LYMPHOMA RESEARCH • FOUNDATION

Understanding

Lymphoma and Chronic Lymphocytic Leukemia/ Small Lymphocytic Lymphoma (CLL/SLL)

Part 3 — Hodgkin Lymphoma

2023

Chapter 13: What is Hodgkin Lymphoma

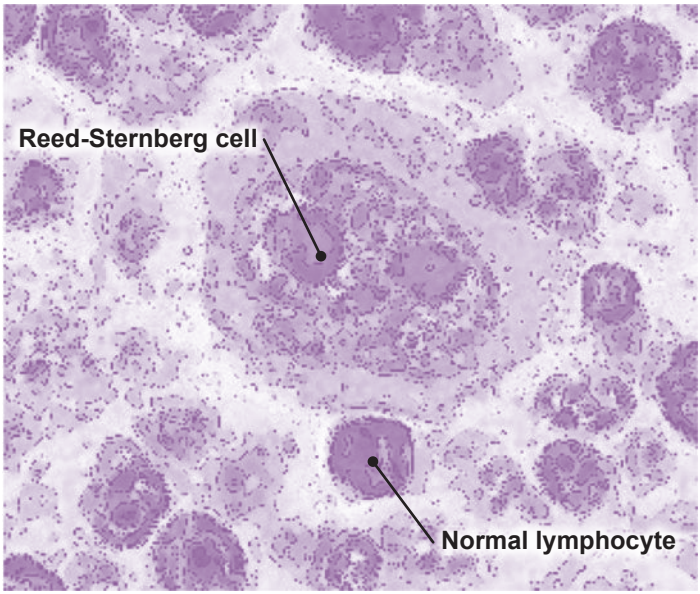
What is Hodgkin Lymphoma?

Hodgkin lymphoma (HL), previously called Hodgkin's disease or Hodgkin disease, is a type of cancer that starts in the lymphatic system (tissues and organs that produce, store and carry white blood cells). HL is named after Dr. Thomas Hodgkin, a British physician who first described the disease in 1832. In the United States, approximately 8,830 people a year are diagnosed with HL. In 2020, there were an estimated 223,512 people living with HL in the United States. Both children and adults can develop HL, but the disease is most common among young adults aged 20 to 34.

How Does HL Develop?

HL develops when abnormal (cancerous) B-cells called Reed-Sternberg (RS) cells start to multiply and grow in an unregulated (uncontrolled) manner and make lymph nodes grow bigger than normal. Most patients with HL have either RS cells or RS cell variants (RS cells that have some differences in their shape, size, and structure compared to typical RS cells) in their lymphatic system. When examined under a microscope, RS cells are usually surrounded by large numbers of inflammatory cells (cells that respond to damage and help the body fight off infections) such as T-cells, histiocytes (a type of large white blood cell), eosinophils (a type of white blood cell), and neutrophils (a type of white blood cell). For this reason, HL was not initially recognized as a cancer; for years doctors thought HL was a type of infection. HL looks different from other cancers in that only a few of the cells (1-2%) in the lymph nodes are cancerous, and the rest help cancerous RS cells stay alive.

A REED-STERNBERG CELL



The presence of cells that look like RS cells does not necessarily mean that a person has HL. In fact, RS-like cells can be found in many other conditions, mainly other types of cancer. A unique characteristic of most types of HL is that the RS cells have an antigen (marker) on their surfaces called CD30. To make an HL diagnosis, a hematopathologist (a doctor who specializes in the diagnosis of blood diseases) examines a sample of the affected lymph node under a microscope and uses tests to determine whether (1) the RS cells are surrounded by inflammatory cells, and (2) the CD30 antigen and CD15 antigen are present on the RS cells. The hematopathologist may also use more sophisticated molecular tests to help confirm the diagnosis.

HL usually starts in the lymph nodes, and the first signs a patient notices may be swelling in the neck, above or below the collarbone, under the arms, in the chest, or in the groin. The lymphoma can then spread throughout the body via lymphatic vessels (tube-like structures that carry a fluid called lymph) and all lymphatic system. HL may also spread to other areas and organs outside of the lymphatic system.

What Distinguishes HL From NHL?

The RS cells seen in patients with HL are not present in patients with non-Hodgkin lymphoma (NHL). Also, HL tends to spread from one group of lymph nodes to adjacent nodes, while NHL may spread to lymph nodes anywhere in the body in an unpredictable manner.

The different types and subtypes of HL are distinguished by how they look under a microscope. The two main forms are classical HL (cHL) and nodular lymphocyte-predominant HL (NLPHL).

Classical HL and Its Subtypes

About 95% of patients with HL are cHL. There are four subtypes of cHL, as described in Table 13.1. However, it is important to remember that these four subtypes are generally treated similarly.

Table 13.1. Subtypes of cHL

Nodular Sclerosis HL	■ Affects 70% of patients with cHL. ■ Involved lymph nodes often form *nodules* (lumps) separated by broad bands of *fibrotic* (fiber-like) or *sclerotic* (hardened) tissue. ■ More common in young adults and women. ■ Most frequently involves lymph nodes in the neck or chest.
Mixed Cellularity HL	■ Affects 20-40% of patients with cHL. ■ Characterized by many classic RS cells mixed with other types of inflammatory cells. ■ More common in older adults, children under 10 years, and people with underlying immunodeficiency disorders (diseases that weaken the immune system and cause infections and other health problems).Often associated with an infection of Epstein Barr virus (EBV, the virus that causes mono).
Lymphocyte- Rich HL	■ Affects 5% of patients with cHL. ■ Characterized by many normal lymphocytes and relatively few RS cells. ■ More common in men.
Lymphocyte-Depleted HL	■ Affects less than 1% of patients with cHL. ■ Characterized by very few normal lymphocytes and many RS cells. ■ More common in older adults or people living with human immunodeficiency virus (HIV, a virus that weakens the body's immune system by destroying cells that fight off infections). ■ Often not diagnosed until the disease is in an advanced stage.

Nodular Lymphocyte-Predominant Hodgkin Lymphoma (NLPHL)

This type of HL accounts for about 5 percent of all HL cases. It is indolent (slow-growing) and characterized by a different type of RS cells, called lymphocyte-predominant (LP) cells. These are also called "popcorn cells," because the cell nuclei (structure in the center of the cell) resemble popped kernels of corn. The antigens on cell surfaces of LP cells are different from those found on RS cells in cHL. For example, LP cells are positive for the CD20 antigen (often found in B-cell NHL) and typically negative for the CD30 antigen seen in cHL. This form of HL is often found in the lymph nodes of the neck, groin, or underarms. The treatment for NLPHL differs from the treatment for cHL. NLPHL should not be confused with lymphocyte-rich HL, which is a subtype of cHL described in Table 13.1.

Do Certain People Develop HL?

The reasons why certain people develop HL are not totally understood. However, scientists have found that people with particular characteristics called "risk factors," have a slightly higher chance of developing HL compared with people who do not have these risk factors. Having one or more HL risk factors does not mean a person will definitely develop the disease. In fact, most people with the known risk factors never develop HL, and many people diagnosed with HL do not have any of these risk factors. However, there does seem to be a link between the risk factors described in Table 13.2 and the development of HL.

Table 13.2. Risk Factors for HL

Age	■ People who are 15-40 years of age or over 55 years have a higher risk of developing HL than people in other age groups.
Family History	■ A family history of HL, especially among first-degree relatives (parent, sibling, or child), increases the risk of developing HL (but still a very low risk overall). ■ Siblings of patients with HL have a 3- to 7-fold increased risk of developing this disease, and the risk is higher in identical twins. However, the risk of a first-degree relative developing HL is still very rare. ■ Fewer than 1% of patients with HL have a family history of the disease.
Gender	■ Men have a slightly higher risk of developing HL than women. ■ Women are more likely to be diagnosed with the nodular sclerosis subtype.
Immunodeficiency Disorders	■ People with inherited (for example, common variable immunodeficiency disorder, X-linked lymphoproliferative disorder) or acquired (for example, chronic immunosuppression following a solid organ transplant or treatment of certain immune conditions such as juvenile rheumatoid arthritis) immunodeficiency disorders are at an increased risk of developing HL.
Infection by Certain Viruses	■ People infected with the Epstein-Barr virus (EBV; the virus that can cause infectious mononucleosis) or the human immunodeficiency virus (HIV; the virus that can cause acquired immunodeficiency syndrome [AIDS]) have a higher risk of developing HL compared with people who have not been infected with these viruses.

HL cannot be caused by injury and cannot be caught from someone who has the disease. While parents, children, and siblings of patients with HL have a slightly increased risk of developing this disease compared with the general population, there are no clearly identifiable genetic or hereditary factors that can predict this slightly increased risk. Therefore, routine screening for HL among the immediate family members of patients with HL is not recommended as most will never develop HL.

What Are the Signs and Symptoms of HL?

Most patients present with enlarged lymph nodes that continue to grow over several months to more than 3 centimeters in size (roughly the size of a banana slice). Enlarged lymph nodes are extremely common, so there is nothing to do or worry about if a person is feeling healthy and well until they are too big to be considered normal. Some patients with HL do not have any obvious signs or symptoms of the disease at the time of diagnosis. Their doctors might detect the lymphoma during routine blood tests and/or a physical examination. For others, lymphoma is discovered when symptoms occur and patients go to the doctor because they are worried, uncomfortable, or not feeling well.

As shown in Table 13.3, HL may cause different signs and symptoms depending on where it is located in the body. Keep in mind that many of these signs and symptoms are not specific to HL and may be due to other conditions.

Table 13.3. Signs and Symptoms Commonly Found in Patients with HL

Sign or Symptom	Possible Reasons
■ Lumps under the skin on the sides of the neck, above the collarbone, or in the underarms, elbows, or groin	■ Lymph nodes, or "glands," that swell when the lymphocytes respond to an infection or because of an increased number of abnormal lymphocytes
■ "B symptoms," including fevers for no known reason, unexplained drastic weight loss, and drenching night sweats that soak clothing and sheets	■ Increased levels of inflammatory chemicals in the blood that are released by lymphoma cells or by the immune system reacting to the lymphoma cells
■ Unexplained itching (sometimes severe)	■ Unknown cause but often associated with "B symptoms" or reactivation of viruses
■ Coughing, trouble breathing, or chest pain or pressure	■ Lymphoma in the chest, which may press on the windpipe or *bronchi* (tubes leading to the lungs) ■ *Pleural effusion* (fluid surrounding the lungs)
■ Feeling tired	■ *Anemia* (low red blood cell count) or the cancer process in general
■ Increased sensitivity to alcohol, or pain in the lymph nodes after drinking alcohol	■ Poorly understood cause, but thought to be due to increased blood flow through the lymph nodes in response to alcohol

What is Relapsed or Refractory HL?

Relapsed HL means that the disease has returned after responding to treatment, which is sometimes also called a *recurrence*. *Refractory* HL means that the patient's disease does not respond to a specific treatment or that the response to treatment does not last very long.

Chapter 14: Treatment of Hodgkin Lymphoma

This chapter reviews the most common therapies currently used in the treatment of HL. Keep in mind that new therapies may have been approved by the U.S. Food and Drug Administration (FDA) since this guide was published. Read Chapter 15 to learn more about emerging treatments under investigation in clinical trials.

There are important differences between different types of HL, and a treatment that works for one type of HL may not necessarily be the best treatment choice for another type. There are also small but important differences between patients diagnosed with the same type of HL. Because of these differences, a treatment that may work very well in one patient may not have the same positive effect in another.

What Types of Treatments are Used in Patients with cHL?

There are three general types of treatments for patients with cHL:

- Drug therapy, including one or more of the following types of drugs
  - Chemotherapy, which affects general cell growth and *proliferation* (the ability of cells to multiply). Chemotherapy is the main treatment for most people with HL (except for some people with NLPHL).
  - Immunotherapy, which helps the body's immune system attach to lymphoma cells (immune checkpoint inhibitors).
- Radiation therapy, which uses high-energy radiation to kill lymphoma cells.
- Stem cell transplantation, usually in combination with high-dose chemotherapy, which replaces the patient's immune system with healthy immune cells.

Chemotherapy

Most patients treated for cHL receive combination chemotherapy (two or more drugs), with or without radiation therapy, as their *frontline* (first) treatment. Most chemotherapy for HL is given by IV. In North America, the

standard frontline chemotherapy regimen is known as ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine); this regimen and other common frontline regimens for adults are listed in Table 14.1.

Table 14.1. Common Frontline Chemotherapy Regimens for Adults with cHL

Chemotherapy regimen (abbreviation)	Generic Name of Drugs (Brand Names)
ABVD	■ Doxorubicin/hydroxydaunorubicin (Rubex, Adriamycin PFS) ■ Bleomycin (Blenoxane) ■ Vinblastine (Velban) ■ Dacarbazine (DTIC-Dome)
AVD	■ Doxorubicin (Adriamycin) ■ Vinblastine (Velban) ■ Dacarbazine (DTIC-Dome)
BV-AVD (A-AVD)	■ Brentuximab vedotin (Adcetris) ■ Doxorubicin (Adramycin) ■ Vinblastine (Velban) ■ Dacarbazine (DTIC-Dome)
Escalated BEACOPP	■ Bleomycin (Blenoxane) ■ Etoposide/VP16 (VePesid, Toposar, Etopophos) ■ Doxorubicin (Adriamycin) ■ Cyclophosphamide (Cytoxan, Neosar) ■ Vincristine (Oncovin and others) ■ Procarbazine (Matulane) ■ Prednisone
MOPP	■ Mechlorethamine (Mustargen) ■ Vincristine (Oncovin and others) ■ Procarbazine (Matulane) ■ Prednisone
Stanford V	■ Mechlorethamine (Mustargen) ■ Doxorubicin (Adriamycin) ■ Vinblastine (Velban) ■ Vincristine (Oncovin and others) ■ Bleomycin (Blenoxane) ■ Etoposide/VP16 (VePesid, Toposar, Etopophos) ■ Prednisone

Patients usually receive 2 chemotherapy cycles, followed by positron emission tomography-computed tomography (PET-CT, a scan that uses a special dye to show where the cancer is located) imaging to evaluate how the lymphoma is responding to the treatment. The results are used to determine whether any of the chemotherapy drugs (most often bleomycin) can be eliminated, or if radiation therapy will be required as part of treatment. Even if a patient has a *complete response* (no signs of cancer on scans or tests) it is important to complete all of the prescribed cycles of therapy in order to achieve a "cure".

The ABVD regimen is the most widely used first-line combination chemotherapy regimen for cHL. All four agents are given intravenously every two weeks in 28-day cycles. Patients may receive 2 to 6 cycles depending on the disease stage (how severe the disease is), prognosis (how well the patient will do), other treatments, and tolerability. Bleomycin may be stopped after the third cycle to prevent lung complications. Some regimens today are more effective and less toxic, so you should ask your provider if there are other regimens that are an option for you.

Common frontline chemotherapy regimens used in children with cHL are listed in Table 14.2.

Table 14.2. Common Frontline Chemotherapy Regimens for Children with cHL

Chemotherapy regimen (abbreviation)	Generic Name of Drugs (Brand Names)
ABVE-PC	■ Doxorubicin (Adriamycin) ■ Bleomycin ■ Vincristine (Oncovin and others) ■ Etoposide (Vepesid, Toposar, Etopophos) ■ Prednisone ■ Cyclophosphamide
OEPA/COPDac	■ Doxorubicin (Adriamycin) ■ Vincristine (Oncovin and others) ■ Etoposide (VePesid, Toposar, Etopophos) ■ Prednisone ■ Doxorubicin (Adriamycin) ■ Cyclophosphamide (Cytoxan, Neosar) ■ Dacarbazine (DTIC-Dome)

Pediatric patients usually receive 2 chemotherapy cycles, followed by PET-CT imaging to determine whether any chemotherapy can be eliminated and/or a radiotherapy regimen is needed.

What Other Types of Drugs Are Used to Treat Patients With HL?

In addition to chemotherapy, immunotherapy, radiation therapy and stem cell transplantation can be used to treat HL.

Immunotherapy

The term *immunotherapy* refers to treatments that help boost the body's own immune response (see Chapter 7 in Part 1 of this guide). Immunotherapy drugs used to treat cHL include antibody-drug conjugates and immune checkpoint inhibitors.

For more information, read the sections below about types of immunotherapy and see the *Immunotherapy and Other Targeted Therapies* fact sheet on LRF's website at lymphoma.org/publications.

Antibody-Drug Conjugates

An antibody-drug conjugate is a chemotherapy drug attached to a monoclonal antibody (see Chapter 7 in Part 1 of this guide). Antibody-drug conjugates used to treat cHL are described below.

Brentuximab vedotin (Adcetris)

Brentuximab vedotin (Adcetris) is a combination of the chemotherapy drug monomethyl auristatin E (MMAE or vedotin) and a monoclonal antibody against CD30 (brentuximab). The CD30 antigen is present on the surface of all RS cells (the cancer cells in HL). Thus, the monoclonal antibody part of this drug is like a "guided missile" that is directed against and attaches itself to RS cells. Once the antibody is attached to the lymphoma cell, it is taken inside the cell (internalized). The MMAE is then released inside the HL cell, causing it to stop multiplying and die.

Brentuximab vedotin (Adcetris) is approved by the FDA to treat:

- Adult patients with previously untreated Stage III or IV cHL, in combination with doxorubicin, vinblastine, and dacarbazine.
- Pediatric patients 2 years and older with previously untreated high risk cHL, in combination with doxorubicin, vincristine, etoposide, prednisone, and cyclophosphamide.
- Adult patients with cHL at high risk of relapse or progression after autologous stem cell transplantation consolidation.
- Adult patients with cHL after failure of autologous stem cell transplantation or after failure of at least two prior multi-agent (including two or more drugs) chemotherapy regimens in patients who are not candidates for stem cell transplantation.

Brentuximab vedotin (Adcetris) in monotherapy is given as an IV infusion once every 3 weeks until disease progression or unacceptable toxicity. Doctors may use this drug in monotherapy after bone marrow transplantation as maintenance to try and keep patients in *remission* (no signs or symptoms of cancer). When combined with chemotherapy in previously untreated stage III or IV cHL, it is given every 2 weeks for a maximum of 12 doses.

Immune Checkpoint Inhibitors

Immune checkpoint inhibitors are monoclonal antibodies that restore the immune system's ability to attack the cancer cells and rid them from the body (see Chapter 7 in Part 1 of this guide). Immune checkpoint inhibitors used to treat cHL are given intravenously every 3 or 6 weeks, target the PD-1/PD-L1 protein on the lymphoma cell and are described below.

Nivolumab (Opdivo)

Nivolumab (Opdivo) is approved by the FDA for adult patients with cHL that has relapsed or progressed after autologous stem cell transplantation and post-transplantation treatment with brentuximab vedotin (Adcetris) or 3 or more lines of systemic therapy that includes autologous stem cell transplantation.

Pembrolizumab (Keytruda)

Pembrolizumab (Keytruda) is approved by the FDA for adult and pediatric patients with relapsed or refractory cHL, or pediatric patients with cHL that has relapsed after 2 or more previous lines of therapy.

Radiation Therapy

Radiation therapy (also called *radiotherapy*) uses high-energy X-rays or other types of radiation to kill cancer cells and shrink tumors. This was the first cure for HL and works very well for this cancer. The term is generally used to describe *external-beam radiotherapy,* in which a radiation beam is delivered from a machine. In the past, common areas of the body that received radiation included lymph nodes in the neck, chest, and underarms (called the "mantle field"); lymph nodes in the abdomen and possibly spleen; and lymph nodes in the pelvis and groin. In certain circumstances, extended-field radiation was given to both the mantle and upper abdominal fields. However, these fields are no longer used in the modern treatment of HL. The most common types of radiation therapy and delivery methods used for HL are described below.

Involved-field Radiation Therapy (IFRT)

IFRT includes the lymph node regions that contain HL and is usually given after chemotherapy.

Involved-Site Radiation Therapy (ISRT)

The radiation field is narrower than IFRT so that nearby healthy tissues and organs are not affected.

Proton Therapy

Uses positively charged particles called protons delivered by an external beam. This can reduce the radiation exposure of nearby healthy tissues, allowing higher doses to be delivered to the tumor. It may be useful to treat tumors near places that are difficult to treat (e.g. heart, lungs, or esophagus).

Total Body Irradiation

The whole body is exposed to radiation along with high-dose chemotherapy (to kill all lymphoma cells in the body). It may be given to patients who are preparing for a stem cell transplant.

Stem Cell Transplantation

A stem cell transplant adds new stem cells (blood-forming cells) back into the body after chemotherapy with or without radiation, replacing the cells that were destroyed and restoring the bone marrow's ability to make new blood cells (see Chapter 7 in Part 1 of this guide). In deciding if transplantation is a good option, doctors consider the patient's health status, age, medical history, cancer stage, and responses to previous therapy.

There are three types of stem cell transplantation that differ based on the source of the stem cells: *autologous*, *allogeneic* and *syngeneic*.

Autologous Stem Cell Transplant

In an autologous stem cell transplant, patients are their own donor. Autologous stem cell transplantation is used in patients with cancers that are responding to chemotherapy. The ability to transplant the patient's own stem cells (autologous stem cell transplant) allows doctors to use higher doses of chemotherapy than the body would normally tolerate, increasing the probability of treatment success. The curative part of this process is that it resets the patient's immune system and increases the chance that their body will kill and clear these cancer cells in the future.

Allogeneic Stem Cell Transplant

In an allogeneic stem cell transplant, the donor is another person who is genetically similar to the patient; this person is often a brother or sister. Donor stem cells may also come from the patient's child, the patient's parent, an unrelated person, or donated umbilical cord blood. This gives the patient a new immune system if their own continues to allow cancer to grow.

Syngeneic Stem Cell Transplant

In a syngeneic stem cell transplant, the donor is the patient's identical twin.

For additional information about the process of stem cell transplantation, please view the *Understanding Cellular Therapy* guide on LRF's website at lymphoma.org/publications.

Treatment of Patients With Relapsed or Refractory cHL

Patients with cHL whose disease does not go into complete remission (CR, disappearance of all signs of cancer) after initial therapy or whose disease relapses after achieving CR are often treated with second-line treatment. The preferred second-line treatment for transplant-eligible patients with relapsed HL is another chemotherapy regimen (typically different from the frontline therapy) or immunotherapy, followed by high-dose chemotherapy with autologous stem cell transplantation. Table14.3 shows examples of second-line chemotherapy regimens used in patients with relapsed or refractory cHL.

Table 14.3. Common Second-line Chemotherapy Regimens for Adults with Relapsed or Refractory cHL

Chemotherapy regimen (abbreviation)	Generic Name of Drugs (Brand Names)
BVB	■ Brentuximab vedotin (Adcetris) ■ Bendamustine (Treanda)
BEGEV	■ Bendamustine (Treanda) ■ Gemcitabine (Gemzar) ■ Vinorelbine (Navelbine)

Chemotherapy regimen (abbreviation)	Generic Name of Drugs (Brand Names)
ChlVPP	■ Chlorambucil (Leukeran) ■ Vinblastine (Velban) ■ Procarbazine (Matulane) ■ Prednisone
DHAP	■ Dexamethasone ■ Cytarabine/high-dose Ara-C (Cytosar-U, Tarabine PFS) ■ Cisplatin (platinol)
DICE	■ Dexamethasone ■ Ifosfamide (Ifex) ■ Cisplatine (Platinol) ■ Etoposide/VP 16 (VePesid, Toposar, Etopophos)
ESHAP	■ Etoposide/VP16 (VePesid, Toposar, Etopophos) ■ Methylprednisolone ■ Cytarabine (high-dose Ara-C) ■ Cisplatin (Platinol)
GCD	■ Gemcitabine (Gemzar) ■ Carboplatin (Paraplatin) ■ Dexamethasone
GDP	■ Gemcitabine (Gemzar) ■ Dexamethasone ■ Cisplatin (Platinol)
GEMOX	■ Gemcitabine (Gemzar) ■ Oxaliplatin (Eloxatin)
GVD	■ Gemcitabine (Gemzar) ■ Vinorelbine (Navelbine) ■ Liposomal doxorubicin(Doxil)
ICE	■ Ifosfamide (Ifex) ■ Carboplatin (Paraplatin) ■ Etoposide/VP16 (VePesid, Toposar, Etopophos)
IGEV	■ Ifosfamide (Ifex) ■ Gemcitabine (Gemzar) ■ Vinorelbine (Navelbine)

Regimens commonly used in the treatment of pediatric cHL include gemcitabine (Gemzar) plus vinorelbine (Navelbine), and ifosfamide (Ifex) plus vinorelbine (Navelbine).

For some patients with relapsed cHL, including those who are not good candidates for a stem cell transplant, other second line treatment options include the following:

- Radiation therapy alone.
- Chemotherapy alone.
- Chemotherapy combined with radiation therapy.
- An antibody-drug conjugate (brentuximab vedotin [Adcetris], see page 137).
- A checkpoint inhibitor (nivolumab [Opdivo] or pembrolizumab [Keytruda], see page 138).
- A clinical trial.

Patients who do not go into CR following treatment or who do not respond to treatment should not lose hope. Lasting responses to therapy may be achieved after a diagnosis of relapsed or refractory disease. Many patients seek second opinions at any point from diagnosis onward, and some choose to do so if their disease relapses or is considered refractory.

Clinical trials are also an important option for patients at all stages of disease, including from the start. They offer a chance to receive new treatments that may be more effective or tolerable. Many of the novel therapeutic agents (new treatments) being investigated in clinical trials are used specifically for patients with relapsed or refractory disease. Chapter 15 describes some of the options currently under investigation. For more information about clinical trials for patients with cHL, please contact the LRF Helpline at (800) 500-9976 or helpline@lymphoma.org and ask about the LRF “Clinical Trials Information Service”.

When Should a Clinical Trial Be Considered?

Clinical trials are appropriate for patients at all stages of disease, whether newly diagnosed or relapsed/refractory disease. See Chapter 8 for more general information about Clinical Trials.

If patients are interested in participating in a clinical trial, they should ask their doctor if there is an appropriate trial for them and what the potential risks and benefits may be. For more information about clinical trials for patients with HL, please contact the LRF Helpline at (800) 500-9976 or helpline@lymphoma.org and ask about the LRF "Clinical Trials Information Service".

What Types of Treatments are Used in Patients with NLPHL?

NLPHL tends to grow slowly and may relapse later in life, no matter what type of treatment a patient receives. This form of HL is treated more like *indolent* (slow-growing) NHL than like cHL. In addition to chemotherapy and radiation therapy, immunotherapy with monoclonal antibodies and radioimmunotherapy can be used to treat NLPHL. Table 14.4 shows treatments used for various stages of NLPHL.

Active Surveillance

With the active surveillance approach (watchful waiting), patients' health and disease are monitored through regular checkups and periodic evaluation procedures, such as laboratory and imaging tests, but they do not receive any anti-lymphoma treatments. These patients continue to remain untreated as long as they do not show any signs or symptoms and there is no evidence that the lymphoma is growing or spreading. Active surveillance is an option for some patients who have early- stage or advanced-stage disease that is not bulky (no tumor greater than 10 centimeters) or with complete resection (removal through surgery) of a single involved node. For more information about active surveillance see Chapter 7 in Part 1 of this guide.

Doctors recommend active surveillance for selected patients with early-stage NLPHL. This approach may be used after the initial diagnosis or after relapse, depending on the situation. Patients are switched from active

surveillance to active treatment if they begin to develop lymphoma-related symptoms or if there are signs that the disease is progressing.

Active surveillance is not a treatment option for patients with symptomatic NLPHL.

Monoclonal Antibodies

Monoclonal antibodies are molecules that have been engineered in a laboratory to attach to one specific target (antigen) on the surface of cancer cells and they are effective for patients with cancer cells expressing that specific antigen (see Chapter 7 in Part 1 of this guide). Once injected in the patient, the monoclonal antibodies travel through the blood and attach themselves to the cells that have the antigen they recognize, most of which are HL cells. This can either stop or slow down the growth of the cancer cell, or it can trigger an "alarm" that makes it easier for other immune cells to recognize and destroy the cancer cell.

The monoclonal antibody rituximab (Rituxan) used in the treatment of NLPHL is described below.

Rituximab (Rituxan)

Rituximab is a monoclonal antibody that targets the antigen CD20, a specific molecule found on the surface of almost all B-cells and other cancer cells in NLPHL (but not cHL).

While not approved by the FDA to treat HL, rituximab is sometimes given either as monotherapy (without other drugs) or in combination with chemotherapy to patients with NLPHL. Rituximab treatment is given as an IV infusion usually once weekly for a certain number of cycles, but the schedule varies depending on the type of combination regimen used. When combined with chemotherapy, rituximab is usually given during the first day of each chemotherapy cycle.

In patients with relapsed (disease comes back) or refractory (does not respond to treatment) NLPHL whose disease responds well to rituximab monotherapy, rituximab may also be used as maintenance therapy (ongoing treatment to prevent cancer from returning) for up to two years.

Whether used as monotherapy, combination therapy, or maintenance therapy, any use of rituximab for patients with NLPHL is considered off-label, meaning that the FDA has not specifically approved using rituximab for this purpose. However, it is listed as an option in the National Comprehensive Cancer Network (NCCN) guidelines. You may consult with your doctor to determine whether this is an option for you.

Radioimmunotherapy

Radioimmunotherapy consists of a targeted antibody attached to a radioisotope (a particle that emits radiation). These drugs act as a "guided missile" to destroy lymphoma cells by attaching to them and delivering small doses of radiation.

Table 14.4. Treatment for Various Stages of NLPHL

Stage	Commonly Used Treatments
Early Disease	■ Observation/active surveillance ■ Involved-site radiation therapy (ISRT) ■ Rituximab (Rituxan) ■ ISRT plus ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) chemotherapy, with or without rituximab ■ AVPC (doxorubicin, vincristine, prednisone, cyclophosphamide) or CVP (cyclophosphamide, vincristine, prednisone) for pediatric patients
Advanced Disease	■ Rituximab (Rituxan) ■ ABVD chemotherapy plus rituximab, with or without ISRT ■ CHOP chemotherapy plus rituximab ■ Local radiation therapy ■ ABVE-PC (doxorubicin, bleomycin, vincristine, etoposide, prednisone, procarbazine) with or without ISRT for pediatric patients
Relapsed or Refractory Disease	■ Clinical trial ■ Observation/active surveillance if recurrence is limited and there are no symptoms ■ ABVD chemotherapy, rituximab (Rituxan), or involved-field radiation therapy (IFRT) alone or in any combination ■ Chemotherapy regimens used for aggressive NHL ■ Radioimmunotherapy (RIT)

In some rare cases, NLPHL can transform into aggressive NHL. Rapid growth of one or more lymph nodes is a clear indication for a biopsy to see if such a transformation has occurred. If transformation occurs, treatment of the resulting NHL is necessary.

Table 14.4 shows treatments used for various stages of NLPHL.

Alternative and Complementary Therapies for HL

Alternative therapy refers to any treatment used instead of a standard therapy (the proper treatment that is widely used by healthcare professionals and accepted by medical experts). Alternative therapies are not recognized as effective by the medical profession. **Currently, there are no proven alternative therapies to conventional cancer care for patients with HL. Patients should not use alternative remedies to replace the care suggested by their doctors.**

Complementary therapy can be used in addition to standard therapy to help improve a patient's quality of life and to relieve the effects of drug therapy, radiation, and surgery.

For more information about complementary therapies, please view Chapter 7 of this guide and the *Integrative Oncology* fact sheet on LRF's website at lymphoma.org/publications.

Some forms of complementary therapy, also known as integrative medicines or integrative oncology are described as follows.

Chiropractic and Massage Therapy

These are the most used complementary therapies to help relieve side effects and stress. A special type of massage called oncology massage for patients with cancer can help manage stress, pain, swelling and other side effects without causing harm or interfering with cancer treatments.

Acupuncture

Uses ultra-thin needles applied to specific points on the body. It may help to relieve some side effects associated with chemotherapy like pain, nausea, fatigue, hot flashes (sudden feeling of warmth in the upper body), and neuropathy (numbness or tingling in the hands or feet).

Herbal Therapy

Uses herbal medicines made with active ingredients from plant parts, such as leaves, roots or flowers. Patients should talk to their doctor before using herbal therapies, because some may interfere with cancer treatments (e.g. vitamin C, St. John's wort). Some vitamins can actually clear the chemotherapy from the body and therefore decrease its effect. It is important to talk to your provider before taking any supplements.

Mind/Body Therapies

Meditation, guided imagery and self-hypnosis may help patients manage stress. Other practices like Tai Chi and yoga may also help improve balance and flexibility.

Chapter 15: Clinical Trials and Advances in Treatment of Patients with HL

Overview of Clinical Trials

Drugs that are not yet approved for sale by the FDA are said to be investigational. Some of these investigational drugs are being studied in laboratory experiments. This stage is often referred to as the preclinical phase. The drugs in more advanced stages of research are being studied in patients in clinical trials; these are referred to as being in the clinical phase of development. The most common way for a patient to receive an investigational drug is through a clinical trial.

A *clinical trial* is a carefully designed research study that involves patients who volunteer to participate. The purpose of cancer clinical trials is to use information from all the patient outcomes (how the patients responded to treatment) on past trials and design specific questions about new ways to prevent, diagnose, treat, or manage a disease or the side effects caused by a new or existing treatment. The goal is to "do better" than the previous trial. The investigators in clinical trials want to determine the safety and effectiveness of the treatment being investigated by making specific assessments before, during, and after the trial.

Clinical trials are not a "last resort" for patients. Every drug available today had to be tested in clinical trials before it was approved for general use, and all new and emerging treatments for HL must be tested this way before patients can use them in the future. Participating in a clinical trial can help to improve the treatment options for HL patients for many years to come. Patients with all stages of HL can participate in clinical trials, whether at the time of initial diagnosis or at relapse.

To find out more about getting access to investigational drugs and clinical trials, visit the National Cancer Institute's (NCI's) website at www.cancer.gov and search for "access to investigational drugs."

Alternatively, visit www.clinicaltrials.gov to search for trials using a particular drug or to find clinical trials nearby. Patients should check with their doctor or the Lymphoma Research Foundation (LRF) Helpline "Clinical Trials Information Service" for additional information and recent updates.

See Chapter 8 of this guide for more general information about the topics below:

- What is a Clinical Trial?
- Why Is a Placebo Sometimes Used in Phase III Trials?
- Should a Patient Participate in a Clinical Trial?
- What Is Informed Consent in a Clinical Trial?
- Questions to Ask About a Clinical Trial
- What Is the Cost of Participating in a Clinical Trial?

Advances in Treatment of Patients With HL

Doctors and scientists around the world are working very hard to improve currently available treatment options and find better and safer drugs to treat patients with HL. Advances are being made in different areas including genetics, molecular biology, immunology, treatments, and supportive care. In particular, recent developments have provided a better understanding of the biology of the disease. Ongoing research and advances in treatment of patients with HL are described below.

Chemotherapy

Researchers are trying to develop new chemotherapy drugs, improve existing drugs, and find better ways to combine different dosages and sequences of existing drugs. The goal is to develop treatment regimens that are better at killing HL cells while leaving healthy cells alone, decreasing the chance of side effects. Researchers are also investigating the best way to use imaging techniques to evaluate responses to therapy and to determine future doses.

Stem Cell Transplantation

Ongoing research in stem cell transplantation is focused on finding better ways to collect stem cells from the bone marrow or peripheral blood; reducing or

eliminating *graft-vs-host disease* (where the graft attacks the patient's healthy cells) in allogeneic transplants; improving ways to remove all lymphoma cells from stem cell samples used for autologous transplants; and developing more effective regimens for reduced-intensity stem cell transplantation (uses less chemotherapy and radiation than a standard transplant).

Immunotherapy

Monoclonal antibodies

Monoclonal antibodies under study for HL include magrolimab, a first-in-class therapy against CD47, and favelezimab, directed against the inhibitory receptor lymphocyte activation gene-3 protein (LAG3). Although they have different targets, both these monoclonal antibodies activate the body's mechanisms of defense against the HL cells. Another example of a monoclonal antibody under study for HL is axatilimab (SNDX-6352), which inhibits colony stimulating factor-1 receptor (CSF-1R) and blocks mechanisms that cancer cells use to survive and spread.

Bispecific antibodies

Bispecific antibodies bind to two different antigens at once and bring together cells that have these two targets. An example of a bispecific antibodies under study for relapsed and refractory HL is AFM13, which binds to both natural killer (NK) cells (cells of the immune system) that express CD16A and HL cells that express CD30. Blinatumomab (Blincyto), a bispecific CD19-directed CD3 T-cell engager, is also being studied in patients with HL.

Radioimmunotherapy

Yttrium-90-labeled basiliximab is a monoclonal antibody which targets the CD25 receptor. It is being studied in clinical trials as a potential vehicle to deliver radioactive substances to HL cells and kill them.

Checkpoint inhibitors

Just like the HL therapies nivolumab (Opdivo) and pembrolizumab (Keytruda), other checkpoint inhibitors that target the PD-1/PD-L1 pathway—avelumab (Bavencio), camrelizumab(SHR-1210), sintilimab (Tyvyt), and tislelizumab (BGB-A317)—are currently being investigated for use in patients with HL. Another checkpoint inhibitor called ipilimumab

(Yervoy) that targets the CTLA-4 checkpoint is also in clinical trials for the treatment of HL. Ipilimumab is currently approved by the FDA to treat melanoma (skin cancer), but it has also shown promise as an HL therapy. Vudalimab (XmAb20717) is a bispecific antibody that inhibits both PD-1 and CTLA-4 checkpoints and is also in clinical trials for HL.

Immunomodulatory drugs

Immunomodulatory drugs (IMiDs) interact with the immune system to encourage the destruction of cancer cells. The IMiD agent lenalidomide (Revlimid), which is already approved for the treatment of other blood cancers such as multiple myeloma and mantle cell lymphoma (MCL), is currently being evaluated for use in the treatment of patients with HL, both alone and in combination with other therapies such as checkpoint inhibitors.

CAR T-Cell Therapy

Chimeric antigen receptor (CAR) T-cells are a special type of cellular immunotherapy that uses a modified version of the patient's T-cells to fight cancer. These are being studied to treat patients with relapsed and refractory HL. Some patients have had very good responses to CAR T-cell therapy, with no malignant tumor cells detected after treatment. However, this therapy can sometimes result in serious side effects such as cytokine release syndrome, which is characterized by mild to moderate flu-like symptoms, reduced blood pressure, heart arrhythmias, and difficulty breathing, as well as neurologic toxicity. Medicines are now available to prevent or alleviate many of these symptoms. Research is ongoing to improve this novel therapy.

Targeted therapies

A better understanding of the biology and genetics of HL is helping researchers identify specific molecules in lymphoma cells that may be good targets for new drugs. These molecules usually have important roles in controlling the growth and survival of lymphoma cells. The drugs that target these molecules are called *targeted therapies*. Targeted therapies attack cancer cells in a more specific way than chemotherapy drugs and are less likely to kill or damage healthy cells, making it less likely for these agents to cause serious side effects.

Examples of targeted therapies, some of which have been FDA-approved for use in other types of lymphoma, leukemia, and solid cancers, that are being studied for HL in clinical trials include:

- Histone deacetylase (HDAC) inhibitors and vorinostat (Zolinza)
- Kinase inhibitors, including:
  - Bruton tyrosine kinase (BTK) inhibitors such as ibrutinib (Imbruvica)
  - Janus-associated kinase (JAK) inhibitors such as ruxolitinib (Jakafi) and itacitinib (INCB039110)
  - Mammalian target of rapamycin (mTOR) inhibitors such as everolimus (Afinitor)

Other Systemic Therapies

Systemic drugs are therapies that work throughout the body. Ongoing investigation of many novel non-chemotherapeutic agents may lead to the development of HL treatments that may attack HL cells that are resistant to conventional chemotherapy and radiation therapy. These therapies are being tested for use in both newly diagnosed and relapsed/refractory HL and include a modified interleukin-2 (a type of protein) (THOR-707) and regenerative medicine (that replaces and repairs the normal function of cells, organs, and tissues) (AB-205). The research being conducted today is changing the entire landscape of HL treatment now and in the future. The promise of this research is a compelling reason for patients with HL to consider participating in a clinical trial at any stage of treatment.

Radiation Therapy

Researchers are working to continue reducing the size of radiation therapy treatment fields and the dose of radiation delivered, with the goal of limiting radiation exposure to normal organs and tissues and hopefully reducing long-term risks of radiation therapy.