Understanding Lymphoma and Chronic Lymphocytic Leukemia (CLL)

Hodgkin Lymphoma: Relapsed/Refractory

Lymphoma Research Foundation

Hodgkin lymphoma (HL), also known as Hodgkin disease, represents about 10% of all lymphomas in the United States. It is estimated that 8,830 new cases of HL will be diagnosed in the United States in 2023. HL can occur in both children and adults, but it is most common in young adults between the ages of 20 and 29 years.

HL is often characterized by the presence of very large cells called Reed-Sternberg (RS, Figure 1) cells. This type of lymphoma usually starts in the lymph nodes (small bean-shaped structures that help the body fight disease, Figure 2) and can spread to other lymph nodes and, rarely, to other organs.

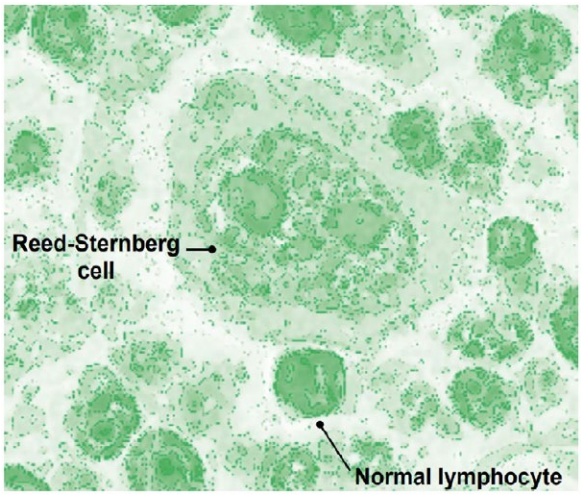

Figure 1: Example of a normal *lymphocyte* (a type of white blood cell that fights infection and cancer) and a Reed-Sternberg cell found in HL. HL, Hodgkin lymphoma.

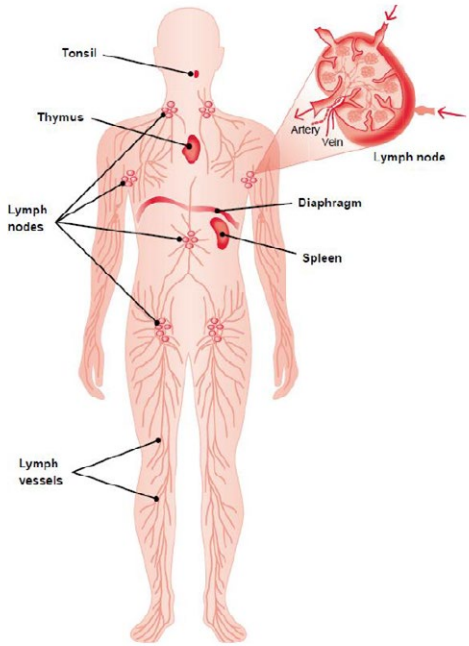

Figure 2: The lymphatic system and lymph nodes.

Common signs and symptoms of HL include:

- Swelling of the lymph nodes (usually painless).
- Fever.
- Night sweats.
- Unexplained weight loss.
- Itching.
- Lack of energy.

While most people who have these complaints do not have HL, anyone with persistent symptoms should see a physician to make sure that lymphoma is not present.

For more information on diagnosis and disease staging for relapsed and refractory HL, please view the *Understanding Lymphoma and CLL Guide* on the Foundation's website (visit **lymphoma.org/publications**).

Common Types of HL

The two main types of Hodgkin lymphoma are classical HL (cHL, which accounts for over 90% of all cases) and nodular lymphocyte-predominant HL (NLPHL, around 5 percent of all cases).

The four subtypes of cHL are:

- Nodular sclerosis.
- Mixed cellularity.
- Lymphocyte-depleted.
- Lymphocyte-rich.

Treatment options for patients with NLPHL differ from those available to patients with cHL.

Relapsed or Refractory Disease

For patients who *relapse* (disease returns after treatment) or become *refractory* (disease does not respond to treatment), secondary therapies are often successful in providing remission (disappearance of signs and symptoms) and may even cure the disease. For cHL, most relapses usually occur within the first three years following diagnosis, although some relapses occur much later. Patients who relapse often have the same symptoms they had when first diagnosed with HL.

Treatment Options

A number of treatment options are available for patients with relapsed or refractory cHL. The exact treatment a doctor recommends depends on several factors, including the *timing of the relapse* (how long it takes to relapse after the treatment), age and overall health of the patient, *disease stage* (how much the cancer has grown and if it has spread in the body), and previous therapies received.

The standard treatment (the proper treatment that is widely used by healthcare professionals and accepted by medical experts) for patients with relapsed/refractory cHL without other major health conditions consist of systemic therapy (treatment with drugs that travel in the bloodstream throughout the body), and can include:

- *Immunotherapy* (drugs that stimulate the immune system to fight cancer, see **Table 1**). These can be used alone or in combination with each other:
  - *Monoclonal antibodies* (a protein made in the laboratory that binds to cancer cells and helps the immune system destroy them) such as nivolumab (Opdivo) and pembrolizumab (Keytruda).
  - An *antibody-drug conjugate* (ADC) such as brentuximab vedotin (Adcetris) is a monoclonal antibody attached to a chemotherapy drug. The monoclonal antibody in the ADC recognizes and binds to a protein on the cancer cell surface. Once the ADC is inside the cell, the chemotherapy drug separates from the ADC and kills the cancer cell by targeting cell multiplication.
- *Chemotherapy* (drugs that stop the growth of or kill cancer cells) regimens (see Table 2).
- *Chemoimmunotherapy* which is a combination of chemotherapy with immunotherapy such as BvB (brentuximab vedotin [Adcetris] and bendamustine [Treanda]).
- *Stem cell transplantation* (SCT, the patient is treated with high-dose chemotherapy or radiation to remove their blood-forming cells or stem cells, and then receives healthy stem cells to restore the immune system and the bone marrow's ability to make new blood cells).
  - *Autologous* SCT (a patient's own stem cells are infused after high-dose chemotherapy). For more information on transplantation, view the *Understanding Cellular Therapy* publication on the Lymphoma Research Foundation's website (**lymphoma.org/publications**).
- *Radiation therapy* (uses high-energy radiation to kill cancer cells) as consolidation therapy (treatment given after cancer has disappeared following initial therapy, to kill any cancer cells that may be left in the body).
  - Involved-site radiation therapy (radiation therapy that is applied to treat a specific area where the cancer is located at)

Therapeutic options for relapsed or refractory NLPHL include systemic therapy with the anti-CD20 antibody rituximab (Rituxan) either alone or in combination with chemotherapy. Radiation therapy may also be used.

Treatments Under Investigation

In addition to conventional (traditional) chemotherapies, there are several new agents (treatments) currently being tested in clinical trials for patients with relapsed or refractory cHL:

- Anti-CD30-chimeric antigen receptor (CAR) T cells
- Axatilimab
- AFM13 (Acimtamig)
- AZD7789
- Camrelizumab (SHR-1210)
- Everolimus (Afinitor)
- Ibrutinib (Imbruvica)
- Itacitinib (INCB039110)
- Ipilimumab (Yervoy)
- Lenalidomide (Revlimid)
- Magrolimab (5F9)
- Penpulimab
- Prolgolimab
- Ruxolitinib (Jakafi)
- Tislelizumab (BGB-A317)

Table 1: Immunotherapy drugs approved to treat relapsed or refractory cHL.

Treatment	Approved Indications
Brentuximab vedotin (Adcetris) Antibody-drug conjugate that targets the CD30 protein	• Adult patients with a) previously untreated Stage III or IV cHL (in combination with AVD), b) at high risk of relapse or progression after auto-HSCT, c) after failure of auto-HSCT, d) or after failure of ≥ 2 chemotherapy regimens (in patients who are not auto-HSCT candidates) • Pediatric patients (≥ 2 years old) with previously untreated high risk cHL (in combination with EPOCH)
Nivolumab (Opdivo) Immune checkpoint inhibitor that blocks the PD-1 receptor	• Adult patients with cHL that has relapsed or progressed after auto-HSCT and brentuximab vedotin (Adcetris) or ≥ 3 lines of systemic therapy (including auto-HSCT)
Pembrolizumab (Keytruda) Immune checkpoint inhibitor that blocks the PD-1 receptor	• Adult patients with relapsed or refractory cHL • Pediatric patients with refractory cHL, or cHL that has relapsed after ≥ 2 lines of therapy

AVD, doxorubicin, vinblastine and dacarbazine; cHL, classical Hodgkin lymphoma; EPOCH, etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin; auto-HSCT, autologous hematopoietic stem cell transplant; PD-1, programmed death receptor-1.

Table 2: Chemotherapy regimens used to treat relapsed or refractory cHL.

Regimen	Description
BeGEV	Bendamustine (Treanda), gemcitabine, and vinorelbine
DHAP	Dexamethasone, cisplatine, high-dose cytarabine
GVD	Gemcitabine, vinorelbine, and doxorubicin
ICE	Ifosfamide, carboplatin, and etoposide
IGEV	Ifosfamide, gemcitabine, and vinorelbine

cHL, classical Hodgkin lymphoma.

Patients with relapsed or refractory NLPHL may enroll in a clinical trial or be treated with a combination of rituximab (Rituxan) and chemotherapy such as:

- Bendamustine
- ·DHAP (dexamethasone, cisplatin, and high-dose cytarabine)
- ICE (ifosfamide, carboplatin, and etoposide)
- IGEV (ifosfamide, gemcitabine, and vinorelbine)

It is critical to remember that scientific research is always changing. Treatment options may change as new treatments are discovered and current treatments are improved. Therefore, it is important that patients check with their physician or with the Foundation for any treatment updates that may have recently appeared.

Clinical Trials

Clinical trials are crucial in identifying effective drugs and optimal treatment doses for patients with lymphoma. Because the optimal HL treatment may vary for each patient, clinical trials are very important and will identify the best treatment options in this disease. Patients interested in participating in a clinical trial should view the *Understanding Clinical Trials* fact sheet on the Foundation's website (**lymphoma.org/publications**), talk to their physician, or contact the Foundation's Helpline for an individualized clinical trial search by calling **(800) 500-9976** or emailing **helpline@lymphoma.org**.

Follow-up

Patients with lymphoma should have regular visits with a physician who is familiar with their medical history and the treatments they have received. During these visits, medical tests (like computed tomography [CT] or positron emission tomography [PET] scans) may be required to evaluate the need for additional treatment.

Some treatments can cause long-term side effects (occur during treatment and continue for months or years) or late side effects (appear only months, years or decades after treatment has ended). These can vary depending on the following factors:

- Duration of treatment (how long the treatment has lasted)
- Frequency of treatment (how often the treatment was administered)
- Type of treatment given
- Patient's age and gender
- Patient's overall health of at the time of treatment.

A physician will check for these effects during follow-up care. Visits may become less frequent the longer the patient stays in remission (lack of signs and symptoms of disease).

Patients and their care partners are encouraged to keep copies of all medical records. This includes test results as well as information on the types, amounts, and duration of all treatments received. Medical records are important for keeping track of any side effects resulting from treatment or potential disease recurrences. The Foundation's award-winning Focus On Lymphoma mobile app and Lymphoma Care Plan (lymphoma.org/publications) can help patients manage this documentation.

Lymphoma Care Plan

Keeping your information in one location can help you feel more organized and in control. This also makes it easier to find information pertaining to your care and saves valuable time. The Foundation's Lymphoma Care Plan document organizes information on your health care team, treatment regimen, and follow-up care. You can also keep track of health screenings and any symptoms you experience to discuss with your health care provider during future appointments. The Lymphoma Care Plan document can be accessed by visiting **lymphoma.org/publications**.

Patient Education Programs

The Foundation also offers a variety of educational activities, including live meetings and webinars for individuals looking to learn directly from lymphoma experts. These programs provide the lymphoma community with important information about the diagnosis and treatment of lymphoma, as well as information about clinical trials, research advances and how to manage/cope with the disease. These programs are designed to meet the needs of a lymphoma patient from the point of diagnosis through long-term survivorship. To view our schedule of upcoming programs, please visit **lymphoma.org/programs**.

Helpline

The Foundation's Helpline staff are available to answer your general questions about lymphoma and treatment information, as well as provide individual support and referrals to you and your loved ones. Callers may request the services of a language interpreter. The Foundation also offers a one-to-one peer support program called the Lymphoma Support Network and clinical trials information through our Clinical Trials Information Service. For more information about any of these resources, visit our website at **lymphoma.org**, or contact the Helpline at **(800) 500-9976** or **helpline@lymphoma.org**.

Para información en Español, por favor visite **lymphoma.org/es**. (For Information in Spanish please visit **lymphoma.org/es**).

Focus on Lymphoma Mobile App

Focus on Lymphoma is the first app to provide patients and their care partners with tailored content based on lymphoma subtype, and actionable tools to better manage diagnosis and treatment. Comprehensive lymphoma management, conveniently in one secure and easy-to-navigate app, no matter where you are on the care continuum. Get the right information, first, with resources from the entire Lymphoma Research Foundation content library, use unique tracking and reminder tools, and connect with a community of specialists and patients. To learn more about this resource, visit our website at **lymphoma.org/mobileapp**, or contact the Foundation's Helpline at **(800) 500-9976** or **helpline@lymphoma.org**.

Lymphoma Research Foundation

Research. Community. Cure.

Helpline
(800) 500-9976
helpline@lymphoma.org

lymphoma.org
lymphoma@lymphoma.org

Stay Connected

The Lymphoma Research Foundation appreciates the expertise and review of our Editorial Committee:

Leo I. Gordon, MD, FACP
Co-Chair
Robert H. Lurie Comprehensive Cancer Center of Northwestern University

Kristie A. Blum, MD
Co-Chair
Emory University School of Medicine

Jennifer E. Amengual, MD
Columbia University

Carla Casulo, MD
University of Rochester Medical Center

Alex Herrera, MD
City of Hope

Shana Jacobs, MD
Children's National Hospital

Patrick Connor Johnson, MD
Massachusetts General Hospital

Manali Kamdar, MD
University of Colorado

Ryan C. Lynch, MD
University of Washington

Peter Martin, MD
Weill Cornell Medicine

Neha Mehta-Shah, MD, MSCI
Washington University School of Medicine in St. Louis

M. Lia Palomba, MD
Memorial Sloan Kettering Cancer Center

Pierluigi Porcu, MD
Thomas Jefferson University

Sarah Rutherford, MD
Weill Cornell Medicine

GLOW
The Global nLPHL One Working Group

Supported through grants from:

Genentech
A Member of the Roche Group
Biogen
AstraZeneca
MERCK
AFFIMED