Diffuse large B-cell lymphoma (DLBCL) is the most common form of non-Hodgkin lymphoma (NHL). It accounts for approximately one in three 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 located.

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 needle 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 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 on the following page.
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)

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 Central Nervous System Lymphoma fact sheet on LRF’s website [lymphoma.org/publications].

DLBCL can also result from the transformation of slow-growing lymphoma, such as follicular lymphoma (FL), chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL), or nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL). These transformed lymphomas usually require more-intensive types of treatment. For more information about transformed lymphoma, please view the Transformed Lymphomas fact sheet on LRF’s website [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 (HGDL). For more information, patients should view the High-Grade B-Cell Lymphoma fact sheet on LRF’s website [lymphoma.org/publications].

TREATMENT OPTIONS

DLBCL treatment typically begins shortly after diagnosis. The aim is to achieve durable remission (disappearance of signs of cancer for a long period) or a cure. A combination of chemotherapy and a monoclonal antibody (a protein produced in the laboratory that recognizes cancer cells and helps the body fight cancer) targeting CD20 (a protein found at the surface of lymphoma cells) remains the backbone of most treatments. The most commonly used anti-CD20 monoclonal antibody is rituximab (Rituxan), 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.

The most widely used 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 EPOCH-R. Another treatment option for DLBCL is polatuzumab vedotin-piiq (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 refractory (no longer respond to treatment) or relapse (disease returns after treatment), the standard second-line therapy is CAR T-cell therapy with axicabtagene ciloleucel (Yescarta) or lisocabtagene maraleucel (Breyanzi). Patients should talk to their doctors about having a consultation with a physician at an authorized CAR T-cell 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.

### Table 1. Second- and Third-Line Treatment Options for Relapsed or Refractory DLBCL

<table>
<thead>
<tr>
<th>Patients Who Are Candidates for a Stem Cell Transplant</th>
<th>Preferred second-line treatment is chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>DHAP +/- rituximab (Rituxan)</td>
<td>GDP +/- rituximab (Rituxan)</td>
</tr>
<tr>
<td>DHAX +/- rituximab (Rituxan)</td>
<td>ICE +/- rituximab (Rituxan)</td>
</tr>
<tr>
<td>GDP +/- rituximab (Rituxan)</td>
<td>ESHAP +/- rituximab (Rituxan)</td>
</tr>
<tr>
<td>ICE +/- rituximab (Rituxan)</td>
<td>GEMOX +/- rituximab (Rituxan)</td>
</tr>
<tr>
<td>ESHAP +/- rituximab (Rituxan)</td>
<td>MINE +/- rituximab (Rituxan)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patients Who Are Not Candidates for a Stem Cell Transplant</th>
<th>Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>GemOx +/- rituximab (Rituxan)</td>
<td>CEPP +/- rituximab (Rituxan)</td>
</tr>
<tr>
<td>CEOP +/- rituximab (Rituxan)</td>
<td>Dose-adjusted EPOCH +/- rituximab (Rituxan)</td>
</tr>
<tr>
<td>GDP +/- rituximab (Rituxan)</td>
<td>Gemcitabine and vinorelbine +/- rituximab (Rituxan)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other second-line regimens</th>
<th>Polatuzumab vedotin-piiq (Polivy) +/- rituximab (Rituxan) and +/- bendamustine hydrochloride (Treanda)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rituximab (Rituxan)</td>
</tr>
<tr>
<td></td>
<td>Tafasitamab-cxix (Monjuvi) and lenalidomide (Revlimid)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>After &gt; 2 lines of systemic therapy</th>
<th>Polatuzumab vedotin (Polivy) +/- rituximab (Rituxan) and +/- bendamustine (Treanda)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Loncastuximab tesirine-lyl (Zynlonta)</td>
</tr>
<tr>
<td></td>
<td>Axicabtagene ciloleucel (Yescarta)</td>
</tr>
<tr>
<td></td>
<td>Tisagenlecleucel (Kymriah)</td>
</tr>
<tr>
<td></td>
<td>Lisocabtagene maraleucel (Breyanzi)</td>
</tr>
<tr>
<td></td>
<td>Selinexor (Xpovio)</td>
</tr>
<tr>
<td></td>
<td>Glofitamab-gxbm (Columvi)</td>
</tr>
<tr>
<td></td>
<td>Epcoritamab-bysp (Epkinly)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other therapies for DLBCL</th>
<th>Brentuximab vedotin (Adcetris)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Ibrutinib (Imbruvica)</td>
</tr>
<tr>
<td></td>
<td>Lenalidomide (Revlimid) +/- rituximab (Rituxan)</td>
</tr>
</tbody>
</table>

Abbreviations: 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; 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.

For more information, view the Relapsed/Refractory Diffuse Large B-Cell Lymphoma publication on the LRF’s website (lymphoma.org/publications).
TREATMENTS UNDER INVESTIGATION

Many new treatments (also referred to as investigative drugs) and combination therapies are currently being studied in clinical trials for patients with both newly diagnosed DLBCL and 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 LRF’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.

Table 2. Selected Agents Under Investigation for Newly Diagnosed DLBCL in Phase 2-3 Clinical Trials

<table>
<thead>
<tr>
<th>Agent (Drug)</th>
<th>Class (Type of Treatment)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atezolizumab (Tecentriq)</td>
<td>Immune checkpoint inhibitor; anti-PD-1</td>
</tr>
<tr>
<td>Brentuximab vedotin (Adcetris)</td>
<td>Antibody-drug conjugate; anti-CD30</td>
</tr>
<tr>
<td>Camrelizumab</td>
<td>Immune checkpoint inhibitor; anti-PD-1</td>
</tr>
<tr>
<td>Lenalidomide (Revlimid)</td>
<td>Immunomodulatory drug</td>
</tr>
<tr>
<td>Loncastuximab tesirine-lpyl (Zynlonta)</td>
<td>Antibody-drug conjugate; anti-CD19</td>
</tr>
<tr>
<td>Mosunetuzumab-axgb (Lunsumio)</td>
<td>Bispecific monoclonal antibody; anti-CD20</td>
</tr>
<tr>
<td>Orelabrutinib</td>
<td>Targeted therapy, BTK inhibitor</td>
</tr>
<tr>
<td>Purinostat mesylate (PM)</td>
<td>Targeted therapy; HDAC inhibitor</td>
</tr>
<tr>
<td>Selinexor (Xpovio)</td>
<td>Targeted therapy; selective inhibitor of nuclear export</td>
</tr>
<tr>
<td>Sintilimab (Tyvyt)</td>
<td>Immune checkpoint inhibitor; anti-PD-1</td>
</tr>
<tr>
<td>Tafasitamab-cxix (Monjuvi)</td>
<td>Monoclonal antibody; anti-CD19</td>
</tr>
<tr>
<td>Tazemetostat (Tazverik)</td>
<td>Targeted therapy: EZH2 inhibitor</td>
</tr>
<tr>
<td>Tislelizumab (BGB-A317)</td>
<td>Immune checkpoint inhibitor; anti-PD-1</td>
</tr>
<tr>
<td>Tucidinostat</td>
<td>Targeted therapy; HDAC inhibitor</td>
</tr>
<tr>
<td>Zanubrutinib (Brukinsa)</td>
<td>Targeted therapy; BTK inhibitor</td>
</tr>
<tr>
<td>Zilovertamab vedotin (MK-2140)</td>
<td>Antibody-drug conjugate; anti-extracellular ROR1</td>
</tr>
</tbody>
</table>

BTK, Bruton 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.

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 LRF 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 optimal treatment 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 (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 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 [computed tomography] 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 was given)
- 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 caregivers 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. LRF’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 AND PATIENT EDUCATION PROGRAMS

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’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. LRF also offers a variety of educational activities, including live meetings and webinars, for individuals looking to learn directly from lymphoma experts. To view our schedule of upcoming programs, please visit lymphoma.org/programs.

LRF Helpline

The LRF 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. LRF also offers both 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 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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