Understanding

Primary Central Nervous System Lymphoma



Resource Center

Lymphoma Research Foundation

Overview

Primary central nervous system (CNS) lymphoma is an aggressive form of non-Hodgkin lymphoma (NHL) in which malignant (cancer) cells are found only in the CNS (the brain and spinal cord). Primary CNS lymphoma can start in the brain, spinal cord, meninges (sheets of tissue that protect the CNS) or the eye. When the lymphoma begins in other parts of the body and spreads to the CNS, it is referred to as secondary CNS lymphoma. In more than 95% of patients with primary CNS lymphoma, the cancer starts in white blood cells (cells that help the body fight infections and cancer) called B-cells.

The cause of primary CNS lymphoma is unknown but having a weakened immune system (for example, people with acquired immunodeficiency syndrome [AIDS] or patients who have undergone organ transplant) may increase the risk of developing the disease. Having one or more of these risk factors does not mean a person will develop primary CNS lymphoma. Most people diagnosed with primary CNS lymphoma have never been exposed to any clearly known risk factors.



Symptoms, Staging, and Diagnostic Procedure

The symptoms of CNS lymphoma depend on the part of the CNS that is affected. These can occur suddenly or develop over time, and may include:

- Language problems, such as difficulties with finding words or forming sentences, and slurred or slow speech.
- Paralysis (inability to move part of the body).
- Loss of vision or blurred vision.
- Confusion.
- Headaches.
- Vomiting.
- Seizures.
- Personality changes.



Early identification of symptoms and diagnosis of CNS lymphoma is important, followed by a quick start of treatment to reverse neurological deficits (problems in bodily functions due to damage in the brain, spinal cord or nerves) and improve outcomes (how well the patient will do). Upon diagnosis, tests are done to find out which parts of the CNS are involved as well as to determine if there is cancer elsewhere in the body. These can include:

- Magnetic resonance imaging (MRI), an imaging procedure that uses a powerful magnet and X-rays to take detailed pictures of areas inside the body.
- Computed tomography (CT), an imaging procedure that uses X-rays to take detailed pictures of areas inside the body.
- Positron emission tomography (PET), an imaging procedure that uses a special dye to find out where the cancer is in the body (generally reserved to ensure the cancer is not located elsewhere in the body).
- Lumbar puncture (or spinal tap), where a needle is inserted in the lower back to collect a sample of the fluid that surrounds the CNS.
- Bone marrow biopsy, where a needle is used to take samples of the spongy tissue inside the bones.
- Eye exams.

Primary CNS lymphoma usually does not spread beyond the CNS or the eye, but it often relapses (disease returns after treatment).

Subtypes

Diffuse large B-cell lymphoma (DLBCL) accounts for up to 95% of the cases of primary CNS lymphoma in adults, and 49% to 70% of the cases in children and adolescents. The subtype of DLBCL may affect a patient's prognosis (how well a patient will do with standard treatment [the proper treatment that is widely used by healthcare professionals and accepted by medical experts]) and treatment options. Most cases of DLBCL do not fall into a specific subtype and are referred to as DLBCL-not otherwise specified (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)

The most common subtype in systemic DLBCL. Patients with the GCB subtype may have a better response to standard chemotherapy and, consequently, GCB is associated with better clinical outcomes.

Activated B-cell-like (ABC)

Less responsive to chemotherapy compared to GCB in patients with systemic DLBCL and associated with worse clinical outcomes in systemic DLBCL. This subtype is more common in patients with primary CNS lymphoma. How it impacts clinical outcomes vs. GCB primary CNS lymphoma is less clear.

Other less common subtypes of primary CNS lymphoma include follicular lymphoma, marginal zone lymphoma, mantle cell lymphoma, chronic lymphocytic leukemia/ small lymphocytic lymphoma, Burkitt lymphoma, and peripheral T-cell lymphoma.



Treatment Options

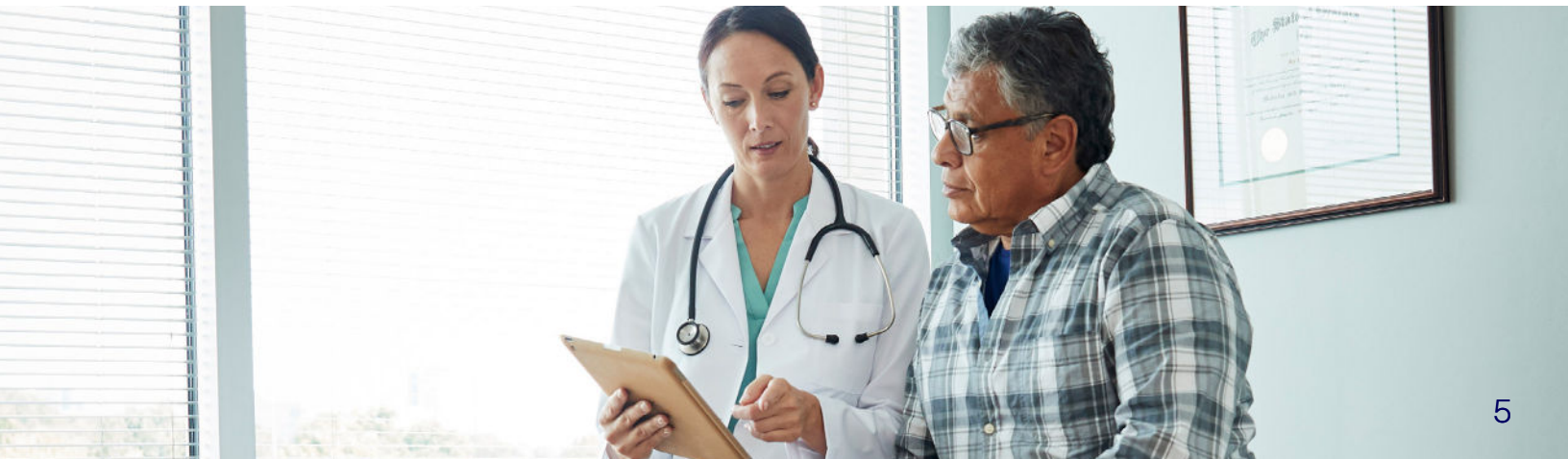
First Treatment after Diagnosis

Until the mid-1990s, radiation was the standard therapy for patients with CNS lymphoma. Now, chemoimmunotherapy which is a combination (two or more drugs given at the same time) of chemotherapy (drugs that stop the growth of or kill cancer cells) with immunotherapy (drugs that use the body's immune system to fight cancer) is recommended for most patients as induction (initial) treatment. The most common combination regimen is high-dose methotrexate with the monoclonal antibody (a protein made in the laboratory that binds to cancer cells and helps the immune system destroy them) rituximab (Rituxan). Sometimes, this is given in combination with other chemotherapy agents such as cytarabine (Cytosar), vincristine (Oncovin), procarbazine (Matulane), ifosfamide (Ifex), thiotepa (Tepadina), or temozolomide (Temodar).

The initial treatment is often followed by other regimens or consolidation therapies (treatments given once the cancer has disappeared after initial treatment to kill any cancer cells that may be left in the body), to reduce the risk of relapse. These consolidation therapies include:

High-dose chemotherapy alone such as cytarabine (Cytosar) or in combination with etoposide (Etopophos, Toposar).

Consolidative chemotherapy with thiotepa based regimen (preferred in primary CNS lymphoma versus BEAM), carmustine (BiCNU), cytarabine (Cytosar), melphalan and etoposide (Etopophos, Toposar) (BEAM).



Stem cell transplantation (SCT, a procedure in which the patient is treated with high-dose chemotherapy or radiation to remove their blood-forming cells or stem cells and then receives healthy stem cells to restore the immune system and the bone marrow's ability to make new blood cells).

- Autologous SCT (patient's own stem cells are infused after high-dose chemotherapy consolidation).

- For more information about stem cell transplantation, please see the Understanding Cellular Therapy Guide on Lymphoma Research Foundation's (The Foundation's) website (lymphoma.org/publications).

Radiation therapy (uses high-energy radiation to kill cancer cells).

- Whole brain radiation therapy. This type of radiation therapy is rarely used in patients over the age of 65 because of permanent and progressive neurological complications (for example, loss of memory, problems with balance, or muscle coordination).



Relapsed and Refractory CNS Lymphoma

Some patients with CNS lymphoma respond to initial treatment and go into remission (disappearance of signs and symptoms of the disease). In other cases, the disease may relapse or become refractory (does not respond to treatment). For these patients, different therapies may result in improved treatment outcomes.

If the disease relapses or becomes refractory, alternative therapies are available. Retreatment with high-dose methotrexate with rituximab (Rituxan) can be used. Other treatment options for patients with relapsed or refractory primary CNS lymphoma include:

- Chemoimmunotherapy with the regimen R-MBVP (rituximab [Rituxan] plus methotrexate, carmustine [BiCNU], etoposide [Etopophos, Toposar] and prednisone).
- Targeted therapies (drugs that target molecules that cancer cells use to grow and spread) with Bruton's tyrosine kinase (BTK) inhibitors such as ibrutinib (Imbruvica).
- Immunomodulatory drugs (IMIDs) (drugs that modulate and promote changes in the immune system). This is typically the agent lenalidomide (REVLIMID).
- High-dose chemotherapy regimens with high-dose methotrexate or high-dose cytarabine (Cytosar) plus thiotepa (Tepadina), etoposide (Etopophos, Toposar), carmustine (BiCNU), busulfan (Myleran, Busulfex) or cyclophosphamide, with autologous SCT.



Treatments Under Investigation

Many treatments (also referred to as investigational drugs) are currently being tested in clinical trials (a type of research study that tests how well new treatments work) in patients with primary CNS lymphoma. Results from these clinical trials may improve or change the current standard of care. The table below lists some of these investigational drugs that can be accessed through a clinical trial.

Table 1. Treatments Under Investigation for Primary CNS Lymphoma Under Phase 2 or 3 Clinical Trials.

Agent (Drug)	Class (Type of treatment)	Condition
Abemaciclib (Verzenio)	Targeted therapy; CDK inhibitor	R/R PCNSL
Acalabrutinib (Calquence)	Targeted therapy; BTK inhibitor	R/R PCNSL
Copanlisib (Aliqopa)	Targeted therapy; PI3K inhibitor	R/R PCNSL
Emavusertib (CA4948)	Targeted therapy; IRAK4 inhibitor	R/R PCNSL
GLPG5101 (19CP02)	Autologous CAR T-cell; anti-CD19	R/R PCNSL
Nivolumab (Opdivo)	Immunotherapy; immune checkpoint inhibitor, antiPD1	Untreated PCNSL and R/R PCNSL
Obinutuzumab (Gazyva)	Immunotherapy; monoclonal antibody, antiCD20	Untreated PCNSL
Orelabrutinib (ICP022)	Targeted therapy; BTK inhibitor	Untreated PCNSL and R/R PCNSL
Paxalisib (GDC-0084)	Targeted therapy; PI3K/mTOR inhibitor	Untreated PCNSL

Agent (drug)	Class (Type of treatment)	Condition
Pembrolizumab (Keytruda)	Immunotherapy; immune checkpoint inhibitor, antiPD1	R/R PCNSL
Sintilimab (Tyvyt)	Immunotherapy; immune checkpoint inhibitor, antiPD-1	R/R PCNSL
Tafasitamab (Monjuvi)	Immunotherapy; monoclonal antibody, anti CD19	Untreated PCNSL and R/R PCNSL
Tirabrutinib (ONO4059)	Targeted therapy; BTK inhibitor	Untreated PCNSL and R/R PCNSL
Varlilumab (CDX-1127)	Immunotherapy; monoclonal antibody, anti-CD27	R/R PCNSL
Zamtocabtagene autoleucel (MB-CART2019.1)	CAR T-cell therapy; anti-CD19 and anti-CD20	R/R PCNSL
Zanubrutinib (Brukinsa)	Targeted therapy; BTK inhibitor	Untreated PCNSL and R/R PCNSL

BTK, Bruton's kinase; CD, cluster of differentiation; CDK, cyclin-dependent kinase; CAR, chimeric antigen receptor; PCNSL, primary central nervous system lymphoma; IRAK4, interleukin-1 receptor-associated kinase 4; PD-1, programmed cell death protein-1; PI3K/mTOR, phosphatidylinositol-3-kinase/mammalian target of rapamycin.

Treatment options may change as new treatments are discovered, and current treatments are improved. Because today's scientific research is continuously evolving, it is important that patients check with their physician or with the Foundation for any treatment updates that may have recently appeared. It is also very important that patients consult with a specialist to clear up any questions.

How to Be a Self-Advocate

Being a self-advocate and an active participant in healthcare decisions can be a positive experience. It may help patients regain a sense of control that they may have lost following the lymphoma diagnosis by making sure patients receive the best care. Patients and care partners should remember they are partners in their treatment plan.

- Do not be afraid to ask your doctors or nurses questions about your care. An educated patient asking questions is not 'being a challenge to your physician' (or 'being a difficult patient').
- Learn more about lymphoma by asking your doctor for information and visiting reliable websites, such as the Foundation's at www.lymphoma.org.
- Take advantage of counseling, support groups, nutritional counseling, fitness classes, expressive arts, and other services offered at your doctor's office, cancer center, or hospital.
- Consider joining the Foundation's Lymphoma Support Network, a nationwide peer support program that matches patients and care partners with people who have had similar experiences. For information about the program, call **(800) 500-9976** or email connect@lymphoma.org.
- Finally, it is important that patients not be afraid to talk with the healthcare team about nonmedical issues such as transportation, finances, insurance, working through treatment or taking time off, and childcare. There are nurses, social workers, and physician's assistants that are able to provide the support and resources to help.



Clinical Trials



Clinical trials are crucial in identifying effective drugs and optimal treatment doses for patients with lymphoma. They are not a "last resort" for patients. Every drug available today had to be tested in clinical trials before it was approved for general use, and all new and emerging treatments. There are four main types or phases of clinical trials. The phase is based on the study's objective and the number of participants.

Phase I

- To identify a safe dose of a new drug
- To decide on a dosing schedule for the drug
- To see what side effects are related to the therapy

Phase II

- To see if a new treatment is effective against a certain type of cancer at the dose determined in Phase I
- To confirm and learn more about the side effects identified in Phase I



Phase III

- To compare the new treatment or new use of an existing treatment with the current standard treatments
- To obtain detailed information about how well the treatment works and the types and severity of side effects it causes

Phase IV

- To look at long-term safety and effectiveness that take place after a new treatment has been approved by the FDA and is available to the public.

Patients interested in participating in a clinical trial should view the Understanding Clinical Trials fact sheet on the Foundation's website (visit lymphoma.org/publications), and the Clinical Trials Search Request Form at lymphoma.org, talk to their physician, or contact the Foundation's Resource Center for an individualized clinical trial search by calling **(800) 500-9976** or emailing connect@lymphoma.org.

Follow-Up

Survivorship

As a cancer survivor, it is important that you practice self-care regularly to reset your physical and emotional well-being. Adopting routines of self-care will help you recharge your batteries and stay healthy. Talk with your healthcare team about developing a wellness plan to help you stay physically and emotionally healthy and improve your mood. Consider the following suggestions:

- Watch your health. Stay up-to-date with your own medical appointments and take any medications as prescribed.
- Exercise. Stay active with short periods of daily exercise (30 minutes of power walking, jogging or biking). If not possible, take the stairs instead of the elevator or park farther away than usual.
- Eat well. Include fruits and vegetables in your meals and maintain a balanced diet.
- Cut down on risk factors. Quit smoking and reduce alcohol intake.
- Sleep. Try to get 7 hours of sleep per night, or take naps when needed.
- Rest. Meditation, deep breathing and stretching can help you relax and reduce stress.
- Write it down. Keeping a journal with thoughts and feelings may help to let go of worries and fears.

View the Foundation's Survivorship Series fact sheet on the Foundation's website at lymphoma.org/publication for more info.

Care Partners

There are many ways you can help a loved one with lymphoma, as follows:

- Be present. The most important thing that a care partner can do is to "just show up."
- Be prepared. Talk with the healthcare team so that you know what to expect throughout the treatment, how to manage symptoms and when to ask for help.
- Listen. Each person asks for help in different ways, verbally (through words) and nonverbally, and some may require more comfort while others are more action oriented.
- Avoid "cheer-leading". Do not disregard your love one's negative feelings (sadness, anger or worry).
- Organize the help. A rush of sudden help upon diagnosis can make the situation harder to manage and create unproductive tension.
- Set up remote access with computer and/or phone access. This is helpful for regular communication with your loved one.
- Offer rides. This is important for people with decreased mobility or limited resources.
- Take notes. If you go into the appointments, write down notes with the doctor's plan, medications, potential side effects and other relevant information.

Patients and their care partner 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 are important for keeping track of any side effects resulting from treatment or potential disease recurrences. The Foundation can help patients manage this documentation.

View the Care Partners fact sheet on the Foundation's website at lymphoma.org/publication for more info.

Questions to Ask Your Healthcare Team

- What is my exact diagnosis? What subtype of lymphoma do I have? May I have a copy of the report from the pathologist?
- What is the stage of my disease? In what area of the body is it specifically located?
- What are my treatment choices? Which do you recommend for me and why? Would choosing one treatment prevent me from getting a different kind of treatment later on? How are the different treatments administered?
- Do I need more than one type of treatment?
- What is the goal of treatment? What are the expected benefits of each type of treatment?
- How will we know if the treatment is working? What tests will I need to determine if treatment is working, and how often will I need to be tested?
- How long will the treatment last?
- What are the chances the treatment will be successful?
- What is a clinical trial? Are clinical trials available that are studying new treatments for my type of lymphoma? Would a clinical trial be appropriate for me? How would I benefit? Are there any drawbacks of participating in a clinical trial?
- Will I be able to work during treatment? Will I be able to drive or take public transportation during my treatment?
- Should I take care of other medical or dental issues before I start treatment?
- How much will the treatment cost? Will my insurance cover some or all of it? What will my out-of-pocket costs be?



The Foundation's Programs and Services

Patient Education Programs

The Foundation also offers a variety of educational activities, including live meetings and webinars for individuals looking to learn directly from lymphoma experts. These programs provide the lymphoma community with important information about the diagnosis and treatment of lymphoma, as well as information about clinical trials, research advances and how to manage/cope with the disease. These programs are designed to meet the needs of a lymphoma patient from the point of diagnosis through long-term survivorship. To view our schedule of upcoming programs, please visit **lymphoma.org/programs.**

Lymphoma Resource Center (LRC)

The LRC 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. The Foundation also offers a one-to-one peer support program called the Lymphoma Support Network and clinical trials information through our Treatment Navigation Service. For more information about any of these resources, visit our website at lymphoma.org, or contact the Foundation's Lymphoma Resource Center at **800-500-9976** or **connect@lymphoma.org.**

Lymphoma Support Network

The Foundation's one-to-one peer support program – Lymphoma Support Network – connects patients and care partners with volunteers who have experience with lymphomas, similar treatments, or challenges, for mutual emotional support and encouragement. You may find this useful whether you or a loved one is newly diagnosed, in treatment, or in remission. For more information about this program, please contact the Foundation's Lymphoma Resource Center at **800-500-9976** or visit **lymphoma.org/resources/supportservices/lsn.**

Treatment Navigation Service

The Foundation provides a "Treatment Navigation Service" to increase awareness about trials being conducted at cancer treatment centers nationwide. Upon request, our Lymphoma Resource Center staff can conduct a customized search for potential lymphoma treatment trials in a patient's area. Trial search results can be mailed or emailed so that they may be discussed with the patient's treating healthcare team and loved ones. Individuals interested in having a trial search conducted for them can contact the Lymphoma Resource Center at **800-500-9976** or **connect@lymphoma.org** or complete a trial search request form on our website at **lymphoma.org/ctis**.

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For individuals outside of the U.S. seeking information, the Foundation recommends the Lymphoma Coalition. The Lymphoma Coalition is a global network of worldwide nonprofit/NGO lymphoma patient organizations with information appropriate for non-U.S.-based audiences. Additional information can be found by visiting their website at https://lymphomacoalition.org/.

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