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Primary Central Nervous System Lymphoma (PCNSL)

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PCNSL basics

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Primary central nervous system lymphoma (PCNSL) is an uncommon and aggressive type of non-Hodgkin lymphoma. It can start in the brain, spinal cord, or eyes but does not tend to spread to other parts of the body. Having a weakened immune system may increase the risk of PCNSL. In people with healthy immune systems, PCNSL is most common in older adults.

About

Together the brain and spinal cord form the central nervous system (CNS). PCNSL occurs most often in the brain, but can also involve the spinal cord, eyes, or the liquid that surrounds the brain and spinal cord, called cerebrospinal fluid (CSF). When PCNSL involves the eyes, it is called intraocular lymphoma. Although PCNSL may spread within the CNS, it rarely spreads to other areas of the body.

Lymphoma is cancer that forms from infection-fighting white blood cells called lymphocytes. Lymphocytes are found throughout the body in the lymphatic system. This system includes a lymphocyte-rich fluid (lymph), the network of vessels that transport it, and small filters through which it passes (lymph nodes).

There are B lymphocytes ("B cells") and T lymphocytes ("T cells"). When viewed under a microscope, almost all PCNSL tumors are made of oversized B cells known as "diffuse large" B cells. Cancer that forms from these cells is known as diffuse large B-cell lymphoma (DLBCL). PCNSL is a rare type of DLBCL that affects the central nervous system.

PCNSL (and DLBCL) belong to a group of over 90 different cancers known as non-Hodgkin lymphomas. They are called "non-Hodgkin" because, when viewed under a microscope, they do not have a unique type of cell seen only in Hodgkin lymphoma.

The focus of this guide is PCNSL. For information on other types of DLBCL, see NCCN Guidelines for Patients: Diffuse Large B-Cell Lymphoma at NCCN.org/patientguidelines.

Who is at risk?

Having a weakened immune system increases the risk of developing PCNSL. This is especially true for people with human immunodeficiency virus (HIV), the virus that causes AIDS. HIV-positive patients need antiretroviral (ARV) therapy in addition to cancer treatment. An HIV specialist or pharmacist should be involved in treatment planning. The focus of this patient guide is non–AIDS-related PCNSL.
PCNSL basics

People with a post-transplant lymphoproliferative disorder (PTLD) are at increased risk of PCNSL. PTLDs are lymphomas that can develop after a solid organ transplant or a donor (allogeneic) bone marrow (stem cell) transplant. They are caused by B-cells growing out of control (proliferating), usually in people taking medicines to prevent rejection of the transplant.

Patients with autoimmune disease are also at increased risk. In people with healthy immune systems, the factors that cause PCNSL to develop are not well understood.

About 2 out of 100 brain tumors are PCNSL. It is more common in men than women, and older adults are most often affected.

Signs and symptoms

PCNSL can cause symptoms. About half of people diagnosed with PCNSL experience some sort of change in brain function. These mental status changes may affect mood, personality or behavior, short-term memory, speech, or coordination. Symptoms linked to increased pressure in the brain such as headaches, nausea, vomiting, and seizures are possible. Eyesight changes can also occur.

Brain MRI

MRI is the preferred imaging method to help diagnose PCNSL and to monitor how well treatment is working.
Diagnosis

Testing for PCNSL includes obtaining images of the brain and examining a small piece of the tumor. These tests are described in more detail next.

MRI

Pictures of the brain and spinal cord are needed to help diagnose PCNSL. MRI is the preferred imaging technique. MRI uses radio waves and powerful magnets to take pictures of the inside of the body. It does not use radiation. An MRI scan is good at showing the spine and soft tissues, including the brain.

MRI is performed using a tunnel-shaped piece of equipment. The patient lies on a table that slides into the tunnel. Inside the scanner, a magnetic field surrounds the head and a radiofrequency pulse is introduced to the area. Patients with certain cardiac monitors, pacemakers, or some types of surgical clips cannot generally undergo MRI scanning because of the magnetic fields.

If MRI is unavailable or not recommended for you, computed tomography (CT) may be used instead. The patient lies on a table that slides into a doughnut-shaped opening. The CT scanner circles the head to allow the x-rays to penetrate the brain from many directions.

Before either type of scan a substance called gadolinium is put into the bloodstream to make the pictures clearer. Gadolinium is known as a contrast agent or simply “contrast.” If a brain MRI (or CT) suggests PCNSL, the next step is a biopsy.

Tumor biopsy

If MRI (or CT) pictures suggest PCNSL, a sample of the tumor is removed for testing. The method of removing tumor tissue used for suspected PCNSL is called a stereotactic biopsy. Stereotactic biopsy is a computer-directed needle biopsy. The computer, using information from the CT or MRI scan, provides precise information about a tumor’s location.

A stereotactic biopsy aims only to remove enough of the tumor to make a diagnosis without causing harm or complications. It is the least invasive type of biopsy used for brain tumors.

Stereotactic biopsy is done in the operating room under general anesthesia. After making a small opening in the skull, the neurosurgeon guides a stereotactic biopsy needle into the brain. A computerized navigation system allows the surgeon to target and remove tumor tissue with a high degree of precision. The incision is closed with sutures.

A doctor called a neuropathologist will examine the removed tissue to determine the tumor type. If biopsy results confirm PCNSL, corticosteroid therapy may be started. It is preferred to wait until a final diagnosis is made because steroids can distort the tumor’s appearance on imaging techniques and when viewed under a microscope.

Other testing

Your doctor may or may not order a lumbar puncture to help diagnose PCNSL. If not performed for diagnosis, expect to have this procedure after PCNSL is confirmed to help determine the extent of the cancer. This procedure is described in more detail in the next section, Testing after diagnosis.
Testing after diagnosis

After a diagnosis has been made using MRI and brain biopsy, tests are needed to learn the extent of cancer in the body. This process is known as staging. It is used to help plan treatment.

Eye exam
PCNSL can form in the eyes. It most often forms in the retina or the optic nerve. The retina is a thin, light-sensitive layer of tissue in the back of the eye. It receives light that the lens has focused on and converts it into visual signals. The signals are sent to the brain via the nearby optic nerve, allowing you to see. Cancer cells may also be found in the vitreous, a clear gel inside the eye. It fills the space between the front of the eye (the lens) and the retina.

Lumbar puncture
The fluid that flows in and around the brain and spinal cord is called cerebrospinal fluid (CSF). A simple bedside procedure called a lumbar puncture (also known as a spinal tap) is used to remove a small amount of CSF for testing. Testing this fluid can help confirm whether the tumor is PCNSL and provide other helpful information needed for treatment planning. A lumbar puncture will only be done if your doctor feels that it can be performed safely and it will not delay treatment. If cancer cells are found in spinal fluid, or if they are causing symptoms, a spine MRI may be needed.

Slit lamp eye exam
A microscope with a bright light (a “slit lamp”) is used to look for signs of cancer in the eyes. PCNSL most often forms in the back of the eye, in the retina or the optic nerve.
Imaging
Although it is uncommon for PCNSL to spread to other areas of the body, it is important to have imaging to rule it out. The imaging procedures most commonly used for this purpose are computed tomography (CT) and positron emission tomography (PET). CT creates images of areas inside the body using radiation, similar to x-ray imaging exams. A computer combines the x-rays to make one detailed picture. The picture is saved for later viewing by the radiologist.

A CT scan of the chest, abdomen, and pelvis is recommended. The scan is done “with contrast.” This means that a substance, such as gadolinium, is put into the bloodstream before the scan to make the pictures clearer.

Sometimes CT is combined with PET. When used together, it is called a PET/CT scan. PET/CT may be done with one or two machines depending on the cancer center. For PET, a radioactive drug (a “tracer”) is first injected into your body. The tracer is a sugar molecule that is attached to a small amount of radioactive material. The radiotracer is detected with a special camera during the scan. Cancer cells appear brighter than normal cells because they use sugar more quickly. PET can show even small amounts of cancer.

For some older men with PCNSL, imaging after diagnosis may also include an ultrasound of the testicles.

HIV and other blood tests
Blood tests can also help establish the extent of the cancer and provide other information needed for treatment planning. The following blood tests are recommended. Your doctor may order others as needed.

Lumbar puncture
Cancer cells in spinal fluid may or may not cause symptoms. A lumbar puncture is used to learn whether cancer has spread to the spinal fluid. If cancer cells are found in spinal fluid, or if they are causing symptoms, a spine MRI may be needed.
A complete blood count (CBC) is a common blood test that measures the number of red blood cells, white blood cells, and platelets in a sample of blood.

A comprehensive metabolic panel (CMP) is a group of 14 different blood tests that provides information about the health of your liver and kidneys, and other information including your blood sugar, calcium, and other electrolytes.

A lactate dehydrogenase (LDH) test measures the level of an enzyme involved in converting food into energy for the body. A high level of LDH can be a sign of cell damage caused by cancer or other health problems.

A human immunodeficiency virus (HIV) blood test is needed for everyone with PCNSL. HIV-related PCNSL requires specialized care and treatment with antiretroviral (ARV) therapy in addition to cancer treatment.

**Bone marrow biopsy**

Most bones have soft, spongy tissue in the center called marrow. This is where new blood cells are made. Although it is uncommon to find cancer cells in the bone marrow when PCNSL is diagnosed, your doctor may recommend a bone marrow biopsy. In this procedure, a sample of bone and soft marrow is removed (usually from the hip) with a needle and tested.

**Overview of treatments**

**Corticosteroids**

Corticosteroids are used to control brain swelling. Steroids can rapidly improve the signs and symptoms of PCNSL. Steroid therapy is generally not started, however, until PCNSL is officially diagnosed using imaging with MRI and a brain biopsy. This is because steroids...
can distort the appearance of lymphoma cells obtained by biopsy, making it difficult for the pathologist to make a definitive diagnosis.

**Systemic therapy**
Systemic therapy is the use of medicine(s) to kill cancer cells. It is the primary (main) treatment for PCNSL. Types of systemic therapy include chemotherapy, targeted therapy, and immunotherapy. Systemic therapies are often combined to treat cancer. For example, a chemotherapy drug may be given with an immunotherapy drug, or several chemotherapy drugs may be given together.

Most commonly, systemic therapy is given intravenously. This means the medicine(s) are slowly infused into the bloodstream through a vein. The medicine(s) travel in the bloodstream to reach cells throughout the body. Systemic therapy can kill normal, healthy cells in addition to cancer cells. The damage to healthy cells causes potentially harsh side effects.

**Intrathecal chemotherapy**
Cerebrospinal fluid (CSF) is the fluid that flows in and around the brain, spinal cord, and the innermost layers of tissue that protect them. In addition to systemic chemotherapy that works throughout the body, chemotherapy can be put directly into the CSF. This is known as “intrathecal” or “intra-CSF” chemotherapy. Intrathecal chemotherapy may be used in select cases or as part of specific treatment regimens to treat PCNSL if cancer cells are found in CSF, or if an MRI of the spine shows cancer.

**High-dose chemotherapy with stem cell rescue**
Red blood cells, white blood cells, and platelets are the three main types of blood cells. Each has a different and important job in the body. Red blood cells carry oxygen. White blood cells fight infection. Platelets help stop bleeding.

Before becoming one of these types, all blood cells start as “stem” cells. Stem cells that become blood cells are known as hematopoietic stem cells. Hematopoietic (blood-forming) stem cells are found in bone marrow. When hematopoietic stem cells are damaged, they may not form the blood cells needed by the body.

High-dose chemotherapy can damage or destroy hematopoietic stem cells. High-dose chemotherapy may be used for the second phase of PCNSL treatment in people who have very good results in the first phase. To protect your blood-forming stem cells from high-dose chemotherapy, they are first removed (“rescued”) from your blood or bone marrow.

After chemotherapy, your rescued, healthy stem cells are transplanted back into your body. The transplanted stem cells form new red blood cells, white blood cells, and platelets. This restores your body’s ability to protect itself from infection.

A number of names are used to refer to this procedure, including:

- Autologous bone marrow transplant
- Autologous stem cell transplant
- Hematopoietic cell transplant (HCT)
- High-dose therapy with autologous stem cell rescue (HDT/ASCR)
The stem cell rescue process
The first step is to increase the number of stem cells in the blood. This is known as “mobilization.” Medicines are used to cause stem cells to move from the bone marrow into the blood. When your doctor determines that your stem cell count is high enough, the next step is collection.

A process called apheresis is used to collect the stem cells from blood. Your blood will be removed from a large vein, most likely in your arm. It will flow through a tube and into a machine that removes stem cells. The rest of your blood will be returned to you in your other arm. Apheresis typically takes 4 to 6 hours and does not require anesthesia. It may take two or more sessions to obtain enough stem cells. During the procedure, you may have lightheadedness, chills, numbness around the lips, and cramping in the hands. After apheresis, the collected (“harvested”) cells are frozen and stored.

When high-dose chemotherapy is complete, your harvested stem cells will be put back into your body using a transfusion. A transfusion is a slow injection of blood products through a central line into a large vein. A central line (or central venous catheter) is a thin tube. The tube will be inserted into your skin through one incision (cut), then into your vein through a second cut. Local anesthesia will be used. This process can take several hours to complete.

The transplanted stem cells travel to your bone marrow where they grow and form new, healthy blood cells. This is called engraftment. It usually takes about 2 to 4 weeks. Until engraftment is fully achieved, you will have little or no immune defense. You will need to stay in a very clean room at the hospital. You may be given an antibiotic to prevent or treat infection. You may also be given blood transfusions to prevent bleeding and to treat low red blood counts (anemia) and low platelets (thrombocytopenia). While waiting for the cells to engraft, you will likely feel tired and weak.

Radiation therapy
Before effective systemic therapies became available to treat PCNSL, radiation therapy was the most commonly used treatment. It remains an option for treating PCNSL in people who cannot have systemic therapy. Other situations in which radiation may be used include:

- In combination with systemic therapy in the first phase of treatment (induction)
- In the second phase of treatment (consolidation) to kill leftover cancer cells

Radiation therapy uses beams of intense energy (radiation) to kill cancer cells. For the treatment of PCNSL, the radiation comes from a machine outside of the body. This is known as external beam radiation therapy (EBRT). This distinction is made because to treat some types of cancer, a radiation source is implanted into the body.

If radiation therapy is planned, treatment of the entire brain with whole-brain radiation therapy (WBRT) is most commonly used to treat PCNSL. The total dose of radiation is usually divided into small doses given over several weeks. This is referred to as fractionation.

Radiation therapy is more likely to damage the nervous system than systemic therapy, especially in older adults. Your doctor will weigh the benefits of radiation as a treatment...
for PCNSL with the risk of nervous system damage.

**Radiation for intraocular PCNSL**
Radiation therapy may also be used to treat PCNSL in the eyes. Treatment with radiation to muscle, nerves, or skin around the eye is known as orbital radiation therapy. Treatment with radiation to the eyeball itself is known as intraocular radiation therapy.

**Radiation therapy**
Radiation therapy kills cancer cells using beams of intense energy (radiation). Whole-brain radiation therapy (WBRT) is most commonly used to treat PCNSL.

**Everyone with PCNSL is encouraged to enroll in a clinical trial for treatment.**
Review

- The brain and spinal cord make up the central nervous system (CNS).
- PCNSL is an uncommon and aggressive form of non-Hodgkin lymphoma found only in the CNS at the time of diagnosis. It rarely spreads to other parts of the body.
- Having a weakened immune system due to HIV or other conditions increases the risk of developing PCNSL.
- Symptoms of PCNSL can include changes in mood, personality or behavior, short-term memory, speech, and/or coordination. Headaches, seizures, nausea and vomiting, and eyesight changes are also possible.
- MRI and stereotactic brain biopsy are most commonly used to diagnose PCNSL.
- Testing after diagnosis includes an eye exam, lumbar puncture, blood tests, and CT scans. A bone marrow biopsy may also be performed in select cases.
- Treatment for PCNSL may include systemic therapy, intrathecal chemotherapy, high-dose chemotherapy with stem cell rescue, and radiation therapy.
2

Treatment guide

18 Induction
21 Consolidation
22 Follow-up care
24 Review
Treatment is started as soon as possible after a diagnosis of primary central nervous system lymphoma (PCNSL). This chapter describes what to expect from the treatment process and explains the options for each phase of treatment. Everyone with PCNSL is encouraged to consider enrolling in a clinical trial.

Doctors use the terms induction and consolidation to describe the phases of treatment for PCNSL and similar cancers. In the first phase (induction), the treatment expected to be most effective is used to kill as many cancer cells as possible. The purpose of the second phase (consolidation) is to kill cancer cells that may remain in the body after induction. Consolidation therapy helps prevent cancer from returning.

**Induction**

The options for the first phase of treatment (induction) are described next and shown in Guide 1.

**Consider a clinical trial**

Clinical trials allow you to receive treatment while also helping researchers learn more about this uncommon cancer. Everyone with PCNSL is encouraged to consider enrolling in a clinical trial. The treatment you receive in the trial may or may not work better than the standard treatments for PCNSL. Ask your care team if there is a clinical trial for which you may be eligible.

**Systemic therapy**

The chemotherapy medicine methotrexate (MTX) is the most effective treatment against PCNSL. Methotrexate has been used for many years to treat a variety of cancers. In lower doses, it is also used to treat autoimmune diseases such as psoriasis and rheumatoid arthritis. Methotrexate works by blocking the body’s use of folate, a form of vitamin B. Cancer cells cannot divide and spread as quickly without folate.

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**Guide 1**

**Options for induction treatment**

- Treatment in a clinical trial
- Systemic therapy that includes high-dose methotrexate and rituximab (Rituxan®)
- Systemic therapy that does not include methotrexate (if methotrexate is not recommended for you)
- Whole-brain radiation therapy (if you cannot have systemic therapy)
As induction therapy for PCNSL, methotrexate is given in high doses together with the immunotherapy drug rituximab (Rituxan®). Rituxan® is an antibody therapy. Antibodies are proteins made by your immune system to help fight infection. Blood cells with cancer (and some healthy blood cells) have a protein on their surface called CD20. Rituxan® acts like an antibody, targeting and attaching to the CD20 protein. This helps your immune system find and attack the cancer cells.

In addition to methotrexate and rituximab, one or more other medicines such as temozolomide (TMZ), vincristine, and procarbazine may be included in the systemic therapy regimen.

Some methotrexate-based systemic therapy regimens are used in combination with whole-brain radiation therapy for induction therapy of PCNSL.

**Side effects of methotrexate**

Once in the bloodstream, methotrexate is eliminated (“cleared”) from the body by the kidneys. When given in high doses, methotrexate can damage the kidneys and liver. This makes it more difficult for the kidneys to eliminate it, leading to a harmful buildup of methotrexate in the blood. In severe cases, kidney failure is possible. A medicine called glucarpidase may be used to rapidly lower the level of methotrexate in the blood and help prevent severe kidney problems.

The medicine leucovorin is given after treatment with high-dose methotrexate to help prevent or minimize side effects. When used to counteract the toxic effects of chemotherapy, leucovorin is called a “rescue” medicine. Your treatment team will take or recommend other steps to offset kidney problems caused by high-dose methotrexate, such as hydration.

Like many other systemic therapies, methotrexate can cause the levels of white blood cells, red blood cells, and platelets in your blood to drop. Having low blood cell counts increases your risk of infection, anemia, and bleeding problems during treatment.

Other common side effects of methotrexate include:

- Mouth sores
- Poor appetite
- Nausea and vomiting
- Skin reactions
- Diarrhea
- Liver problems
- Hair loss

**Side effects of rituximab**

The most common side effects of rituximab are infusion-related reactions, infections, body aches, tiredness, and nausea. Rituximab can activate the hepatitis B virus in people who are carriers. Being a carrier means you have the hepatitis B virus in your body, but you do not have any signs or symptoms of the disease. Before starting treatment with rituximab, everyone should be tested for the hepatitis B virus. If you are a carrier, you will be closely monitored for signs and symptoms of active hepatitis B infection during treatment and for several months afterwards. Your doctor may prescribe antiviral medication to prevent reactivation of the hepatitis B virus.
Other serious side effects of rituximab include infusion-related reactions, severe skin and mouth reactions, and a rare, viral brain infection affecting people with weakened immune systems.

**PCNSL in the spine**
If testing finds cancer cells in the spine or spinal fluid, and if treatment with high-dose methotrexate is thought to be too harsh for you, intrathecal chemotherapy may be considered.

Intrathecal chemotherapy may be used alone or with systemic therapy to treat PCNSL in the spine or spinal fluid. In intrathecal chemotherapy, anti-cancer medicine(s) are put directly into the spinal fluid. Intrathecal chemotherapy medicines used for PCNSL include:

- Methotrexate
- Cytarabine
- Rituximab (Rituxan®)

**Alternatives to methotrexate**
Although systemic therapy that includes high-dose methotrexate is preferred for induction treatment of PCNSL, it is not always the best option for everyone. Your doctor may recommend an alternative systemic therapy regimen if:

- Cancer was found in the spine or spinal fluid
- Your kidneys don’t work well
- High-dose chemotherapy is thought to be too harsh for you for other reasons

If you cannot have high-dose methotrexate there are other options for systemic therapy. Your doctor may recommend one of the following regimens for induction:

- Ibrutinib (Imbruvica®)
- Temozolomide (Temodar®)
- Rituximab with or without temozolomide
- Lenalidomide with or without rituximab
- High-dose cytarabine
- Pemetrexed
- Pomalidomide

**PCNSL in the eye(s)**
Intraocular (eye) PCNSL that does not improve with induction systemic therapy requires other treatment. Radiation therapy may be an option. Treatment with radiation to muscle, nerves, or skin around the eye is known as orbital radiation therapy. Treatment with radiation to the eyeball itself is known as intraocular radiation therapy.

Another option for treating ocular PCNSL may be intraocular chemotherapy. This involves injecting anti-cancer medicines directly into the eye(s). If intraocular chemotherapy is planned, your doctor may refer you to an ophthalmologist that specializes in this type of treatment.

**If you cannot have systemic therapy**
If you cannot have systemic therapy with high-dose methotrexate or with an alternative regimen, treatment with radiation therapy is an option. Whole-brain radiation therapy may be used for treatment in people who are not candidates for systemic therapy.
If testing found cancer cells in the eyes, treatment of the eyes with intraocular chemotherapy or radiation therapy is recommended. If testing found cancer in the spine or spinal fluid, your doctor may recommend intrathecal chemotherapy and possibly radiation therapy to the spine.

Consolidation

Consolidation is the second phase of treatment. The purpose of this phase is to kill cancer cells that may be left in the body after induction. Your options for consolidation depend in part on how well induction worked.

**Very good induction results**

If there are no signs of cancer after systemic therapy containing high-dose methotrexate, it is called a complete response. The next best outcome is an “unconfirmed” complete response, which means that there are minimal signs of cancer left in the body. If you have a complete (or unconfirmed complete) response to induction, there is often more than one option for consolidation. The options are discussed below and listed in Guide 2.

**High-dose chemotherapy with stem cell rescue**

In people expected to be healthy enough to tolerate it, high-dose chemotherapy with stem cell rescue will be considered as an option for consolidation. If you are already at increased risk of infection or are not expected to tolerate a stem cell transplant well for other reasons, this may not be the best option.

**Chemotherapy alone**

Chemotherapy without stem cell rescue is another option for consolidation. This may be a better fit for people who are not expected to tolerate a stem cell transplant well. If chemotherapy alone is planned, high-dose cytarabine with or without etoposide is a recommended option. Continuing high-dose methotrexate-based systemic therapy is also an option for killing leftover cancer cells. When used for consolidation, methotrexate is typically given monthly for up to 1 year.

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**Guide 2**

Options for consolidation treatment

| Very good induction results | • High-dose chemotherapy with stem cell rescue  
|                           | • Chemotherapy alone  
|                           | • Low-dose whole-brain radiation therapy |

| Other induction results | • Systemic therapy that does not include methotrexate  
|                        | • Whole-brain radiation therapy |
Radiation therapy
If more systemic therapy is expected to be too harsh or is not recommended for other reasons, radiation therapy can be used to kill leftover cancer cells. Low-dose whole-brain radiation therapy is typically used for consolidation.

Radiation therapy is more likely to damage the nervous system than systemic therapy, especially in older adults. Your doctor will weigh the benefits of radiation as a consolidation treatment for PCNSL with the risk of nervous system damage.

Other induction results
If cancer remains after methotrexate-based induction therapy, treatment with a different systemic therapy is recommended. If systemic therapy is not a feasible option, whole-brain radiation therapy is recommended.

If treatment with systemic therapy is planned, chemotherapy alone with high-dose cytarabine with or without etoposide may be an option.

If you are not a candidate for another systemic therapy or whole-brain radiation therapy, supportive care is another option. Supportive care can help with cancer-related pain or discomfort as well as medication-related side effects.

Follow-up care
After treatment, brain MRI is used to monitor for the return of PCNSL. NCCN experts recommend imaging of the brain with MRI according to the schedule described below.

- Every 3 months for the first 2 years
- Every 6 months for the following 3 years
- Once a year after 5 years

Your doctor may request that you have brain MRIs more or less often. Talk to your treatment team about how often you should expect to have them.

If cancer cells were found in your spine or spinal fluid, your follow-up care will also include imaging of the spine and testing of cerebrospinal fluid (CSF). If you received cancer treatment to your eyes for ocular PCNSL, eye exams with an ophthalmologist are recommended as part of your follow-up care. Talk to your doctor about how often you should have these tests.

If cancer persists or returns
Cancer that does not improve with treatment is called refractory. The return of cancer after a cancer-free period is known as a relapse. There is not much research on the best way to treat refractory or relapsed PCNSL. Seeking treatment in a clinical trial is strongly encouraged. The treatment you receive may or may not work better than standard cancer care. Ask your care team about current clinical trials you may be eligible for.

Supportive care or palliative care is an option for everyone with relapsed or refractory PCNSL. Supportive care can help with cancer-related pain or discomfort as well as medication-related side effects. The goal of supportive care is not to treat the cancer, but to help with the emotional, physical, and practical demands of living with cancer.

Outside of a clinical trial, options your doctor will consider depend in part on your treatment...
history. If you had a lasting response to methotrexate-based systemic therapy, your doctor may recommend further treatment with high-dose methotrexate. It may be given alone, with rituximab (Rituxan®), or with both rituximab and ibrutinib (Imbruvica®). Treatment with systemic therapy that does not include high-dose methotrexate is also an option.

If high-dose methotrexate-based systemic therapy did not work, or did not result in a lasting cancer-free period, there is more than one possibility. Your doctor may recommend systemic therapy that does not include methotrexate. Another option is radiation therapy with or without chemotherapy.

If the cancer is in remission after re-induction chemotherapy, high-dose chemotherapy with stem cell rescue may also be an option.

You’ve had a stem cell transplant
If you did not have a lasting response to high-dose chemotherapy with stem cell rescue, radiation therapy may be an option. Whole-brain radiation therapy or stereotactic (targeted) radiation therapy to the tumor(s) may be used.

Other options include treatment with a different systemic chemotherapy (without stem cell rescue). A number of different systemic therapy regimens may be used in this situation. Talk to your care team about the regimen(s) that may be right for you.

You’ve had whole brain radiation
If cancer returns after initial treatment that included whole-brain radiation therapy, radiation should not be used again because of the risk of nervous system damage. Treatment options include:

Supportive care
Supportive care is an option for everyone with relapsed or refractory PCNSL. Supportive care can help with cancer-related pain or discomfort as well as medication-related side effects.
Chemotherapy to whole body (systemic) or to cerebrospinal fluid (intrathecal)
Radiation therapy targeting cancerous areas only

High-dose chemotherapy with stem cell rescue may also be an option. If this option is pursued, a stem cell rescue would only be carried out if the cancer goes into complete remission after chemotherapy.

Review

- Everyone with PCNSL is encouraged to consider receiving cancer treatment in a clinical trial.
- If possible, receiving treatment at a center with experience in treating PCNSL is recommended.
- The first phase of treatment for PCNSL is known as induction. The treatment expected to be most effective is used to kill as many cancer cells as possible.
- High-dose methotrexate-based systemic therapy is preferred for induction treatment of PCNSL in people who can have it.
- Methotrexate is given intravenously, together with the antibody therapy rituximab (Rituxan®). One or more other medicines may be included in the systemic therapy regimen.
- High-dose methotrexate may be too harsh or may not be recommended for other reasons. Other systemic therapy regimens are available for induction.
- If you cannot have any systemic therapy, whole-brain radiation therapy is an option for induction treatment of PCNSL.
- Consolidation is the second phase of treatment. Cancer cells that may remain in the body after induction are killed to help prevent cancer from returning.
- If the results of induction systemic therapy are very good, options for consolidation include high-dose chemotherapy with stem cell rescue, chemotherapy alone, or radiation therapy.
- If cancer remains after methotrexate-based induction therapy, options for consolidation include systemic therapy with a different regimen or radiation therapy. Supportive care is also an option.
- After treatment, brain MRI is used to monitor for the return of PCNSL. Other follow-up testing is needed if cancer was found in the spinal fluid or eyes.
- Enrolling in a clinical trial is strongly encouraged for everyone with refractory or relapsed PCNSL. Outside of a clinical trial, treatment options depend in part on your treatment history.
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Making treatment decisions

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It’s important to be comfortable with the cancer treatment you choose. This choice starts with having an open and honest conversation with your doctor.

It’s your choice

In shared decision-making, you and your doctors share information, discuss the options, and agree on a treatment plan. It starts with an open and honest conversation between you and your doctor.

Treatment decisions are very personal. What is important to you may not be important to someone else.

Some things that may play a role in your decision-making:

- What you want and how that might differ from what others want
- Your religious and spiritual beliefs
- Your feelings about certain treatments like surgery or chemotherapy
- Your feelings about pain or side effects such as nausea and vomiting
- Cost of treatment, travel to treatment centers, and time away from work
- Quality of life and length of life
- How active you are and the activities that are important to you

Think about what you want from treatment. Discuss openly the risks and benefits of specific treatments and procedures. Weigh options and share concerns with your doctor. If you take the time to build a relationship with your doctor, it will help you feel supported when considering options and making treatment decisions.

Second opinion

It is normal to want to start treatment as soon as possible. While cancer can’t be ignored, there is time to have another doctor review your test results and suggest a treatment plan. This is called getting a second opinion, and it’s a normal part of cancer care. Even doctors get second opinions!

Things you can do to prepare:

- Check with your insurance company about its rules on second opinions. There may be out-of-pocket costs to see doctors who are not part of your insurance plan.
- Make plans to have copies of all your records sent to the doctor you will see for your second opinion.

Support groups

Many people diagnosed with cancer find support groups to be helpful. Support groups often include people at different stages of treatment. Some people may be newly diagnosed, while others may be finished with treatment. If your hospital or community doesn’t have support groups for people with cancer, check out the websites listed in this book.

Questions to ask your doctors

Possible questions to ask your doctors are listed on the following pages. Feel free to use these or come up with your own. Be clear about your goals for treatment and find out what to expect from treatment. Keep a notebook handy to record answers to your questions.
Questions to ask your doctors about testing and results

1. Can you tell me about the symptoms of PCNSL?

2. What tests will I have?

3. Where and when will the tests take place?

4. How long will they take?

5. What are the risks?

6. How do I prepare for testing?

7. How soon will I know the results and who will explain them to me?

8. Have any cancer cells spread to other parts of my body?
Questions to ask your doctors about treatment options

1. What are my treatment options? What are the risks of these treatments?

2. Does this hospital or center offer the best treatment for me?

3. Can you provide me with the research that supports this treatment plan?

4. How often will I get treatment and will I need more than one treatment?

5. How much time do I have to think about my options? Do I have time to get a second opinion?

6. Will I have to stay in the hospital for treatment?

7. How soon can I return to my normal activities after treatment?

8. What might happen without treatment?
Questions to ask your doctors about side effects

1. What are the side effects of systemic therapy?

2. What are the side effects of radiation therapy?

3. What are the side effects of chemotherapy?

4. When can they start? How long do they last?

5. When should I contact the care team about my side effects?

6. Are there any medications that can prevent or relieve these side effects?

7. Are there any long-term effects of this treatment?
Questions to ask your doctors about clinical trials

1. Is there an open clinical trial I can join?
2. How many people will be in the clinical trial?
3. How long does a clinical trial last?
4. How often will I have to go to a hospital or treatment center?
5. Will I be able to get other treatment if this treatment doesn’t work?
6. How will you know if the treatment is working?
7. Do I have to pay anything to join a clinical trial?
Websites

American Brain Tumor Association
abta.org/tumor_types/lymphoma

Brain Tumour Research
braintumourresearch.org/info-support/types-of-brain-tumour/cns-lymphoma

Leukemia & Lymphoma Society (LLS)

Lymphoma Research Foundation
lymphoma.org/aboutlymphoma/nhl/cns/

National Brain Tumor Society
braintumor.org/share-your-story/brain-tumors-and-primary-cns-lymphoma/

National Cancer Institute
cancer.gov/types/lymphoma/patient/primary-cns-lymphoma-treatment-pdq

National Organization for Rare Disorders (NORD)
rarediseases.org/rare-diseases/primary-central-nervous-system-lymphoma/

U.S. National Library of Medicine
Clinical Trials Database
clinicaltrials.gov
Words to know

biopsy
Removal of small amounts of tissue or fluid to be tested for disease.

central nervous system (CNS)
The brain and spinal cord.

cerebrospinal fluid (CSF)
The fluid that flows in and around the hollow spaces of the brain and spinal cord, and between two of the meninges (the thin layers of tissue that cover and protect the brain and spinal cord). Also called CSF.

clinical trial
Research on a promising test or treatment to assess its safety or how well it works.

computed tomography (CT)
A test that uses x-rays to view body parts.

consolidation therapy
Treatment given after initial therapy to kill any cancer cells that may be left in the body.

contrast
A substance put into the body to make clearer pictures during imaging tests.

diffuse large B-cell lymphoma (DLBCL)
A type of non-Hodgkin lymphoma that is usually aggressive (fast-growing). PCNSL is a rare type of DLBCL.

induction therapy
The first phase of treatment for PCNSL. When used by itself, induction therapy is the one accepted as the best treatment. Also called first-line therapy, primary therapy, and primary treatment.

magnetic resonance imaging (MRI)
A test that uses radio waves and powerful magnets to make pictures of areas inside the body.

persistent cancer
Cancer that is not completely removed or destroyed by treatment.

positron emission tomography (PET)
A test that uses radioactive material to see the shape and function of body parts.

slit-lamp eye exam
An eye exam using an instrument that combines a low-power microscope with a light source that makes a narrow beam of light.

stereotactic biopsy
A minimally invasive biopsy procedure that uses a computer and a 3-dimensional scanning device to find a tumor site and guide the removal of tissue for examination under a microscope.

stereotactic radiation therapy
A type of external radiation therapy that uses special equipment to position the patient and precisely deliver radiation to a tumor.

stereotactic radiosurgery
A type of external radiation therapy that uses special equipment to position the patient and precisely give a single large dose of radiation to a tumor.

systemic therapy
The use of medicine(s) that travel in the bloodstream and reach cells throughout the body. Systemic therapy can kill both cancer cells and healthy cells.

supportive care
Care given to improve the quality of life of patients who have a serious or life-threatening disease. Also called palliative care.
Words to know

**tumor**
An abnormal mass of cells.

**ultrasound**
A test that uses sound waves to take pictures of the inside of the body.

**whole-brain radiation therapy (WBRT)**
A type of external radiation therapy used to treat patients who have cancer in the brain. Radiation is given to the whole brain over a period of weeks.
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