

Diffuse Large B-Cell Lymphoma

Overview

Lymphoma is the most common blood cancer. The two main forms of lymphoma are Hodgkin lymphoma and non-Hodgkin lymphoma (NHL). Lymphoma occurs when cells of the immune system called lymphocytes, a type of white blood cell, grow and multiply uncontrollably. Cancerous lymphocytes can travel to many parts of the body, including the lymph nodes, spleen, bone marrow, blood, or other organs, and form a mass called a tumor. The body has two main types of lymphocytes that can develop into lymphomas: B lymphocytes (B cells) and T lymphocytes (T cells).

B-cell lymphomas are much more common than T-cell lymphomas and account for approximately 92 percent of all NHLs. Diffuse large B-cell lymphoma (DLBCL) is the most common form of NHL, accounting for about 22 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. Although DLBCL can occur in childhood, its incidence generally increases with age, and roughly half of patients are over the age of 60.

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 lymphoma and is treated differently than DLBCL that affects areas outside of the brain. 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 molecular subtypes of DLBCL that are diagnosed using gene expression profiling or testing for protein biomarkers on the surfaces of the cancerous 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 different prognosis with treatment. Additionally, a related type of aggressive lymphoma called "double-hit" lymphoma demonstrates specific genetic abnormalities that may affect outcome. The use of this information to potentially alter treatment is under active study.

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 the microscope. This can be done under local or general anesthesia.

Once the diagnosis of DLBCL is confirmed, the next step (called staging) 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 or positron emission tomography (PET)/CT scan. 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. Limited-stage disease represents lymphoma affecting only one area of the body, while advanced-stage disease 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.

Treatment Options

Since DLBCL often causes symptoms, treatment is typically begun shortly after diagnosis. A combination of chemotherapy and the monoclonal antibody rituximab (Rituxan [for intravenous infusion] and Rituxan Hycela [for subcutaneous injection]), with or without radiation therapy, can lead to disease *remission* (disappearance of signs or 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.

High-dose chemotherapy coupled with stem cell transplantation can be used to treat patients with DLBCL whose disease is refractory or relapsed following initial chemotherapy. Many patients undergoing a stem cell transplant will 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 alternative therapies that may be used in these patients in combination with rituximab (Rituxan) or other monoclonal antibodies, although none of these agents or regimens have been specifically indicated for DLBCL patients. Select patients may be candidates for chimeric antigen receptor (CAR) T-cell therapy with axicabtagene ciloleucel (Yescarta) or tisagenlecleucel (Kymriah). For more information, view the *CAR T-cell Therapy in Lymphoma* fact sheet on LRF's website at lymphoma.org/publications.

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. Therapies in phase 3 clinical trials include: avelumab (Bavencio), MOR208, polatuzumab vedotin, ublituximab, umbralisib, and utomilumab.

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 double-hit lymphoma (DHL) are also being actively investigated; view the *Double-Hit Lymphoma* fact sheet on LRF's website at lymphoma.org/publications for more information. The 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 (such as blood tests and PET/CT 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.

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.

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.

Resources

LRF offers a wide range of resources that address treatment options, the latest research advances, and ways to cope with all aspects of lymphoma and DLBCL, including our award-winning mobile app (lymphoma.org/mobileapp). LRF also provides many educational activities, from in-person meetings to teleconferences and webcasts for people with lymphoma, as well as DLBCL e-Updates that provide the latest disease-specific news and treatment options. 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.

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