

Understanding Double-Hit Lymphoma

Double-hit lymphoma (DHL) is a type of B-cell non-Hodgkin lymphoma (NHL) characterized by genetic rearrangements called *translocations* (parts of genes switch places within chromosomes) in two particular genes.

One rearrangement involves the *MYC* gene, and the other involves the *BCL2* gene or, less commonly, the *BCL6* gene. If rearrangements are present in all three genes—*MYC*, *BCL2*, and *BCL6*—the condition is called “triple-hit lymphoma”.

With respect to gene mutations, DHL shares many features with two other types of B-cell lymphomas—diffuse large B-cell lymphoma (DLBCL) and Burkitt lymphoma. Approximately 20-35 percent of cases of DLBCL express *MYC/BCL2* proteins (called “double-expressor lymphoma”), but less than 10 percent present the chromosomal rearrangements observed in DHL. The *morphology* (shape, structure, and form) of DHL cells is also different from that of Burkitt lymphoma cells. Furthermore, research has shown that DHL differs in several important ways from the forms of DLBCL and Burkitt lymphoma that do not have dual gene rearrangements. For this reason, in 2016 the World Health Organization designated DHL as its own category of B-cell NHL, “High grade B-cell lymphoma with rearrangements of *MYC* and *BCL2* or *BCL6*”.

DHL is an *aggressive* (fast-growing) lymphoma with signs and symptoms that may be similar to those of DLBCL and Burkitt lymphoma. View the *Diffuse Large B-Cell Lymphoma* and *Burkitt Lymphoma* fact sheets on the Lymphoma Research Foundation’s [LRF’s] website at lymphoma.org/publications for more information. Molecular tests (such as fluorescence in situ hybridization [FISH] or immunohistochemistry [IHC]) that allow doctors to check for abnormalities under a microscope are used to confirm a diagnosis of DHL.



TREATMENT OPTIONS

Because DHL is a relatively new classification of lymphoma, ongoing research is helping doctors learn more about the best ways to treat this disease. DHL is treatable, but more likely to recur than DLBCL. DHLs are generally treated with one of the following combination chemotherapy regimens:

DA-EPOCH-R (dose-adjusted etoposide/VP16 [VePesid, Toposar, Etopophos], prednisone [Deltasone and others], vincristine [Oncovin and others], cyclophosphamide [Cytoxan, Neosar], and doxorubicin/hydroxydaunorubicin [Rubex, Adriamycin PFS] plus rituximab [Rituxan])

R-Hyper-CVAD/MA (rituximab plus hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone [Decadron and others], alternating with high-dose methotrexate [Mexate and others] and cytarabine/high-dose Ara-C [Cytosar-U, Tarabine PFS])

R-CODOX-M/R-IVAC (rituximab plus cyclophosphamide, vincristine, doxorubicin, and methotrexate, alternating with rituximab plus ifosfamide [Ifex], etoposide, and cytarabine)

R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone)

Biosimilar therapies (drugs that are modeled after an existing

biologic therapy) may be an option for patients who are taking rituximab. These include rituximab-abbs and rituximab-pvvr.

Some patients with DHL may undergo high-dose chemotherapy followed by either an *autologous stem cell transplant* (patient’s own cells are infused after high-dose chemotherapy) or an *allogeneic stem cell transplant* (patients receive stem cells from a donor).

Compared with DLBCL, DHL may have a higher risk of recurring in the patient’s *central nervous system* (CNS; the brain and spinal cord). To reduce this risk, some patients with DHL may receive *CNS prophylaxis* (medication to prevent a disorder) in addition to one of the combination chemotherapy regimens described above. CNS prophylaxis may include methotrexate and/or cytarabine that is administered through a *lumbar puncture* (spinal tap), which allows the doctor to inject directly into the *cerebrospinal fluid* surrounding the brain and spinal cord.



TREATMENTS UNDER INVESTIGATION AND CLINICAL TRIALS

Clinical trials are crucial in identifying effective drugs and determining optimal doses for patients with lymphoma. We encourage you to discuss clinical trials with your physician and determine if there is a trial available to you. Patients interested in participating in a clinical trial should view the *Understanding*

Clinical Trials fact sheet on LRF's website (click [here](#)) or talk to their physician. The LRF Helpline can also be contacted for an individualized clinical trial search by calling (800) 500-9976, by emailing helpline@lymphoma.org, or by submitting the *Clinical Trials Search Request Form* at lymphoma.org.

Clinical trials are underway to test new drugs in patients with DHL. Some of these new drugs include:

- Venetoclax
- Bromodomain and Extra-Terminal (BET) inhibitors including, GSK525762 and INCB057643
- CAR-T therapy
- BiTE therapy including Epcoritamab, Mosunetuzumab, Glofitamab, and Odronextamab
- PI3 kinase inhibitors sP Cyclin dependent kinase inhibitors

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. Therefore, it is important that patients check with their physician or with LRF for any treatment updates that may have recently emerged.



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, computed tomography [CT] scans, and positron emission tomography [PET] scans) may be required to evaluate for relapse (disease returns after 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 side effects during follow-up care. Visits may become less frequent the longer the disease remains in remission (disappearance of signs and symptoms).

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 our *Lymphoma Care Plan* (lymphoma.org/publications) can help patients manage this documentation.

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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 program, Lymphoma Support Network. This program connects patients and caregivers with volunteers who have experience with DHL, 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 DHL, 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. For additional information on the mobile app, visit FocusOnLymphoma.org. 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.

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 DHL. LRF also provides many educational activities, including our in-person meetings, podcasts, and webinars for people with lymphoma. For more information about any of these resources, visit our websites at lymphoma.org/DHL or lymphoma.org, or contact the LRF Helpline at (800) 500-9976 or helpline@lymphoma.org.

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