LYMPHOMA RESEARCH • FOUNDATION

Understanding Lymphoma
Diffuse Large B-Cell Lymphoma

Diffuse large B-cell lymphoma (DLBCL) is the most common form of non-Hodgkin lymphoma (NHL), accounting for about 25 percent of newly diagnosed cases of B-cell NHL in the United States.

DLBCL occurs in both men and women, although it is slightly more common in men. DLBCL can occur in childhood, however its incidence generally increases with age, as roughly half of patients are over the age of 60 years and 30% are over the age of 75 years.

DLBCL is an aggressive (fast-growing) lymphoma that can arise in lymph nodes and often the spleen, liver, bone marrow, or other organs are also affected. Often, the first sign of DLBCL is a painless, rapid swelling in the neck, underarms, or groin that is caused by enlarged lymph nodes. For some patients, the swelling may be painful. Other symptoms may include night sweats, fever, and unexplained weight loss. Patients may notice fatigue, loss of appetite, shortness of breath, or pain.

DIAGNOSIS AND STAGING

A tissue biopsy is needed for a definitive diagnosis of DLBCL. A biopsy is a surgical procedure to remove part or all of an affected lymph node or other abnormal area to look at it under a microscope. This can be done under local or general anesthesia. Once the diagnosis of DLBCL is confirmed, the next step is to understand the progression and 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, in which a small amount of radioactive dye is injected to better identify areas of disease activity. Staging may also include a bone marrow biopsy to look for lymphoma cells in the bone and sometimes a spinal tap (lumbar puncture) to determine if there are lymphoma cells in 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 to IV. Limited-stage disease (Stages I and II) represents lymphoma affecting only one area of the body, while advanced-stage disease (Stages III and IV) indicates that lymphoma has spread to several organs. Staging is needed to choose an appropriate course of treatment. The majority of patients with DLBCL have advanced-stage disease, and treatment can still be very effective in this scenario.

Patients interested learning more about scans and staging should view the Understanding NHL booklet on LRF's website (visit **lymphoma.org/publications**).

SUBTYPES OF DLBCL

There are several subtypes of DLBCL. Classification of the DLBCL subtype requires examination of cell *morphology* (shape, structure, and form) as well as specialized tests including immunohistochemistry, flow cytometry, fluorescence in situ hybridization (FISH) and molecular testing.

The subtype of DLBCL may affect a patient's *prognosis* (how well a patient will do with standard treatment) and treatment options. For instance, primary mediastinal B-cell lymphoma is a subtype of DLBCL that occurs mainly in younger patients and grows rapidly in the mediastinum (in the center of the chest). Another example is DLBCL that only affects the central nervous system (CNS) or eyes, called primary diffuse large B-cell lymphoma of the CNS, which has a poor prognosis and is treated differently than DLBCL that affects areas outside of the brain. For more information about CNS lymphoma, patients should view the *CNS Lymphoma* fact sheet on LRF's website (visit **lymphoma.org/publications**).

Most cases do not fall into one of these categories, and they are considered diffuse large B-cell lymphoma not otherwise specified (DLBCL-NOS). However, these NOS cases can be grouped into subtypes of DLBCL according to genetic features of the cancer cells. These subtypes are named according to their cell of origin and include germinal center B-cell-like (GCB) and activated B-cell-like (ABC). Each disease subtype has a different prognosis with treatment.

TREATMENT OPTIONS

DLBCL treatment is typically begun shortly after diagnosis with the intent of obtaining a durable remission or cure. A combination of chemotherapy and a monoclonal antibody targeting CD20 remains the backbone of most treatments. CD20 is a molecule expressed on the cell surface of lymphoma cells, and antibodies such as rituximab (Rituxan [for intravenous infusion]) target this molecule. Rituxan Hycela, a form of

rituximab that is injected subcutaneously (under the skin), may be an option for some patients. The most widely used combination chemotherapy regimen for DLBCL is R CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) that is usually given in 21-day cycles. Sometimes etoposide (VePesid, Toposar, Etopophos) is added to the R-CHOP regimen, resulting in a drug combination called R-EPOCH. Sometimes treatment may involve radiation therapy. For many patients with DLBCL, the initial treatment can lead to disease *remission* (disappearance of signs and symptoms). However, for patients in whom the disease becomes *refractory* (no longer responds to treatment) or *relapses* (returns after treatment), secondary therapies may be successful. Second and third-line therapies for relapsed or refractory DLBCL are included in Table 1 below. For more information, view the Relapsed/Refractory DLBCL publication on the Lymphoma Research Foundation's (LRF's) website (visit **lymphoma.org/publications**).

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

Patients Who Are Refractory to First-Line Chemoimmunotherapy or Relapsed within 1 Year of First-Line Chemoimmunotherapy	
Possible second-line treatment is CAR T cell therapy	**Axicabtagene ciloleucel (Yescarta)** **Lisocabtagene maraleucel (Breyanzi)**
Patients Who Are Candidates for a Stem Cell Transplant	
Possible second-line treatment is chemotherapy	**DHAP +/- rituximab (Rituxan)** **DHAX +/- rituximab (Rituxan)** **GDP +/- rituximab (Rituxan)** **ICE +/- rituximab (Rituxan)** **ESHAP +/- rituximab (Rituxan)** **GemOx +/- rituximab (Rituxan)** **MNE +/- rituximab (Rituxan)**
Other possible second-line regimens	**Rituximab (Rituxan),** **Tafasitamab-cxix (Monjuvi) and lenalidomine (Remvilid)** **Lisocabtagene maraleucel (Breyanzi)**
Second-Line Treatment	**Polatuzumab vedotin (Polivy) +/- rituximab (Rituxan) and +/- bendamustine (Treanda)** **Loncastuximab tesirine (Zynlonta)** **Axicabtagene ciloleucel (Yescarta)** **Tisagenlecleucel (Kymriah)** **Selinexor (Xpovio)**

CAR: chimeric antigen receptor; CEPP: cyclophosphamide, etoposide, prednisone and procarbazine; CEOP: cyclophosphamide, etoposide, vincristine and prednisone; DAHP: 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

TREATMENTS UNDER INVESTIGATION

Many novel individual and combination therapies are currently being studied in clinical trials for the treatment of patients with both newly diagnosed and relapsed/refractory DLBCL. Some investigational drugs under development for newly diagnosed DLBCL are listed below (Table 2).

Table 2. Selected agents under investigation for DLBCL in Phase 2-3 clinical trials

Agent	Class
Atezolizumab (Tecentriq)	**Immune checkpoint inhibitor; anti-PD1**
Blinatumomab (Blincyto)	**Immunotherapy; bispecific antibody**
Brentuximab vedotin (Adcetris)	**Antibody-drug conjugate; anti-CD30**
Camrelizumab	**Immune checkpoint inhibitor; anti-PD1**
Lenalidomide (Revlimid)	**Thalidomide analogue**
Loncastuximab tesirine (Zynlonta)	**Antibody-drug conjugate; anti-CD19**
Mosunetuzumab	**Immunotherapy; bispecific antibody**
Sintilimab (Tyvyt)	**Immune checkpoint inhibitor; anti-PD1**
Tislelizumab	**Immune checkpoint inhibitor; anti-PD1**
Zanubrutinib (Brukinsa)	**Targeted therapy; BTK inhibitor**

BTK, Bruton tyrosine kinase; PD-1, programmed cell death protein 1.

Clinical trials are investigating the use of these agents at various treatment stages (frontline, maintenance, etc.) and for specific patient populations, including newly diagnosed patients, the elderly, and patients with specific molecular subtypes. For example, because patients with the GCB subtype may have a better response to standard R-CHOP chemotherapy treatment than those with the ABC subtype, researchers are exploring new treatments that specifically improve outcomes for patients with ABC DLBCL. Clinical trials investigating these drugs are in various phases of development. It is critical to remember that today's scientific research is continuously evolving. Treatment options may change as new treatments are discovered and current treatments are improved, so it is important that patients check with their physician or with LRF for any treatment updates that may have recently emerged.

CLINICAL TRIALS

Clinical trials are crucial in identifying effective drugs and determining optimal doses for patients with lymphoma. Patients interested in participating in a clinical trial should view the

Understanding Clinical Trials fact sheet on LRF's website (visit **lymphoma.org/publications**), talk to their physician, or contact the LRF 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. Medical tests (CT scans and PET scans) may be required at various times during remission to evaluate the need for additional treatment.

Some treatments can cause long-term side effects or late side effects, which can vary based on duration and frequency of treatments, age, gender, and the overall health of each patient at the time of treatment. A physician will check for these effects during follow-up care. Visits may become less frequent the longer the disease remains in remission.

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

LRF'S HELPLINE AND LYMPHOMA SUPPORT NETWORK

A lymphoma diagnosis often triggers a range of feelings and concerns. In addition, cancer treatment can cause physical discomfort. The LRF Helpline staff members are available to answer your general questions about a lymphoma diagnosis 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. A part of the Helpline is LRF's one-to-one peer support programs, Lymphoma Support Network. This program connects patients and caregivers with volunteers who have experience with DLBCL, similar treatments, or challenges, for mutual emotional support and encouragement. Patients and loved ones may find this useful whether the patient is newly diagnosed, in treatment, or in remission.

MOBILE APP

Focus On Lymphoma is the first mobile application (app) that provides patients and caregivers comprehensive content based on their lymphoma subtype, including DLBCL, and tools to help manage their lymphoma such as, keep track of medications and blood work, track symptoms, and document treatment side effects. The *Focus On Lymphoma* mobile app is available for download for iOS and Android devices in the Apple App Store and Google Play. To learn more about any of these resources, visit our website at **lymphoma.org**, or contact the LRF Helpline at **(800) 500-9976** or **helpline@lymphoma.org**.

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. LRF offers a Lymphoma Care Plan as a resource for patients and their caregivers. LRF'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**.

Resources

LRF offers a wide range of free resources that address treatment options, the latest research advances, and ways to cope with all aspects of lymphoma and DLBCL. LRF also provides many educational activities, including our in- person meetings, and webinars for people with lymphoma. For more information about any of these resources, visit our websites at **lymphoma.org/DLBCL** or **lymphoma.org**, or contact the LRF 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**.)

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