlook is usually not as good as in diffuse B-cell lymphoma, so taking part in a clinical trial of newer treatments is often a good option.

Special types of lymphoma

Some types of lymphoma are treated differently enough to be mentioned separately.

Primary central nervous system (CNS) lymphoma

This lymphoma begins in the brain or spinal cord. It often develops in older people or those with immune system problems caused by AIDS or drugs given to keep transplanted organs from being rejected.

Most patients are treated with chemotherapy and/or radiation. One problem with treating this disease is that most chemo drugs commonly used to treat lymphoma don't reach the brain when given intravenously (IV). For people in reasonably good health, high IV doses of the drug methotrexate have been shown to be the most effective treatment. This is given along with the drug leucovorin and IV fluids, which help limit serious side effects. Other chemo drugs, such as cytarabine, may be added. Rituximab may be added as well. For those who aren't able to tolerate this treatment, other, less intensive chemo regimens or radiation therapy alone may be tried.

One problem with radiation therapy, especially in older patients, is that it often causes mental changes. Therefore, doctors limit the dose of radiation to try to lessen this problem.

If the lymphoma keeps growing or comes back after treatment, further options may include chemotherapy (using different drugs), radiation therapy, or a stem cell transplant if a person is healthy enough.

Historically, the outlook for patients with primary CNS lymphoma has not been as good as for other lymphomas, but this is at least partly related to the fact that they tend to be older or have other serious health problems.

Treatment of lymphoma of the eye (primary intraocular lymphoma) is discussed in our document, *Eye Cancer (Melanoma and Lymphoma)*.

HIV-associated lymphoma

People with HIV infections are at increased risk for lymphoma. Although people with HIV often have aggressive forms of lymphoma such as diffuse large B-cell lymphoma, primary CNS lymphoma, or Burkitt lymphoma, their outlook has improved a great deal in recent years. The use of highly active anti-retroviral therapy (HAART) to treat HIV has allowed patients to better tolerate chemotherapy.

The major problem in the past was that patients with HIV infection tended to have low blood cell counts to begin with, which made it hard to treat them with full courses of chemotherapy. This problem has been relieved somewhat by the use of HAART and by the use of drugs to help the patient's body make new blood cells. Still, doctors give chemo cautiously and monitor blood counts closely.

Most experts believe that the prognosis (outlook) for a person with HIV-associated lymphoma relates at least as much to the HIV infection as to the lymphoma. Modern anti-HIV therapy can often control the immune deficiency in patients with AIDS, so the outlook for those patients who develop lymphoma has improved. The treatment of the lymphoma itself depends on the specific type of lymphoma.

Palliative care for non-Hodgkin lymphoma

Palliative care is treatment aimed at relieving symptoms. Its main purpose is to improve your quality of life. It is often given along with cancer treatment, but may be also used when cancer treatment is no longer working.

Sometimes, the treatments you get to control your symptoms are similar to the treatments used to treat cancer. For example, when lymph nodes become enlarged, they may press on nerves and cause pain. Radiation therapy to these areas may help relieve the pain. Pain medicines, ranging from ibuprofen and similar drugs to more potent medicines such as opioids, may also be given.

Other symptoms such as fatigue and low resistance to infections can be caused by low blood counts. Sometimes blood transfusions or treatment with drugs that boost new blood cell production are needed. Nausea and loss of appetite can be treated with drugs and high-calorie food supplements. If the lymphoma has spread to the lungs, patients may get short of breath. Oxygen may be used to help treat this symptom.

It is important that you tell your health care team about any symptoms you are having, including any side effects from treatment. There are often ways to help control or lessen these symptoms. This is an important part of your overall treatment plan.

More treatment information for non-Hodgkin lymphoma

For more details on treatment options – including some that may not be addressed in this document – the National Comprehensive Cancer Network (NCCN) and the National Cancer Institute (NCI) are good sources of information.

The NCCN, made up of experts from many of the nation's leading cancer centers, develops cancer treatment guidelines for doctors to use when treating patients. These are available on the NCCN Web site (www.nccn.org).

The NCI provides treatment guidelines via its telephone information center (1-800-4-CANCER) and its Web site (www.cancer.gov). Detailed guidelines intended for use by cancer care professionals are also available on www.cancer.gov.

What should you ask your doctor about non-Hodgkin lymphoma?

It is important to have frank, open discussions with your cancer care team. They want to answer all of your questions, no matter how minor they might seem. For instance, consider asking these questions:

- What kind of non-Hodgkin lymphoma do I have?
- Has my biopsy been reviewed by a pathologist who is an expert on lymphoma?
- Are there other tests that need to be done before we can decide on treatment?
- Are there other doctors I need to see?
- What is the stage (extent) of the lymphoma, and what does that mean in my case?
- What is my International Prognostic Index (IPI) score, and does it affect my options?
- How much experience do you have treating this type of lymphoma?
- Should I get a second opinion before starting treatment? Can you suggest someone?
- What treatment options do I have? Do we need to treat the lymphoma right away?
- What do you recommend, and why?
- What risks or side effects are there to the treatments you suggest?
- What should I do to be ready for treatment?
- How long will treatment last? What will it involve? Where will it be done?
- How will treatment affect my daily activities?
- What is my outlook for survival?
- What are the chances of the lymphoma coming back with these treatment plans?
- What would we do if the treatment doesn't work or if the lymphoma recurs?
- What type of follow-up will I need after treatment?

Along with these sample questions, be sure to write down some of your own. For instance, you might want more information about recovery times so that you can plan your work or activity schedule. Or you may want to ask about clinical trials for which you may qualify.

What happens after treatment for non-Hodgkin lymphoma?

For many people with non-Hodgkin lymphoma, treatment may remove or destroy the cancer. Completing treatment can be both stressful and exciting. You may be relieved to finish treatment, but find it hard not to worry about the lymphoma growing or coming back. (When cancer comes back after treatment, it is called *recurrence*.) This is a very common concern in people who have had cancer.

It may take a while before your fears lessen. But it may help to know that many cancer survivors have learned to live with this uncertainty and are leading full lives. Our document, *Living With Uncertainty: The Fear of Cancer Recurrence*, gives more detailed information on this.

For some people, the lymphoma may never go away completely. These people may get regular treatments with chemotherapy, radiation therapy, or other therapies to help keep the lymphoma in check for as long as possible. Learning to live with lymphoma as a more of a chronic disease can be difficult and very stressful. It has its own type of uncertainty.

Follow-up care

Lymphomas are a diverse group of diseases that require different treatments and can have very different prognoses (outlooks). Your care after treatment will depend to a large extent on what type of lymphoma you have, what type of treatment you received, and how effective it was.

If you have completed treatment, your doctors will still want to watch you closely. It is very important to go to all of your follow-up appointments. During these visits, your doctors will ask about any problems you may have, examine you, and may order lab tests or imaging tests such as CT or PET scans to look for signs of cancer or treatment side effects.

Almost any cancer treatment can have side effects. Some may last for a few weeks to months, but others can last the rest of your life. This is the time for you to talk to your cancer care team about any changes or problems you notice and any questions or concerns you have.

Follow-up tests

Your doctor will probably want to see you regularly, usually every few months for the first year or so and gradually less often after that. Your physical exam will include careful attention to size and firmness of lymph nodes.

Imaging tests may be done, based on the type, location, and stage of lymphoma. If internal lymph nodes or other internal organs are or were affected, CT scans and/or PET scans may be used to measure the size of any remaining tumor masses. PET scans are

particularly useful if your doctors aren't sure if a mass seen on CT scan is an active lymphoma or scar tissue.

You may need to have frequent blood tests to check that you have recovered from treatment and to look for possible signs of problems such as lymphoma recurrence. Blood counts can also sometimes become abnormal because of a disease called *myelodysplasia*, which is a defect of the bone marrow that can lead to leukemia. Some chemotherapy drugs can cause this disease. For more on this, see our document, *Myelodysplastic Syndromes*. It is also possible for a person to develop leukemia a few years after being treated for lymphoma.

If the lymphoma does recur at some point, further treatment will depend on what treatments you've had before, how long it's been since treatment, and your health. For more information, see the section "If treatment stops working" For more general information on dealing with a recurrence, you may also want to see the American Cancer Society document, *When Your Cancer Comes Back: Cancer Recurrence*. You can get this document by calling 1-800-227-2345.

Seeing a new doctor

At some point after your cancer diagnosis and treatment, you may find yourself seeing a new doctor who does not know anything about your medical history. It is important that you be able to give your new doctor the details of your diagnosis and treatment. Make sure you have this information handy:

- A copy of your pathology report(s) from any biopsies or surgeries
- Copies of imaging tests (CT or MRI scans, etc.), which can usually be stored on a CD, DVD, etc.
- If you had surgery, a copy of your operative report(s)
- If you were in the hospital, a copy of the discharge summary that doctors prepare when patients are sent home
- If you had chemotherapy or monoclonal antibodies, a list of the drugs, drug doses, and when you took them
- If you had radiation therapy, a summary of the type and dose of radiation and when and where it was given

It is also important to keep health insurance. Tests and doctor visits cost a lot, and even though no one wants to think of their cancer coming back, this could happen.

Lifestyle changes

You can't change the fact that you have had cancer. What you can change is how you live the rest of your life – making choices to help you stay healthy and feel as well as you can. This can be a time to look at your life in new ways. Maybe you are thinking about how to improve your health over the long term. Some people even start during cancer treatment.

Making healthier choices

For many people, a diagnosis of cancer helps them focus on their health in ways they may not have thought much about in the past. Are there things you could do that might make you healthier? Maybe you could try to eat better or get more exercise. Maybe you could cut down on the alcohol, or give up tobacco. Even things like keeping your stress level under control may help. Now is a good time to think about making changes that can have positive effects for the rest of your life. You will feel better and you will also be healthier.

You can start by working on those things that worry you most. Get help with those that are harder for you. For instance, if you are thinking about quitting smoking and need help, call the American Cancer Society at 1-800-227-2345 for information and support.

Eating better

Eating right can be hard for anyone, but it can get even tougher during and after cancer treatment. Treatment may change your sense of taste. Nausea can be a problem. You may not feel like eating and lose weight when you don't want to. Or you may have gained weight that you can't seem to lose. All of these things can be very frustrating.

If treatment caused weight changes or eating or taste problems, do the best you can and keep in mind that these problems usually get better over time. You may find it helps to eat small portions every 2 to 3 hours until you feel better. You may also want to ask your cancer team about seeing a dietitian, an expert in nutrition who can give you ideas on how to deal with these treatment side effects.

One of the best things you can do after cancer treatment is put healthy eating habits into place. You may be surprised at the long-term benefits of some simple changes, like increasing the variety of healthy foods you eat. Getting to and staying at a healthy weight, eating a healthy diet, and limiting your alcohol intake may lower your risk for a number of types of cancer, as well as having many other health benefits.

Rest, fatigue, and exercise

Extreme tiredness, called *fatigue*, is very common in people treated for cancer. This is not a normal tiredness, but a "bone-weary" exhaustion that doesn't get better with rest. For some people, fatigue lasts a long time after treatment, and can make it hard for them to exercise and do other things they want to do. But exercise can help reduce fatigue. Studies have shown that patients who follow an exercise program tailored to their personal needs feel better physically and emotionally and can cope better, too.

If you were sick and not very active during treatment, it is normal for your fitness, endurance, and muscle strength to decline. Any plan for physical activity should fit your own situation. An older person who has never exercised will not be able to take on the same amount of exercise as a 20-year-old who plays tennis twice a week. If you haven't exercised in a few years, you will have to start slowly – maybe just by taking short walks.

Talk with your health care team before starting anything. Get their opinion about your exercise plans. Then, try to find an exercise buddy so you're not doing it alone. Having family or friends involved when starting a new exercise program can give you that extra boost of support to keep you going when the push just isn't there.

If you are very tired, you will need to balance activity with rest. It is OK to rest when you need to. Sometimes it's really hard for people to allow themselves to rest when they are used to working all day or taking care of a household, but this is not the time to push yourself too hard. Listen to your body and rest when you need to. (For more information on dealing with fatigue, please see *Fatigue in People With Cancer* and *Anemia in People With Cancer*.)

Keep in mind exercise can improve your physical and emotional health.

- It improves your cardiovascular (heart and circulation) fitness.
- Along with a good diet, it will help you get to and stay at a healthy weight.
- It makes your muscles stronger.
- It reduces fatigue and helps you have more energy.
- It can help lower anxiety and depression.
- It can make you feel happier.
- It helps you feel better about yourself.

And long term, we know that getting regular physical activity plays a role in helping to lower the risk of some cancers, as well as having other health benefits.

Can I lower my risk of the lymphoma progressing or coming back?

Most people want to know if there are specific lifestyle changes they can make to reduce their risk of cancer progressing or coming back. Unfortunately, for most cancers there is little solid evidence to guide people. This doesn't mean that nothing will help – it's just that for the most part this is an area that hasn't been well studied. Most studies have looked at lifestyle changes as ways of preventing cancer in the first place, not slowing it down or preventing it from coming back.

At this time, not enough is known about non-Hodgkin lymphoma to say for sure if there are things you can do that will be helpful. Adopting healthy behaviors such as not smoking, eating well, and maintaining a healthy weight may help, but no one knows for sure. However, we do know that these types of changes can have positive effects on your health that can extend beyond your risk of lymphoma or other cancers.

How does having non-Hodgkin lymphoma affect your emotional health?

During and after treatment, you may find yourself overcome with many different emotions. This happens to a lot of people.

You may find yourself thinking about death and dying. Or maybe you're more aware of the effect the cancer has on your family, friends, and career. You may take a new look at your relationship with those around you. Unexpected issues may also cause concern. For instance, as you feel better and have fewer doctor visits, you will see your health care team less often and have more time on your hands. These changes can make some people anxious.

Almost everyone who has been through cancer can benefit from getting some type of support. You need people you can turn to for strength and comfort. Support can come in many forms: family, friends, cancer support groups, church or spiritual groups, online support communities, or one-on-one counselors. What's best for you depends on your situation and personality. Some people feel safe in peer-support groups or education groups. Others would rather talk in an informal setting, such as church. Others may feel more at ease talking one-on-one with a trusted friend or counselor. Whatever your source of strength or comfort, make sure you have a place to go with your concerns.

The cancer journey can feel very lonely. It is not necessary or good for you to try to deal with everything on your own. And your friends and family may feel shut out if you do not include them. Let them in, and let in anyone else who you feel may help. If you aren't sure who can help, call your American Cancer Society at 1-800-227-2345 and we can put you in touch with a group or resource that may work for you.

If treatment for non-Hodgkin lymphoma stops working

Lymphomas are a diverse group of diseases, and the chance of progression or recurrence after treatment varies between types.

Generally, when lymphomas come back, they tend to do so 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. In many cases, the lymphoma will respond to new kinds of chemotherapy or other drugs. If a remission can be achieved with the second round of treatment, doctors often recommend high-dose chemotherapy with a stem cell transplant or a low-dose, non-myeloablative transplant, if possible.

If several rounds of chemotherapy have already been tried, the lymphoma is much less likely to respond to additional or new chemo. If the lymphoma does respond, the response may be shorter. Over time, chemo usually provides less benefit, although immunotherapy and other new approaches to treatment available through clinical trials may be effective.

At some point, even newer treatments may no longer be effective. If this happens, it's important to weigh the possible limited benefits of any new treatment against the possible downsides. Everyone has their own way of looking at this.

This is likely to be the hardest part of your battle with cancer – when you have been through many medical treatments and nothing's working anymore. Your doctor may offer you new options, but at some point you may need to consider that treatment is not likely to improve your health or change your outcome or survival.

If you want to continue to get treatment for as long as you can, you need to think about the odds of treatment having any benefit and how this compares to the possible risks and side effects. In many cases, your doctor can estimate how likely it is the cancer will respond to treatment you are considering. For instance, the doctor may say that more chemo or radiation might have about a 1 in 100 chance of working. Some people are still tempted to try this. But it is important to think about and understand your reasons for choosing this plan.

No matter what you decide to do, you need to feel as good as you can. Make sure you are asking for and getting treatment for any symptoms you might have, such as nausea or pain. This type of treatment is called *palliative care*.

Palliative care helps relieve symptoms, but is not expected to cure the disease. It can be given along with cancer treatment, or can even be cancer treatment. The difference is its purpose – the main purpose of palliative care is to improve the quality of your life, or help you feel as good as you can for as long as you can. Sometimes this means using drugs to help with symptoms like pain or nausea. Sometimes, though, the treatments used to control your symptoms are the same as those used to treat cancer. For instance, radiation might be used to help relieve bone pain caused by cancer that has spread to the bones. Or chemo might be used to help shrink a tumor and keep it from blocking the bowels. But this is not the same as treatment to try to cure the cancer.

At some point, you may benefit from hospice care. This is special care that treats the person rather than the disease; it focuses on quality rather than length of life. Most of the time, it is given at home. Your cancer may be causing problems that need to be managed, and hospice focuses on your comfort. You should know that while getting hospice care often means the end of treatments such as chemo and radiation, it doesn't mean you can't have treatment for the problems caused by your cancer or other health conditions. In hospice the focus of your care is on living life as fully as possible and feeling as well as you can at this difficult time. You can learn more about hospice in our document called *Hospice Care*.

Staying hopeful is important, too. Your hope for a cure may not be as bright, but there is still hope for good times with family and friends – times that are filled with happiness and meaning. Pausing at this time in your cancer treatment gives you a chance to refocus on the most important things in your life. Now is the time to do some things you've always wanted to do and to stop doing the things you no longer want to do. Though the cancer may be beyond your control, there are still choices you can make.

What's new in non-Hodgkin lymphoma research and treatment?

Research into the causes, prevention, and treatment of non-Hodgkin lymphoma is being done in many medical centers throughout the world.

Genetics

Scientists are making a lot of progress in understanding how changes in DNA can cause normal lymphocytes to develop into lymphoma cells. This 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, drugs may be developed that block this process.

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 changes such as chromosome translocations or rearrangements or specific gene mutations. Some of these tests are already in use, and others are being developed. They may be used:

- To detect lymphoma cells in a biopsy sample
- To determine what type of lymphoma a person has
- To help determine if a lymphoma is likely to grow and spread, even within a certain subtype of lymphoma
- To help figure out if a certain treatment is likely to be helpful
- To help determine if a lymphoma has been destroyed by treatment and if a relapse is likely

Treatment

Much of the research being done on non-Hodgkin lymphoma is focused on looking at new and better ways to treat this disease.

Chemotherapy

Many new chemotherapy drugs are being studied in clinical trials. In recent years, these studies have led to the approval of drugs such as bendamustine (Treanda) and pralatrexate (Folotyn) for use against certain types of lymphoma. Other studies are looking at new ways to combine drugs using different doses or different sequences of drugs.

Bone marrow and peripheral blood stem cell transplants

Researchers continue to improve bone marrow and peripheral blood stem cell transplant methods, including new ways to collect these cells before the transplant.

Autologous transplants (which use stem cells from the patient rather than from another person) have 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 cells from these stem cell samples before they are returned to the patient. Some of the new monoclonal antibodies developed for treating lymphoma may help remove these remaining cells.

A lot of 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.

Researchers are also studying the effectiveness of non-myeloablative (reduced-intensity) stem cell transplants in people with lymphoma. This approach may allow more people to benefit from stem cell transplants.

Targeted therapies

As researchers have learned more about cancer cells, they have developed newer drugs that target specific parts of these cells. These are different from standard chemotherapy drugs, which work by attacking rapidly growing cells. The newer drugs often have different side effects, and they may work in some cases where chemotherapy doesn't.

Targeted drugs such as bortezomib (Velcade), thalidomide (Thalomid), lenalidomide (Revlimid), romidepsin (Istodax), and temsirolimus (Torisel) have shown some promise in treating certain lymphomas. These and similar drugs are now being studied in clinical trials.

Monoclonal antibodies

Lymphoma cells contain certain chemicals on their surface. Monoclonal 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 and are discussed in the section, "Immunotherapy"

Rituximab is most often given for a limited amount of time during treatment. Because it has few side effects, it has been studied to see if using it long-term will help prevent lymphomas from coming back and help patients live longer. It does seem to help some patients with follicular lymphoma live longer, but using it long term for other lymphomas is still being studied.

Because of the success of rituximab and similar drugs such as ibritumomab and tositumomab, new monoclonal antibodies are being developed. Examples include

epratuzumab, which targets the CD22 antigen on certain lymphoma cells, and obinutuzumab, which targets the CD20 antigen.

Some newer antibodies are attached to substances that can poison cancer cells, and are known as *immunotoxins*. They act as homing devices to deliver the toxins directly to the cancer cells.

An example is brentuximab vedotin (Adcetris), an immunotoxin that is made up of an antibody to CD30 that is attached to a cell poison. It has been shown to help treat patients with anaplastic large cell lymphoma (ALCL) that is not responding to treatment with chemo. ALCL is a rare type of T-cell lymphoma in which the cells have a protein called CD30 on their surface. This drug is also being studied to see if it can be given with chemo and if it is helpful if given earlier in the disease.

Another immunotoxin, known as CAT-3888 (BL22), targets the CD22 antigen on certain lymphoma cells, bringing along a toxin known as PE38. This drug showed a great deal of promise in treating hairy cell leukemia (HCL) in early clinical trials. A newer version of this drug, known as CAT-8015 (moxetumomab pasudotox), is now being studied for use against lymphomas.

Lymphoma vaccines

Doctors have known for some time that people's immune systems may help fight their cancer. In rare instances, these people's immune systems have rejected their cancers, and they have been cured. Scientists are now trying to develop ways to encourage this immune reaction by using vaccines.

Unlike vaccines against infections like measles or mumps, these vaccines are designed to help treat, not prevent, lymphomas. The goal is to create an immune reaction against lymphoma cells in patients who have very early disease or in patients whose disease is in remission. One possible advantage of these types of treatments is that they seem to have very limited side effects. So far, there have been a few successes with this approach, and it is a major area of research in lymphoma treatment. At this time lymphoma vaccines are only available in clinical trials.

BiovaxID[™] is a vaccine based on the unique genetic makeup of a patient's B-cell non-Hodgkin lymphoma. The vaccine uses a unique protein (part of an antibody called an idio type) taken from each patient's own lymphoma cells, which are obtained during a biopsy. This is combined with substances that boost the body's immune response when the combination is injected into the patient. A late-stage clinical trial found that in people with follicular lymphomas that went away after chemotherapy, the vaccine lengthened the time before the lymphoma came back by more than a year. The vaccine has also shown promising early results against mantle cell lymphoma. It is not yet available outside of clinical trials.

Additional resources for non-Hodgkin lymphoma

More information from your American Cancer Society

We have some related information that may also be helpful to you. These materials may be ordered from our toll-free number, 1-800-227-2345.

After Diagnosis: A Guide for Patients and Families (also available in Spanish)

Caring for the Patient With Cancer at Home: A Guide for Patients and Families (also available in Spanish)

Clinical Trials: What You Need to Know

Immunotherapy

Living With Uncertainty: The Fear of Cancer Recurrence

Lymphoma of the Skin

Pain Control: A Guide for People With Cancer and Their Families (also available in Spanish)

Stem Cell Transplant (Peripheral Blood, Bone Marrow, and Cord Blood Transplants)

Understanding Chemotherapy: A Guide for Patients and Families (also available in Spanish)

Understanding Radiation Therapy: A Guide for Patients and Families (also available in Spanish)

When Your Cancer Comes Back: Cancer Recurrence

The following books are available from the American Cancer Society. Call us at 1-800-227-2345 to ask about costs or to place your order.

American Cancer Society Complete Guide to Complementary & Alternative Cancer Therapies

American Cancer Society Complete Guide to Family Caregiving, Second Edition

American Cancer Society Complete Guide to Nutrition for Cancer Survivors

American Cancer Society's Guide to Pain Control, Second Edition

Cancer in the Family: Helping Children Cope with a Parent's Illness

What Helped Me Get Through: Cancer Patients Share Wisdom and Hope

What to Eat During Cancer Treatment

When the Focus Is on Care: Palliative Care and Cancer

National organizations and Web sites*

In addition to the American Cancer Society, other sources of patient information and support include:

Lymphoma

Leukemia & Lymphoma Society

Toll-free number: 1-800-955-4572 or 1-914-949-5213

Web site: www.lls.org

Lymphoma Research Foundation

Toll-free number: 1-800-500-9976

Web site: www.lymphoma.org

National Cancer Institute

Toll-free number: 1-800-4-CANCER (1-800-422-6237)

Web site: www.cancer.gov

National Coalition for Cancer Survivorship

Toll-free number: 1-888-650-9127

1-877-NCCS-YES (622-7937) for some publications and Cancer Survivor Toolbox[®] orders

Web site: www.canceradvocacy.org

Bone marrow and peripheral blood stem cell transplants

Caitlin Raymond International Registry (for unrelated bone marrow transplants)

Toll-free number: 1-800-726-2824

Web site: www.crir.org

National Bone Marrow Transplant Link (nbmtLINK)

Toll-free number: 1-800-LINK-BMT (1-800-546-5268)

Web site: www.nbmtlink.org

National Marrow Donor Program

Toll-free number: 1-800-MARROW-2 (1-800-627-7692)

Web site: www.marrows.org

**Inclusion on this list does not imply endorsement by the American Cancer Society.*

No matter who you are, we can help. Contact us anytime, day or night, for information and support. Call us at **1-800-227-2345** or visit www.cancer.org.

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