B-cell lymphomas are much more common than T-cell lymphomas and account for approximately 90 percent of all non-Hodgkin lymphomas (NHL).

Diffuse large B-cell lymphoma (DLBCL) is the most common form of NHL, accounting for about 23 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, and roughly half of patients are over the age of 60 years.

DLBCL is an aggressive (fast-growing) lymphoma that can arise in lymph nodes or outside of the lymphatic system, in the gastrointestinal tract, testes, thyroid, skin, breast, bone, or brain. 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.

**TYPES OF DLBCL**

There are several subtypes of DLBCL that may affect a patient’s prognosis (how well a patient will do with standard treatment) and treatment options. For example, DLBCL that only affects the brain is called primary central nervous system (CNS) lymphoma 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 at lymphoma.org/publications. Another example is primary mediastinal B-cell lymphoma, which often occurs in younger patients and grows rapidly in the chest (mediastinum).

Most cases do not fall into one of these categories, and they are considered diffuse large B-cell lymphoma not otherwise specified, or DLBCL-NOS. However, these NOS cases can be grouped into subtypes of DLBCL that are diagnosed using genetic testing for markers on the surface of 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). These groups of patients may have a different prognosis with treatment. Additionally, a related type of aggressive DLBCL, called “double-hit” lymphoma (DHL), demonstrates specific genetic abnormalities that may affect outcome. The use of this information to potentially alter treatment is under active study. For more information about DHL, patients should view the Double-Hit Lymphoma fact sheet on LRF’s website at lymphoma.org/publications.

**DIAGNOSIS AND STAGING**

A tissue biopsy is needed for a definitive diagnosis of DLBCL. A biopsy is a small 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 how much lymphoma is present and where it is located in the body. Because DLBCL is a blood cancer, it is important to look at the entire body to find all the lymphoma. This is usually done with a whole-body computed tomography (CT) scan, which is a series of computerized x-rays. A combination positron emission tomography (PET)/CT scan, in which a small amount of radioactive dye is injected to better identify areas of disease activity may also be used. 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. It is common for patients with DLBCL to 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 at lymphoma.org/publications.
**TREATMENT OPTIONS**

**Double-Hit Lymphoma**

DLBCL often causes symptoms, treatment is typically begun shortly after diagnosis. 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) can be an option for some patients. Sometimes treatment may involve radiation therapy. Treatment can lead to disease remission (disappearance of signs and symptoms) in many patients with this form of lymphoma. The most widely used treatment for DLBCL is R CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) that is usually given in 21-day cycles. Sometimes another chemotherapy drug, etoposide (VePesid, Toposar, Etopophos), is added to the R-CHOP regimen, resulting in a drug combination called R-EPOCH. For many patients, the initial treatment is effective and DLBCL does not return after treatment; however, for patients in whom the disease becomes refractory (no longer responds to treatment) or relapses (returns after treatment), secondary therapies may be successful.

Chemotherapy is typically used for second-line treatment. In patients who are able to achieve a second remission, high-dose chemotherapy coupled with stem cell transplantation may be recommended to consolidate their successful second-line treatment. Patients in complete remission undergoing a stem cell transplant commonly receive their own stem cells (autologous stem cell transplant). Occasionally, a patient will receive stem cells from a donor (allogeneic stem cell transplant). For more information on transplantation, view the Understanding the Stem Cell Transplantation Process publication on the Lymphoma Research Foundation’s (LRF’s) website at lymphoma.org/publications.

Relapsed/refractory patients who are not candidates for stem cell transplant, or who choose not to have a stem cell transplant, do have various combination chemotherapy regimens that can sometimes be used for treatment. Chemotherapies such as bendamustine (Treanda) or gemcitabine (Gemzar), or targeted drugs like lenalidomide (Revlimid) or ibrutinib (Imbruvica), are therapies that may be used in these patients in combination with rituximab or other monoclonal antibodies, although none of these agents or regimens have been specifically indicated for DLBCL patients. Polatuzumab vedotin-piiq (Polivy), in combination with bendamustine and rituximab, received approval from the U.S. Food and Drug Administration (FDA) in 2019 and is indicated in select patients after at least two prior therapies. Patients may also be candidates for chimeric antigen receptor (CAR) T-cell therapy with axicabtagene ciloleucel (Yescarta), tisagenlecleucel (Kymriah), or liso-cel (Lisocabtagene). For more information, view the CAR T-cell Therapy in Lymphoma fact sheet on LRF’s website at lymphoma.org/publications. Most importantly, early evaluation at a specialized lymphoma management center is recommended.

**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. Promising therapies in clinical trials being investigated either alone or in combination include: MOR208 with lenalidomide (Revlimid), histone deacetylase (HDAC) inhibitors with and without B-cell lymphoma 2 (BCL2) inhibitors, and Bruton tyrosine kinase (BTK) inhibitors, such as ibrutinib. Also being studied is the oral drug selinexor (Xpovio), which is the first in a new drug class that blocks the transport of several proteins needed for cancer cell growth.

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, patients with relapsed/refractory disease, the elderly, and patients with specific molecular subtypes. For example, because patients with the GCB subtype may in some studies have a better response to the 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. Optimal treatment strategies for DHL are also being actively investigated; view the Double-Hit Lymphoma fact sheet on LRF’s website at lymphoma.org/publications for more information. 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 at 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 [lymphoma.org/mobileapp] and Lymphoma Care Plan [lymphoma.org/publications] can help patients manage this documentation.

PATIENT AND CAREGIVER SUPPORT SERVICES

A lymphoma diagnosis often triggers a range of feelings and concerns. In addition, cancer treatment can cause physical discomfort. One-to-one peer support programs, such as LRF’s Lymphoma Support Network, connect 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.

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Supported through grants from:
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The Understanding Lymphoma series is published by the Lymphoma Research Foundation (LRF) for the purpose of informing and educating readers. Facts and statistics were obtained using published information, including data from the Surveillance, Epidemiology, and End Results (SEER) Program. Because each person’s body and response to treatment is different, no individual should self-diagnose or embark upon any course of medical treatment without first consulting with his or her physician. The medical reviewer, the medical reviewer’s institution, and LRF are not responsible for the medical care or treatment of any individual.

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Last updated 2020