Understanding Lymphoma and
Chronic Lymphocytic Leukemia (CLL)

Diffuse Large B-Cell Lymphoma: Relapsed/Refractory

Lymphoma Research Foundation

Diffuse large B-cell lymphoma (DLBCL) is the most common form of non-Hodgkin lymphoma (NHL), accounting for about 1 out of every 3 NHLs in the United States. DLBCL is slightly more common in men and in people who are over 60 years old.

DLBCL is an *aggressive* (fast-growing) lymphoma that can appear in lymph nodes (bean-shaped structures that help the body fight infection, Figure 1) and often the spleen, liver, and bone marrow (the spongy tissue inside the bones), though it can appear anywhere in the body.

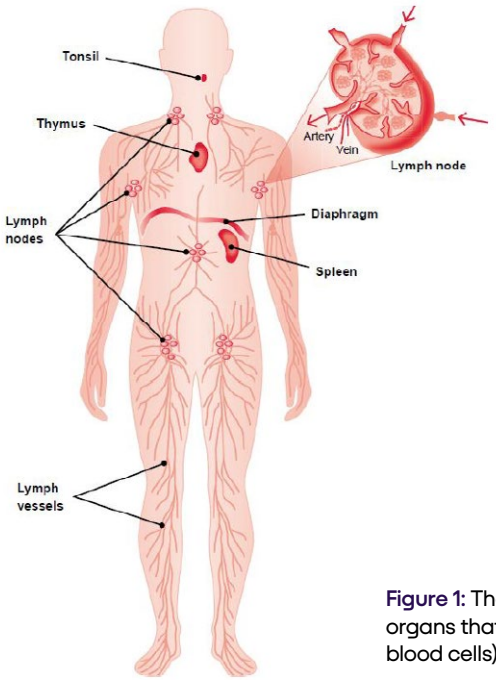

Figure 1: The lymphatic system (tissues and organs that produce, store, and carry white blood cells) and lymph nodes.

Symptoms and Diagnosis

A common first sign of DLBCL is 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

To confirm a diagnosis of DLBCL, doctors need to collect a sample of the affected tissue and examine it under the microscope. This procedure is called a *biopsy*. Once a diagnosis of DLBCL is confirmed, the next step is to understand where the disease is located and how far it has progressed. This is referred to as *disease staging*. For more information on diagnosis and disease staging, please view the *Understanding Lymphoma Guide* on the Foundation's website (visit lymphoma.org/publications).

Subtypes of DLBCL

There are several subtypes of DLBCL. Doctors determine the DLBCL subtype based on testing of the tumor tissue, as well as the *clinical presentation* (e.g., signs, symptoms, and location). Each DLBCL subtype has a different *prognosis* (the likely outcome of the disease) and may be treated differently. Most cases of DLBCL do not fall into a specific subtype and are called DLBCL-not otherwise specified (DLBCL-NOS), which are classified according to their cell of origin (the normal white blood cell that originated the cancer) as:

- 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; however, there are also many other factors involved in DLBCL prognosis. Keep in mind that no two patients are alike and that statistics can only predict how a large group of patients will do (not what will happen to an individual patient). The doctor most familiar with the patient's situation is in the best position to interpret these statistics and understand how well they apply.

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**).

Relapsed or Refractory Disease

Although DLBCL is often cured, between 30 to 40% of patients can *relapse* (disease returns after treatment) or become *refractory* (disease does not respond to treatment). These patients are eligible for *second-line treatment* (treatment received after initial treatment), which can reduce symptoms, control cancer growth, provide a second chance at cure, and extend life.

Treatment Options

Early evaluation with a team of specialists is recommended for patients with relapsed/refractory DLBCL. Treatment options will depend on a number of factors, including when the relapse happened and whether the patient is eligible for a *stem cell transplant* (SCT) or *chimeric antigen receptor* (CAR) T-cell therapy. Therapeutic options for relapsed/refractory DLBCL are listed below (**Table 1**) and may include:

- 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 replace the ones that were destroyed). The aim is to restore the patient's immune system and the bone marrow's ability to make new blood cells.
  - *Autologous* SCT (the patient's own stem cells are used for transfusion).
  - *Allogeneic* SCT (a donor's stem cells are used for transfusion).
- CAR T-cell therapy (a special form of immunotherapy that uses the patient's own immune cells to fight cancer).
  - Axicabtagene ciloleucel (Yescarta)
  - Lisocabtagene maraleucel (Breyanzi)
- *Chemoimmunotherapy* which 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).
- *Involved-site radiation therapy* (radiation therapy is applied to treat a specific area where the cancer is located at).
- *Targeted therapy* (drugs that target specific molecules that cancer cells use to survive and spread).

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 CAR T-cell therapy, several other second and third-line therapies are available (**Table 1**):

- Chemotherapy
- Immunotherapy, including:
  - *Monoclonal antibodies* (a protein made in the laboratory that binds to cancer cells and helps the immune system destroy them) such as tafasitamab-cxix (Monjuvi)
  - *Antibody-drug conjugates* (ADC, a monoclonal antibody attached to a chemotherapy drug) such as polatuzumab vedotin (Polivy) and brentuximab vedotin (Adcetris). 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.
  - Immunomodulatory agents (drugs that regulate the immune system directly by activating or slowing down the activity of specific proteins), such as lenalidomide (Revlimid).
  - Bispecific antibodies (antibodies that recognize two different antigens, which can be on the same cell or two different cells). Bispecific antibodies used to treat lymphoma are called T-cell engagers and work by linking cancer cells to healthy immune cells such as glofitamab (Columvi) and epcoritamab (Epkinly)
- CAR T-cell therapies, including:
  - Axicabtagene ciloleucel (Yescarta)
  - Tisagenlecleucel (Kymriah)
  - Lisocabtagene maraleucel (Breyanzi)
- Targeted therapies (drugs that work by blocking molecules that cancer cells use to grow and/or spread) such as ibrutinib (Imbruvica) and selinexor (Xpovio).

Patients seeking more information about targeted therapy and immunotherapy should view the *Immunotherapy and Other Targeted Therapies* fact sheet on the Foundation's website (**lymphoma.org/publications**). For more information about stem cell transplantation and CAR T-cell therapy, please view the *Understanding Cellular Therapy Guide*, also on the Foundation's website.

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

Patients Who Are Candidates for a Stem Cell Transplant	
Chemotherapy is the preferred second-line treatment	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)
	CEPP +/- 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)

CEPP: cyclophosphamide, etoposide, prednisone and procarbazine; 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, and etoposide.

Treatments Under Investigation

Many new treatments (also referred to as investigational drugs) and combination therapies are currently being studied for the treatment of patients with relapsed/refractory 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 Foundation's website (**lymphoma.org/publications**).

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.

Table 2: Selected Agents Under Investigation for Relapsed or Refractory DLBCL in Phase 2-3

Agent (drug)	Class (type of treatment)
Abexinostat	Targeted therapy; HDAC inhibitor
Copanlisib (Aliqopa)	Targeted therapy; PI3K inhibitor
CRG-022	CAR T-cell therapy; anti-CD22
Decitabine	Chemotherapy
Mosunetuzumab (Lunsumio)	Bispecific antibody; anti-CD20
MS-553	Targeted therapy; PKC-β Inhibitor
Odronextamab (REGN1979)	Bispecific antibody; anti-CD20
Orelabrutinib	Targeted therapy; BTK inhibitor
Tislelizumab (BGB-A317)	Immunotherapy, immune checkpoint inhibitor; anti-PD-1
Venetoclax (Venclexta)	Targeted therapy; BCL-2 inhibitor
Zanubrutinib (Brukinsa)	Targeted therapy; BTK inhibitor
Zilovertamab vedotin (MK-2140)	Immunotherapy; antibody-drug conjugate

BCL-2, B-cell lymphoma 2; BTK, bruton's tyrosine kinase; CAR, chimeric antigen receptor; HDAC, histone deacetylase; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PI3K, phosphoinositide 3-kinase; PKC-β, protein kinase C beta.

Clinical Trials

Clinical trials are important in finding effective drugs and the best treatment doses for patients with relapsed or refractory DLBCL. 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 Helpline for an individualized clinical trial search by calling **(800) 500-9976** or emailing **helpline@lymphoma.org**.

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 (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**.

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