Understanding Lymphoma and Chronic Lymphocytic Leukemia (CLL)

Diffuse Large B-Cell Lymphoma

Lymphoma Research Foundation

Diffuse large B-cell lymphoma (DLBCL) is the most common form of non-Hodgkin lymphoma (NHL). It accounts for approximately 1 in 3 new cases of B-cell NHL in the United States.

DLBCL is slightly more common in men, and in people who are over 60 years old. While the incidence (number of new cases) increases with age (half of the patients are over 60 years old), DLBCL can also occur in children.

DLBCL is an *aggressive* (fast-growing) lymphoma that can appear in lymph nodes (bean-shaped structures that help the body fight infection) and often the spleen, liver, or bone marrow (the spongy tissue inside the bones). The first sign of DLBCL is usually a painless, rapid swelling in the neck, underarms, or groin caused by enlarged lymph nodes. For some patients, this swelling may be painful. Other symptoms may include:

- night sweats
- fever
- unexplained weight loss
- fatigue (extreme tiredness)
- loss of appetite
- shortness of breath
- pain

Diagnosis and Staging

To confirm a diagnosis of DLBCL, doctors need to collect a sample of the affected lymph node and examine it under a microscope. This procedure is called a *biopsy*, and it can be done under local or general anesthesia. Once the diagnosis of DLBCL is confirmed, the next step is to understand the location of the disease in the body (disease staging). Because DLBCL is a blood cancer, it is important to look for any signs of lymphoma across the entire body. This is usually done with a positron emission tomography (PET) scan, which uses a special dye that is injected into the patient and shows where the cancer is. Staging may also include:

- *Bone marrow biopsy* (a procedure that collects a small sample of the spongy tissue inside the bone), to search for signs of cancer in the bones.
- *Spinal tap* or *lumbar puncture* (a nzeedle is inserted into the lower back to collect a sample of the fluid that surrounds the brain and spinal cord), to look for signs of cancer in the central nervous system (CNS, the brain and spinal cord).

The physician will use the results of these tests to assess the stage of the lymphoma. NHL is categorized as Stages I (limited disease) to IV (advanced disease), as shown in the figure below.

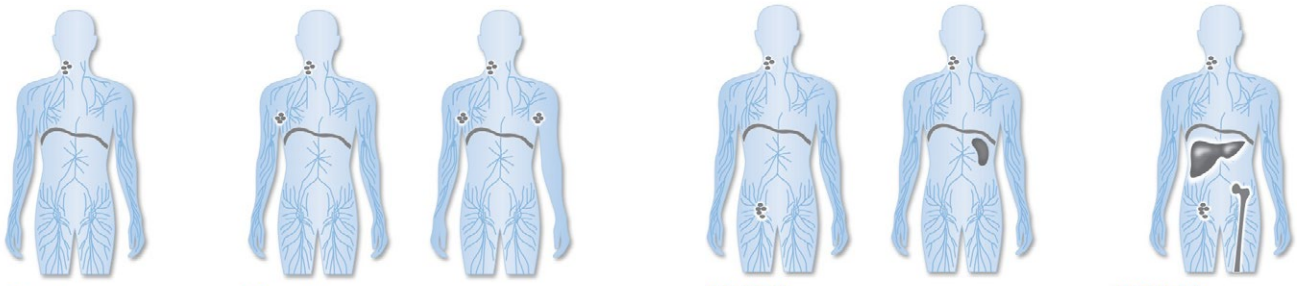
Staging is needed to choose an appropriate treatment. The majority of patients with DLBCL have advanced-stage disease but treatment can help achieve long-term remission (disappearance of signs of cancer for a long period). Patients interested in learning more about scans and staging should view the *Understanding Lymphoma* guide on the Foundation's website (visit **lymphoma.org/publications**).

Subtypes of DLBCL

There are several subtypes of DLBCL. To classify the specific DLBCL subtype, doctors may require additional tests that study:

- Cancer cell morphology: looking at the cancer cells under the microscope to examine their shape, structure, and form.
- Cancer markers: using special methods (like immunohistochemistry and flow cytometry) to look for specific proteins at the surface of cancer cells.
- Cancer genetics: using genetic tests (like fluorescence in situ hybridization or FISH) to detect mutations (permanent changes in the DNA [deoxyribonucleic acid, the molecule that carries genetic information inside the cell]) on a specific gene (a small portion of DNA that has the information needed to determine a person's physical and biological traits).

Figure 1: Staging of NHL according to the Lugano system. This system categorizes NHL from Stage I-II (limited disease) to III-IV (advanced disease), based on whether the cancer is restricted to a single group of lymph nodes, has spread to other lymph nodes, or has reached the bone marrow (the spongy tissue inside the bones) and/or other organs (like the liver or lungs).



Stage I
Involvement of a single lymph node or group of adjacent nodes

Stage II
Involvement of two or more groups of lymph nodes on the same side of the *diaphragm* (muscle that separates the chest from the abdomen)

Stage III
- Involvement of lymph nodes on both sides of the diaphragm, or
- Involvement of lymph nodes above the diaphragm plus spleen involvement

Stage IV
Widespread disease in lymph nodes, bone marrow, and organ involvement, such as liver or lungs

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The subtype of DLBCL may affect a patient's prognosis (how well a patient will do with standard treatment) and treatment options. Most cases of DLBCL do not fall into a specific subtype and are referred to as diffuse large B-cell lymphoma, not otherwise specified (DLBCL-NOS). The different types of DLBCL-NOS are named according to their cell of origin (the normal cell that originated the cancer) and include:

- germinal center B-cell-like (GCB).
- activated B-cell-like (ABC).

Patients with the GCB subtype may have a better response to standard chemotherapy than those with the ABC subtype. Other subtypes of DLBCL are less frequent and include:

- primary mediastinal B-cell lymphoma (affects a specific region of the chest and occurs mainly in younger patients).
- primary CNS lymphoma (affects the brain and/or spinal cord).

For more information about CNS lymphoma, patients should view the *CNS Lymphoma* fact sheet on the Foundation's website (visit lymphoma.org/publications).

DLBCL can also result from the transformation of slow-growing lymphoma, such as follicular lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma, or nodular lymphocyte-predominant Hodgkin lymphoma. These transformed lymphomas usually require more intensive types of treatment. For more information about transformed lymphoma, please view the *Transformed Lymphoma* fact sheet on the Foundation's website (visit lymphoma.org/publications).

It is important to note that DLBCL is a complex disease, and new subtypes may be discovered in the future. On the other hand, some cases that were previously considered to be a subtype of DLBCL are now diagnosed as separate diseases, like high-grade B-cell lymphoma (HGBL). For more information, patients should view the *High-Grade B-Cell Lymphoma* fact sheet on the Lymphoma Research Foundation's website (lymphoma.org/publications).

Treatment Options

DLBCL treatment typically begins shortly after diagnosis. The aim is to achieve durable remission or cure. Treatment types for DLBCL include:

- *Chemoimmunotherapy* is a combination of *chemotherapy* (drugs that stop the growth of or kill cancer cells) with *immunotherapy* (drugs that use the body's immune system to fight cancer).
  - The most common approach is combination of chemotherapy with a *monoclonal antibody* (a protein produced in the laboratory that recognizes cancer cells and helps the body fight cancer) that targets CD20 (a protein found at the surface of lymphoma cells). Rituximab (Rituxan) is the most commonly used anti-CD20 monoclonal antibody and it is given *intravenously* (injected into a vein). Rituxan and hyaluronidase human (Rituxan Hycela), a form of rituximab that is injected *subcutaneously* (under the skin), may be an option for some patients.
- Radiation therapy that uses high-energy radiation to kill cancer cells.

The most widely used chemoimmunotherapy combination regimen for DLBCL is R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone). This regimen is usually given in 21-day *cycles* (a period of treatment followed by a period of rest that is repeated on a regular schedule). Sometimes etoposide (VePesid, Toposar, Etopophos) is added to this regimen, in a drug combination called R-EPOCH. Another treatment option for DLBCL is polatuzumab vedotin (Polivy) in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone (Pola-R-CHP). In some cases, treatment may involve radiation therapy. For many patients with DLBCL, the initial treatment can lead to disease remission (disappearance of signs and symptoms) or a cure.

It is important to understand that patients should speak with their healthcare providers about their options in case they need further treatment in the future. For patients who become primary refractory (no longer respond to first line of treatment) or relapse (disease returns after treatment) within 12 months, the standard second-line therapy include:

- Chimeric antigen receptor (CAR) T-cell therapies (a special type of immunotherapy that uses the patient's immune cells to fight cancer)
  - Axicabtagene ciloleucel (Yescarta)
  - Lisocabtagene maraleucel (Breyanzi)

Patients should talk to their doctors about having a consultation with a physician at an authorized CAR T center early after a relapse or if the lymphoma does not respond to the initial treatment. For more information on the CAR T-cell therapy process, please view the Understanding Cellular Therapy Guide at lymphoma.org/publications. For patients who have a late relapse (disease returns after 12 months) or do not respond to standard second-line CAR T-cell therapy, several other second and third-line therapies are described in Table 1.

For more information, view the *Relapsed/Refractory DLBCL* publication on the Lymphoma Research Foundation's website (visit lymphoma.org/publications).

Table 1: Second- and Third-Line Treatments for Relapsed or Refractory DLBCL

Patients Who Are Candidates for a Stem Cell Transplant	
Preferred second-line treatment is chemotherapy	DHAP +/- rituximab (Rituxan)
	DHAX +/- rituximab (Rituxan)
	GDP +/- rituximab (Rituxan)
	ICE +/- rituximab (Rituxan)
	ESHAP +/- rituximab (Rituxan)
	GemOx +/- rituximab (Rituxan)
	MINE +/- rituximab (Rituxan)
Patients Who Are NOT Candidates for a Stem Cell Transplant	
Chemotherapy	GemOx +/- rituximab (Rituxan)
	CEOP +/- rituximab (Rituxan)
	Dose-adjusted EPOCH +/- rituximab (Rituxan)
	GDP +/- rituximab (Rituxan) or (gemcitabine, dexamethasone, carboplatin) +/- rituximab
Other second-line regimens	Polatuzumab vedotin (Polivy) +/- rituximab (Rituxan) and +/- bendamustine (Treanda)
	Tafasitamab-cxix (Monjuvi) and lenalidomine (Revlimid)
	Axicabtagene ciloleucel (Yescarta)
	Lisocabtagene maraleucel (Breyanzi)
	Rituximab (Rituxan)
After ≥ 2 lines of systemic therapy	Axicabtagene ciloleucel (Yescarta)
	Tisagenlecleucel (Kymriah)
	Lisocabtagene maraleucel (Breyanzi)
	Selinexor (Xpovio)
	Glofitamab (Columvi)
	Epcoritamab (Epkinly)
	Polatuzumab vedotin (Polivy) +/- rituximab (Rituxan) and +/- bendamustine (Treanda)
	Loncastuximab tesirine (Zynlonta)
Other therapies for DLBCL	Brentuximab vedotin (Adcetris)
	Ibrutinib (Imbruvica)
	Lenalidomide (Revlimid) +/- rituximab (Rituxan)

CAR: chimeric antigen receptor; CEOP: cyclophosphamide, etoposide, vincristine and prednisone; DHAP: dexamethasone, cisplatin and cytarabine; DHAX: dexamethasone, cytarabine and oxaliplatin; DLBCL: diffuse large B-cell lymphoma; GDP: gemcitabine, dexamethasone and cisplatin or carboplatin; ICE: ifosfamide, carboplatin and etoposide; EPOCH: etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin; ESHAP: etoposide, methylprednisolone, cytarabine and cisplatin; GemOx: gemcitabine and oxaliplatin; MINE: mesna, ifosfamide, mitoxantrone, etoposide.

Treatments Under Investigation

Many new treatments (also referred to as investigational drugs) and combination therapies are currently being studied in clinical trials for patients with newly diagnosed DLBCL. Results from these clinical trials may improve or change the current standard of care (the proper treatment that is widely used by healthcare professionals and accepted by medical experts). **Table 2** (below) lists some of these investigational drugs that can be accessed through a clinical trial. For more information on clinical trials, view the *Understanding Clinical Trials* publication on the Lymphoma Research Foundation's website at **lymphoma.org/publications**. Please consult with your doctor or a specialist in DLBCL to discuss any questions you may have about clinical trials.

It is important to remember that scientific research is always evolving. Treatment options may change as new treatments are discovered and current treatments are improved. Therefore, it is important that patients check with their physician or with the Foundation for any treatment updates that may have recently appeared. It is also very important that all patients with DLBCL consult a specialist to clear up any questions.

Clinical Trials

Clinical trials are crucial in identifying effective drugs and treatment optimal doses for patients with lymphoma. Patients interested in participating in a clinical trial should view the *Understanding Clinical Trials* fact sheet on the Foundation's website (visit **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**.

Table 2: Selected agents under investigation for newly diagnosed DLBCL in Phase 2-3 clinical trials

Agent (drug)	Class (type of treatment)
Atezolizumab (Tecentriq)	Immune checkpoint inhibitor; anti-PD1
Acalabrutinib (Calquence)	Targeted therapy, BTK inhibitor
Brentuximab vedotin (Adcetris)	Antibody-drug conjugate; anti-CD30
Camrelizumab	Immune checkpoint inhibitor; anti-PD1
Lenalidomide (Revlimid)	Immunomodulatory drug.
Itacitinib	Targeted therapy; JAK1 inhibitor
Mosunetuzumab (Lunsumio)	Bispecific monoclonal antibody; anti-CD20
Orelabrutinib (ICP-022)	Targeted therapy, BTK inhibitor
Odronextamab	Bispecific monoclonal antibody; anti-CD20
Purinostat mesylate (PM)	Targeted therapy; HDAC inhibitor
Selinexor (Xpovio)	Targeted therapy; selective inhibitor of nuclear export
Sintilimab (Tyvyt)	Immune checkpoint inhibitor; anti-PD1
Tafasitamab (Monjuvi)	Monoclonal antibody; anti-CD19
Tazametostat (Tazverik)	Targeted therapy: EZH2 inhibitor
Tislelizumab	Immune checkpoint inhibitor; anti-PD1
Tucidinostat	Targeted therapy; HDAC inhibitor
Zanubrutinib (Brukinsa)	Targeted therapy; BTK inhibitor
Zilovertamab vedotin	Antibody-drug conjugate; anti-extracellular ROR1

BTK, bruton's tyrosine kinase; EZH2, enhancer of zeste homolog 2; HDAC, histone deacetylase; PD-1, programmed cell death protein 1; ROR1, Receptor tyrosine kinase-like orphan receptor 1.

Follow-up

Patients with DLBCL 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 (CT scans and 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 lasted)
- frequency of treatment (how often the treatment was administered)
- type of treatment given
- patient age and gender
- patient overall health 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.

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 will be 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 (lymphoma.org/mobileapp) 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

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Supported through grants from:

Genentech, A Member of the Roche Group | Biogen | MERCK | AstraZeneca

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Last updated May 2024