

Case-based review: primary central nervous system lymphoma

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Abstract

Primary CNS lymphoma (PCNSL) is a rare diffuse large B-cell lymphoma originating within the central nervous system. The overall incidence of PCNSL is rising, particularly in the elderly population. Immunosuppression is a strong risk factor, but most patients with this tumor are apparently immunocompetent. Diagnosis of PCNSL can be challenging. Non-invasive or minimally invasive tests such as ophthalmological evaluation and spinal fluid analysis may be useful, but the majority of patients require tumor biopsy for definitive diagnosis. Our knowledge concerning optimum treatment of PCNSL is fragmentary due to paucity of adequately sized trials. Most patients are now initially treated with high-dose-methotrexate-based chemotherapy alone, as the addition of whole-brain radiotherapy at standard doses has not been shown to increase survival and does increase the risk of neurological toxicity. Ongoing trials are addressing issues such as the roles of reduced-dose radiotherapy, the addition of the CD20 antibody rituximab to chemotherapy, high-dose chemotherapy followed by autologous stem cell transplantation, and maintenance therapy in the primary management of PCNSL.

Key words:

high-dose methotrexate | neurotoxicity | primary CNS lymphoma | whole-brain radiotherapy

Clinical Case Presentation

A 75-year-old woman presented with subacute progressive confusion and unusual behavior. Imaging was obtained and corticosteroid therapy was initiated for symptomatic management. [Figure 1](#) displays the initial imaging findings.

Initial Supportive Care

Patients with PCNSL often demonstrate rapidly evolving symptoms, reflecting aggressive tumor behavior. Symptoms at presentation are typically nonfocal and are often cognitive and/

or behavioral. Focal symptoms, seizures, and symptomatic intracranial hypertension are less common. When intraocular involvement is present (choroid, vitreous, retina, and optic nerve) patients may experience blurred vision and floaters.¹

Corticosteroid Therapy

Corticosteroid therapy may rapidly ameliorate symptoms caused by PCNSL. However, prior to histopathologic diagnosis, they should be avoided because of their lymphocytotoxic effect, which may complicate neuropathologic diagnosis.^{2,3} At the authors' institutions, steroids are reserved until after pathologic diagnosis confirmation when possible, then tapered and stopped as soon as clinically possible. If a significant

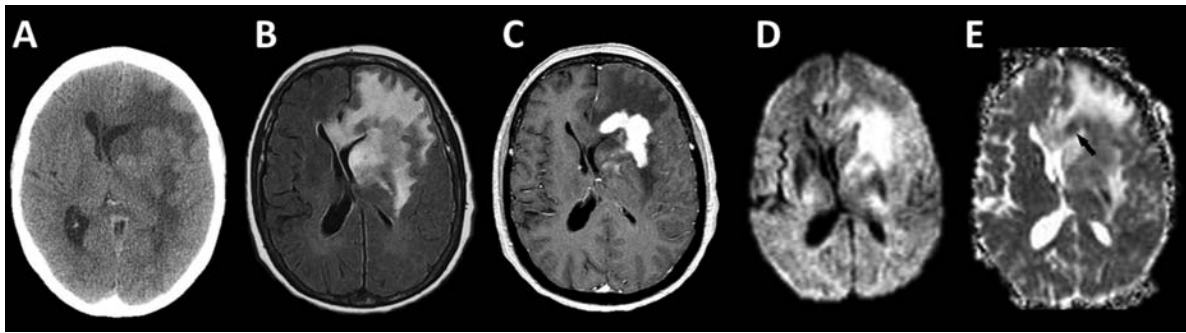


Fig. 1 Initial CT and MR imaging. (A) Noncontrast head CT depicts a deep left-frontal mass lesion isointense to gray matter with surrounding vasogenic edema and subfalcine herniation. (B) T2-weighted fluid-attenuated inversion recovery (FLAIR) MR imaging depicts the extent of edema to better advantage. (C) Postgadolinium T1-weighted MR imaging shows intense, homogeneous enhancement of the deep left-frontal tumor. (D) Diffusion-weighted imaging (DWI) shows increased signal in this region. (E) Apparent diffusion coefficient (ADC) image demonstrates foci of reduced signal (one indicated by black arrow) within the region of increased DWI signal indicating true restricted diffusion.

lymphocytotoxic effect occurs prior to biopsy, it is reasonable to taper and discontinue steroids and begin serial imaging, performing biopsy at the time of tumor regrowth.⁴

Anticoagulation

Patients with PCNSL are at significant risk of venous thromboembolism. In a retrospective analysis of 42 patients with CNS lymphoma, 25 patients (59.5%) had venous thromboembolism, which was fatal in 3 (7%).⁵ The authors of this study suggested that the benefit of anticoagulant prophylaxis with low-molecular-weight heparin probably outweighs the risk in PCNSL, but this approach is not widely employed.

Clinical case relevance

The patient was treated with corticosteroid therapy prior to neurosurgical evaluation. Within a day she was essentially asymptomatic.

Initial Diagnostics

Initial Imaging

PCNSL lesions in the immunocompetent typically present as solitary, uniformly enhancing masses, although multiple lesions are seen in 20% to 40% of patients.⁶⁻⁹ Their most common location is in the cerebral hemispheres (particularly the frontal lobes), followed by the basal ganglia, thalamus, and corpus callosum.^{6,8,9} Nearly all lesions abut either the ependyma or the pia,^{6,9,10} and periventricular white matter involvement is common.¹¹ Leptomeningeal spread constitutes two-thirds of secondary CNS lymphoma,^{12,13} but is uncommon in PCNSL.^{8,9}

Imaging characteristics of PCNSL reflect its hypercellular nature, high nuclear-to-cytoplasmic ratio, and typical disruption of the blood-brain barrier. Lesions are

typically hyper- or isoattenuating on noncontrast CT,^{6,8} hypo- or isointense on T1-weighted MRI, and are variable on T2-weighted MRI.⁶⁻⁸ Calcification and gross hemorrhage within PCNSL lesions are rare prior to treatment,⁶⁻⁸ though pretreatment petechial hemorrhage can sometimes be detected with T2*-weighted and susceptibility weighted imaging.^{14,15} Nearly all PCNSL lesions enhance following intravenous gadolinium administration. Although enhancement is classically homogeneous, it can be heterogeneous.^{6,8-10,16} Necrosis and peripheral, ring-like enhancement are uncommon in the immunocompetent, occurring in 3% to 8% of this patient population.^{8,17} Intratumoral vessels or flow voids are not expected.¹¹ Perilesional edema is variable but often moderate.⁶

The highly cellular nature of PCNSL contributes to the restricted diffusion of water on diffusion-weighted imaging in approximately 90% of cases.¹⁸⁻²⁰ PCNSL is also typically associated with elevated lipid and choline levels on MR spectroscopy.^{18,21} PCNSL has only mildly increased relative cerebral blood volume on perfusion imaging and a characteristic perfusion time-intensity curve that may overshoot the baseline because of gadolinium leakage with T1 effects.^{19,21} Positron emission tomography with 2-deoxy-2-[fluorine-18]fluoro-D-glucose (¹⁸F-FDG PET) readily shows the expected hypermetabolism of PCNSL before and after therapy.²²⁻²⁴ FDG PET can also be used to evaluate treatment response at a very early stage and to diagnose tumor recurrence.²²

A wider range of imaging findings is encountered in patients with compromised immune systems. Multifocal lesions are more common in this population, as are lack of enhancement and ring enhancement.^{7,25,26} Hemorrhage is also more commonly seen in the immunocompromised (up to 35% of patients).²⁶

While the previously discussed imaging findings are characteristic of PCNSL, there are no pathognomonic imaging findings for PCNSL. Intraparenchymal CNS lymphoma arising in the setting of systemic lymphoma (ie, secondary CNS lymphoma) may appear identical to PCNSL on imaging, as may other neoplastic, inflammatory, and

infectious neurological conditions. Advanced imaging techniques may be helpful in some cases. Lymphoma generally has more restricted water diffusion (ie, lower apparent diffusion coefficient) than high-grade gliomas and metastases, perhaps related to its more predictably high cellularity.^{19,20,27,28} Intratumoral microhemorrhages visible on susceptibility weighted imaging sequences are significantly more common and extensive in glioblastoma than in PCNSL.^{15,29-31}

In immunocompromised patients, such as those with AIDS, differentiating PCNSL from cerebral toxoplasmosis has been a notorious challenge because standard anatomic imaging findings often overlap between the 2 entities.²⁰ Thallium SPECT shows increased thallium uptake in lymphoma but not in toxoplasmosis in lesions of sufficient size to be evaluated well with SPECT.³²⁻³⁴

Cerebrospinal Fluid Diagnostics

Cerebrospinal fluid (CSF) diagnostic testing is commonly performed in patients with suspected PCNSL. Though the diagnostic yield is low, CSF analysis carries little risk and may spare a patient the need for brain biopsy. CSF diagnostic testing typically includes conventional cytology, flow cytometry,³⁵ and, at some institutions, monoclonality assessment by polymerase chain reaction (PCR).³⁶ In a large prospective study with data on meningeal involvement available for 415 patients, lymphoma was detected in the CSF by cytology in 12.2%, by PCR in 10.5%, and by MRI in 4.1%. There was a significant correlation between meningeal involvement and CSF pleocytosis, but no correlation with protein elevation.³⁷

Several additional potential diagnostic markers for PCNSL in the CSF have been described. One study found that a particular micro RNA pattern in the CSF discriminated PCNSL patients from controls with neuroinflammatory disease and other miscellaneous neurological disorders with >95% sensitivity and specificity.³⁸ CXC chemokine ligand 13 (CXCL-13), a mediator of B-cell migration; interleukin 10 (IL-10), an anti-inflammatory cytokine; and neopterin,³⁹ a nonspecific marker of CNS inflammation, have been found in CSF of PCNSL patients at significantly higher concentrations than in patients with other CNS malignancies and nonmalignant CNS diseases.^{40,41} All of these markers require validation in independent patient populations before their use in routine practice can be recommended.

Ophthalmologic Evaluation

Ocular involvement can occur prior to brain manifestations (primary intraocular lymphoma), simultaneously with brain lesions (10% to 20% of patients), and at relapse, which might be exclusively intraocular. Many patients remain asymptomatic. In patients with ocular involvement, examination typically reveals vitreous cellular infiltration on slit lamp exam and/or subretinal tumor cell infiltrates on funduscopy. A vitrectomy or chorioretinal biopsy is often needed for definitive diagnosis. Pathologic diagnosis is often difficult due to the predominance of inflammatory cells and relative paucity of lymphoma cells. A high ratio of interleukin 10 to interleukin 6 (>1) in the vitreous

is regarded to be indicative of lymphoma.^{42,43} In patients with seemingly isolated vitreoretinal lymphoma, potential CNS involvement should be evaluated by cranial MRI and CSF examination.⁴⁴ In patients with histopathologic proof of CNS lymphoma and ocular findings highly suggestive of ocular involvement, pathologic confirmation of ocular lymphoma is generally not mandatory.

Additional Diagnostic Work-up

A thorough patient history should be obtained, with specific emphasis on immunocompromising conditions. Blood testing should include an HIV test, serum LDH as a prognostic factor,⁴⁵ and testing for hepatitis, since this may be reactivated under chemotherapy or immunotherapy.

It is important to differentiate PCNSL from systemic lymphoma with CNS involvement, as the treatments are different. Physical examination of all peripheral lymph node regions and the testes should be performed. All patients without contraindications should undergo a CT of the neck, chest, abdomen, and pelvis with contrast. Additionally, according to current guidelines, bone marrow biopsy should be performed in all patients and testicular ultrasound in men.⁴⁴ With conventional staging, systemic disease is found in 4% to 12% of patients.⁴⁶ Not surprisingly, systemic manifestations are diagnosed more frequently when patients are screened with FDG-PET. In a study of 42 patients, suspect systemic disease was found in 8 (19%) patients (only in 2 of the patients were these findings seen on CT). In 6 patients biopsy was performed, revealing lymphoma in 3 patients.⁴⁷

Clinical case relevance

Initial imaging (Figure 1) was concerning for PCNSL. The patient had no systemic symptoms, lymphadenopathy, or history of immunosuppression. Body CT was unremarkable. She had no visual symptoms, and slit-lamp examination was negative. Lumbar puncture was contraindicated by her large intracranial mass with midline shift, so she proceeded on to surgery.

Surgery

Though patients often present with a single visible lesion, PCNSL is considered a whole-brain disease.⁴⁸ Thus, surgical resection has generally not been regarded as part of therapy, and has even been deemed harmful given potential neurological deficits after surgery.⁴⁹ Instead, the role of surgery is typically limited to biopsy for pathologic diagnosis. However, in a secondary analysis of a randomized phase 3 trial,⁵⁰ in the subset of patients with a single lesion, a significant benefit for both progression-free survival (PFS) and overall survival (OS) was found for patients with subtotal resection as compared to biopsy only.⁴⁹ The authors concluded that resection can be considered for single lesions in low-risk locations, though this approach remains controversial and is not yet part of the accepted standard of care. Such an approach, if technically possible, is indicated for patients with a single large lesion and rapid

progressive deterioration of neurologic status⁵¹ and in cases with the risk of imminent brain herniation.⁵²

Clinical case relevance

By the time of surgery, the patient had experienced symptomatic relief from corticosteroid therapy, and there was not felt to be a role for surgical debulking. She underwent a stereotactic needle biopsy, which was tolerated without complication.

Pathology

PCNSL morphologically and phenotypically corresponds to diffuse large B-cell lymphoma. Rarely, low-grade B-cell lymphoma, Burkitt lymphoma, high-grade T-cell lymphoma, and NK/T-cell lymphoma may involve the CNS in isolation.⁵³

Microscopically, PCNSL is a highly cellular neoplasm composed of large lymphoid cells. Geographic necrosis is not typical of PCNSL and suggests immunosuppression. Characteristic angiocentric arrangement of tumor cells is frequently apparent in less cellular areas. Vascular walls with lymphoid cell infiltration show a salient finding of concentric lamellae of reticulin fibers, nearly diagnostic of PCNSL.⁵⁴ Isolated tumor cells diffusely infiltrate brain parenchyma and are associated with reactive astrogliosis and microglial infiltration. Neoplastic cells are larger than macrophages and possess atypical, round nuclei with vesicular chromatin and a prominent single or multiple nucleoli, resembling centroblasts or immunoblasts. Mitotic figures and apoptotic bodies are frequently seen. Immunohistochemically, neoplastic cells express B-cell markers, such as CD20, CD79a, CD19, CD22, and PXA5.^{55,56} Other markers frequently expressed in diffuse large B-cell lymphoma are BCL6 (60% to 80%), MUM1/IRF4 (90%), CD10 (10% to 20%), and BCL2. Cell surface immunoglobulins are IgM and IgD with light chain restriction.

Recent advances in molecular genetic analyses have improved understanding of the molecular mechanism of diffuse large B-cell lymphoma.^{53,57–59} It is now commonly divided into 2 primary subtypes: germinal center B-cell-like (GCB) and activated B-cell-like (ABC), also referred to as non-GCB. In contrast to diffuse large B-cell lymphoma more generally, PCNSL neoplastic B cells almost exclusively demonstrate an ABC immunophenotype and post-germinal center origin.⁵³ Translocation of the *BCL6* gene with promoter substitution, observed in about one-third of PCNSL, induces constitutive BCL6 activity, which has oncogenic properties and contributes to keeping lymphoma cells in the germinal center stage. The toll-like receptor pathway is activated by mutations of *MYD88* (mostly *MYD88* L265P), which has been demonstrated in one-third of PCNSLs.^{60–62} *MYD88* plays a key role as an adaptor molecule to transducing signals from toll-like receptor. B-cell receptor signaling cascade is also altered by mutations of *CD79B* and *CARD11*.^{63–66} The activation of these signaling pathways, alone or in synergy, produces constitutive activation of the nuclear factor (NF)-κB pathway and then contributes to proliferation and survival of lymphoma cells.⁵⁷

The term sentinel lesion is used to indicate a peculiar CNS lesion that is antecedent to the onset of PCNSL.⁶⁷ Contrast-enhancing CNS lesions, clinically suspected to be PCNSL, sometimes exhibit only inflammatory changes and myelin loss mimicking primary demyelination in the biopsy specimen, and may regress spontaneously.⁶ Within several months to 2 years, however, malignant lymphoma will emerge, and the preceding lesion is retrospectively designated as a sentinel lesion. In recognition of this phenomenon, patients older than 50 who present with contrast-enhancing CNS lesions and undergo biopsy with results suggestive of demyelinating disease should be closely followed.⁶⁷

Clinical case relevance

The first biopsy at an outside institution demonstrated a dense inflammatory infiltrate composed predominantly of small reactive T-lymphocytes (Figure 2). Apoptosis and macrophage infiltration were noted, but no large B cells. Serial imaging demonstrated significant improvement in the short period between presentation and biopsy, with ongoing improvement for months despite the discontinuation of corticosteroid therapy (Figure 3). A second stereotactic biopsy was performed shortly thereafter and was also nondiagnostic. The patient then presented to a tertiary care center for a second opinion. She was followed radiographically for nearly two years, until a new region of enhancement developed around the temporal horn of the right lateral ventricle (Figure 4). Biopsy of this lesion revealed diffuse large B-cell lymphoma (Figure 2).

Epidemiology

PCNSL accounts for 2% to 4% of intracranial neoplasms and 4% to 6% of extranodal lymphomas.⁶⁸ Median age at diagnosis is 65 years, and this tumor is extremely rare in children and adolescents.⁶⁹ Immunosuppression is the only risk factor identified thus far. The incidence of PCNSL in the United States increased in the 1980s and 1990s, peaking in 1995 with 10.2 new cases per one million persons per years.⁷⁰ This increase was driven largely by AIDS-related disease. More recently, the incidence of PCNSL in young patients with immunosuppression has decreased, but it is becoming more common in elderly patients without other clear risk factors.⁷¹

Standard-of-Care Treatment

As PCNSL is a diffuse brain disease, systemic chemotherapy is an integral part of effective treatment. The ability to cross the intact blood-brain barrier is a prerequisite for systemic chemotherapy to be effective in PCNSL. When a CHOP-like protocol (cyclophosphamide, doxorubicine, vincristine, and dexamethasone instead of prednisolone)—standard treatment for systemic lymphomas—was given before whole-brain radiotherapy (WBRT) in PCNSL patients, survival was comparable to WBRT alone.⁷²

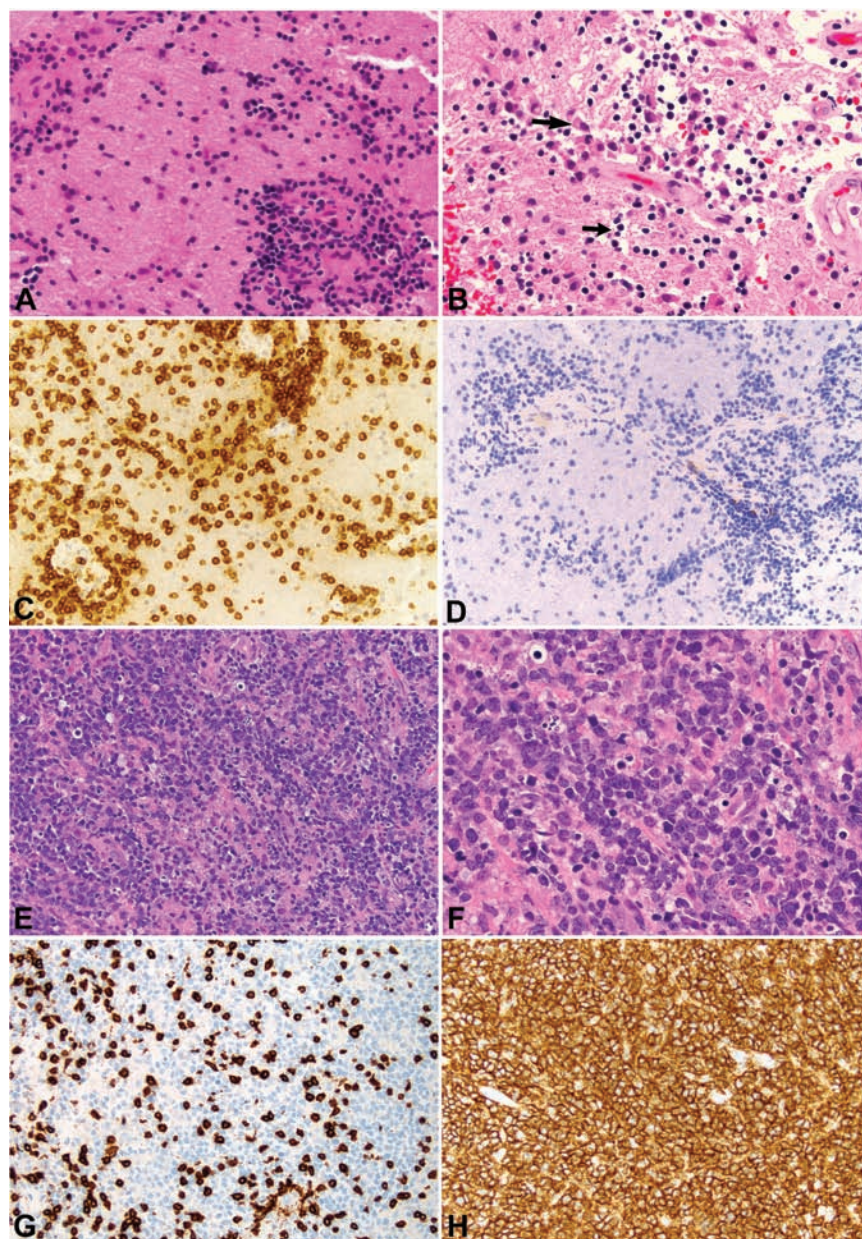


Fig. 2 Initial biopsy after corticosteroid therapy and subsequent diagnostic biopsy at tumor recurrence. Nondiagnostic biopsy after corticosteroid therapy (A-D). White matter shows a marked lymphocytic infiltrate (A, x200) composed of small lymphocytes with dark blue nuclei, parenchymal and perivascular. Small dark apoptotic nuclei (one indicated by the short black arrow) and macrophages (one indicated by the long black arrow) are present in areas of the biopsy (B, x400). The small lymphocytes are nearly exclusively CD3-positive, consistent with reactive T-lymphocytes (C, x200). There are no CD20-positive cells in the infiltrate (D, x200). Diagnostic biopsy at recurrence (E-H). Primary CNS lymphoma cells diffusely infiltrate the parenchyma (E, x200) with monomorphic, large blastic cells largely replacing the tissue (F, x400). While a moderate number of small infiltrating CD3-positive reactive T-lymphocytes is present (G, x200), similar to the first biopsy (C), most cells express the B-cell marker CD20 (H, x200). The morphologic findings in conjunction with the immunophenotype confirm the diagnosis of diffuse large B-cell lymphoma.

Systemic Chemotherapy

The paucity of randomized trials to support therapeutic decisions is a critical problem in the management of PCNSL. While there is no universally accepted treatment, consensus exists that high-dose methotrexate (HDMTX) is the most important drug in the treatment of PCNSL.

However, there is great variability in HDMTX dose and schedule in practice. It is generally accepted that doses ≥ 3 g/m² and infusion times of approximately 4 hours should be used to reliably achieve cytotoxic levels in the CSF.^{73,74}

A wide spectrum of complete response rates with HDMTX monochemotherapy, ranging between 15% (despite a very

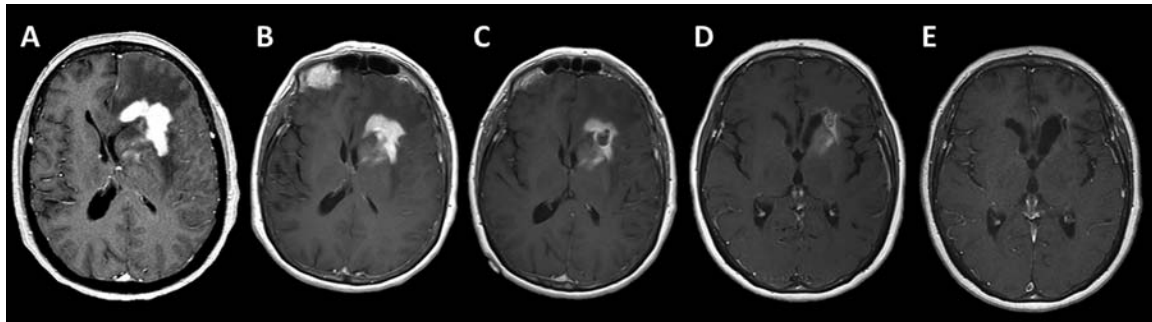


Fig. 3 Serial MR imaging after corticosteroid therapy. Serial gadolinium-enhanced T1-weighted MR images (A) prior to corticosteroid therapy, (B) 3 days after the initiation of corticosteroids, (C) 5 days after the initiation of corticosteroids; note interval biopsy defect within the left frontal region of enhancement, (D) 3 months after biopsy, and (E) 8 months after biopsy.

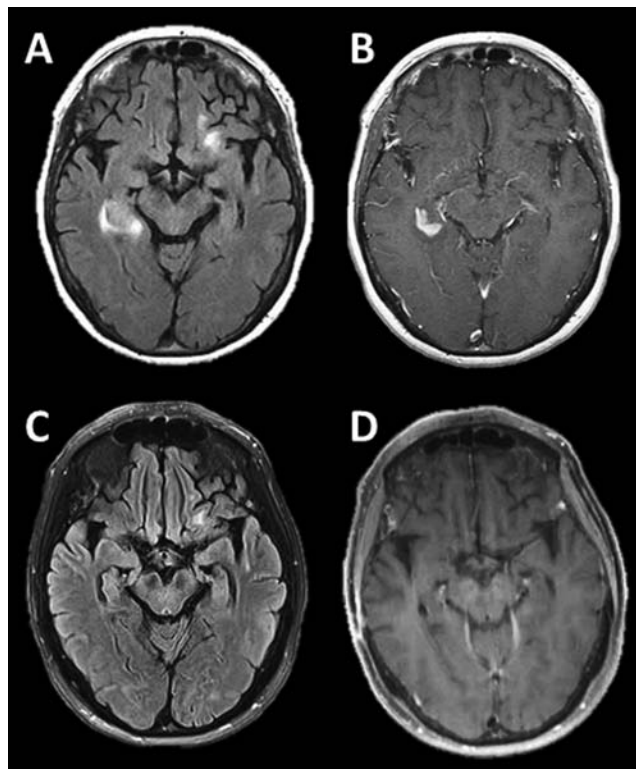


Fig. 4 MR imaging at recurrence and after high-dose methotrexate (HDMTX)-based chemotherapy. (A) T2-weighted fluid-attenuated inversion recovery (FLAIR) and (B) T1-weighted post-gadolinium images at time of radiographic progression. (C) T2-weighted FLAIR and (D) T1-weighted post-gadolinium images following the completion of HDMTX-based chemotherapy demonstrate a complete response.

high dose of 8 g/m² and combination with rituximab) and 52%, has been reported.^{75,76} HDMTX-based polychemotherapy is generally regarded to be more effective than HDMTX alone. Several noncomparative trials using different HDMTX-based combinations have been published. With an intensive chemotherapy regimen, including HDMTX (5 g/m²), high-dose cytarabine (HDArAC) (3 g/m²), vincristine, alkylating agents,

and dexamethasone combined with intensive intraventricular chemotherapy via Ommaya reservoir, a median event-free survival of 21 months and a median OS of 50 months was reached.⁷⁷ However, this regimen has not found broad acceptance because of the risk of Ommaya reservoir infection.

In a small (n = 79), randomized, phase 2 study, HDMTX alone was compared with HDMTX in combination with

HDARA-C, both arms followed by WBRT.⁷⁸ The complete response rate was 46% with the combination vs 18% with HDMTX alone ($P = .006$), and 3-year OS was 46% vs 32% ($P = .07$), respectively. However, this difference was achieved with undertreatment in the “standard” arm, since HDMTX alone (3.5 g/m²) was given every 3 weeks only, thus resulting in exceptionally low complete response rate. A more recent trial compared HDMTX and HDARA-C (group A) with the same combination plus rituximab (group B) and plus both thiotepa and rituximab (group C, MATRix), followed by a second randomization to either WBRT or high-dose chemotherapy (carmustine and thiotepa) and autologous stem cell transplantation (HD-ASCT).⁷⁹ Results of the first randomization have been reported and demonstrated a significant improvement of the complete response rate (primary endpoint) with MATRix (49%; 95% CI, 38–60%) as compared with both comparator arms. This trial, however, was not prospectively designed to test the benefit of addition of rituximab or thiotepa to HDMTX and HDARA-C.

Consolidation of HDMTX-based primary chemotherapy by other non-cross-resistant chemotherapy is the current concept in PCNSL treatment. In the CALGB 50202 study, 44 patients with complete response to 4 courses of rituximab/HDMTX/temozolomide (R-MT) were consolidated with etoposide/HDARA-C. The complete response rate to R-MT was 66%, the 2-year PFS rate was 57%, and median time to progression was 4.0 years.⁸⁰ In a German study of patients <65 years of age, induction chemotherapy with rituximab/HDMTX was followed by rituximab/HDARA-C/thiotepa and HD-ASCT (carmustine/thiotepa). The 3-year PFS was 63% and 3-year OS was 78%.⁸¹ In an American study, 32 patients ≤ 67 years received 5 courses of rituximab/HDMTX/procarbazine/vincristine (R-MPV), which was in responders consolidated by high-dose regimen with thiotepa/cyclophosphamide/busulfan followed by autologous stem cell transplant (ASCT). The complete response rate to R-MPV was 66% and the 3-year PFS estimate was 79%; however, there was a relatively high toxic death rate of 10%.⁸² The final results of the IELSG-32 study mentioned above comparing different consolidations in the second randomization are pending. In the preliminary report it is stated that the PFS at 2 years—the primary endpoint of the second randomization—of 61% was significantly better in the MATRix group, and very poor 2-year PFS of 36% and 46% in groups A and B, respectively.⁸⁶ However, an intrinsic limitation of the 2-stage randomization design is the potential for interaction between the randomization arm for induction chemotherapy and the randomization arm for consolidation.

Since there is no proof of better efficacy of higher HDMTX doses, it is our practice to treat newly diagnosed PCNSL patients with creatinine clearance of ≥50 ml/min with a minimum of 4 cycles of HDMTX at a dose of 3–4 g/m² as a 4-hour infusion and to combine it with an alkylating drug (eg, ifosfamide, temozolomide) or HDARA-C. At many centers, chemotherapy is combined with the CD20 antibody rituximab, as will be discussed below.

Role of Rituximab

As a large protein, penetration of the CD20 antibody rituximab into the CNS is poor, with less than 1% of systemic concentration reaching the leptomeningeal compartment,⁸³

which provides an indirect measure of intraparenchymal concentration. Adding rituximab to HDMTX-based chemotherapy has proved feasible and active in small studies.^{84–86} Retrospective analyses of the role or addition of rituximab to HDMTX yielded conflicting results.^{87–89}

Recently, the first study evaluating the role of rituximab in a randomized fashion was published (IELSG-32). The complete response rate was 23% for HDMTX+HDARA-C (group A), 30% when rituximab was added (group B), and 49% when both rituximab and thiotepa were added (group C). Multivariate logistic regression analysis including treatment group and the IELSG risk score revealed a significant response advantage for group C vs A and B but no significant difference between A and B.⁸⁷

Role of Radiotherapy

Although never proven in a randomized trial, it is concluded from a retrospective analysis,⁹⁰ and generally accepted, that radiotherapy alone is inferior to its combination with HDMTX-based chemotherapy. With WBRT alone, a high response rate, but usually no significant long-term control, can be achieved.

The role of WBRT given in addition to HDMTX-based primary chemotherapy has been defined by the G-PCNSL-SG1 trial. Patients randomized to radiation received HDMTX-based chemotherapy followed by immediate WBRT. Patients randomized to chemotherapy alone received no further therapy if they had achieved complete response, and second-line chemotherapy with HDARA-C if they had not. No significant difference in OS was found, with a median OS in the intent-to-treat population ($n = 411$) of 32.1 months with WBRT and 34.4 months without WBRT. Patients treated with WBRT had prolonged PFS: 15.5 vs 9.9 months ($P = .04$).⁵⁰ These results were confirmed in a long-term analysis of this study with a median follow-up of 82 months.⁹¹ This trial has been a source of controversy, with some experts pointing out that the unmet primary endpoint for noninferiority and the high rate of protocol violations prevent definitive conclusions, and others noting that the results contribute to the accumulating scientific literature,^{90,92} which suggests that omission of WBRT from first-line treatment does not compromise OS and may prevent neurological toxicity.

The role of focal radiotherapy and reduced-dose WBRT, with the aim to reduce neurotoxicity, is unclear due to the lack of comparative trials. A small prospective study of 52 patients suggested that consolidating dose-reduced WBRT (23.4 Gy) given to patients with complete response after HDMTX-based chemotherapy (R-MPV) and before HDARA-C was associated with good tumor control: the 2-year PFS of the 31 patients with complete response after R-MPV was 77% and median PFS was 7.7 years.^{85,86}

In general, WBRT is not routinely utilized for primary treatment of PCNSL and is currently offered primarily to patients for whom systemic chemotherapy is contraindicated.

Side Effect Management

Due to a relatively high risk of complications, HDMTX therapy should be administered in experienced centers. The presence of more than 500 ml of “third space” fluid such as

pleural effusion or ascites may lead to a prolonged effective MTX half-life, and represents a relative contraindication to HDMTX.

HDMTX therapy would be unacceptably toxic without the use of folinic acid (leucovorin), often dosed at 30 mg every 6 hours starting 24 hours after the initiation of HDMTX. Monitoring of MTX elimination is mandatory to ensure normal clearance. In case of disturbed MTX elimination, an intensified leucovorin rescue is necessary. In severe cases, application of carboxypeptidase-G2—an enzyme rapidly cleaving MTX—should be considered since hemodialysis has only modest efficacy in removing MTX.

Renal insufficiency is a serious acute side effect of HDMTX therapy. At many centers, MTX dose is adapted to the creatinine clearance.⁹³ To reduce the risk of renal insufficiency, all potentially nephrotoxic agents should be stopped, and intensive intravenous hydration and urine alkalization (goal urine pH ≥ 7) is necessary. Acute HDMTX-induced lung injury (pneumonitis) with fever, dry cough, and dyspnea is relatively rare and usually managed with steroids. The differentiation from pneumonia caused by infectious agents can be difficult. Nausea and vomiting are only rarely seen with antiemetic prophylaxis based on 5-HT₃-antagonists. Stomatitis is most frequent with 24-hour infusions and rarely seen with a 4-hour infusion. Acute CNS toxicity with somnolence, confusion, fatigue, disorientation, and seizures may occur during or within hours after HDMTX infusion. Subacute neurotoxicity may occur within days to weeks and is characterized by focal symptoms, seizures, and somnolence. Both are transient and reversible without special treatment in most cases.⁹⁴

Delayed treatment-related neurotoxicity represents a major long-term toxicity in patients with PCNSL, particularly after combination of HDMTX-based chemotherapy with WBRT.^{95,96} The risk of neurotoxicity clearly increases with age.⁹⁵ It is appreciated that WBRT rather than chemotherapy is the primary mediator of neurotoxicity in PCNSL.^{96–98} In fact, in a retrospective analysis of 185 patients, WBRT was the only factor associated with late neurotoxicity (evaluated by clinical examination only) in the multivariate setting.⁹⁹ In a recent series, PCNSL patients treated with WBRT had significant impairments across most cognitive domains, interfering with quality of life, while those treated with chemotherapy alone had significantly higher scores in neuropsychometric testing.¹⁰⁰

Treatment of Elderly Patients

Older age is a major negative prognostic factor in PCNSL, being associated both with reduced survival and an increased risk of treatment-related toxicities.^{45,50,101,102}

Due to very high risk of delayed neurotoxicity, reaching 100% after 4 years in patients 60 years and older,⁹⁵ WBRT has largely been abandoned as a primary therapy in this population. Several trials designed for elderly patients using HDMTX-based chemotherapy alone have been published.^{103–107} These trials have demonstrated response rates of approximately 50% and median PFS of 5 to 10 months, but with substantial acute toxicity and high rate of treatment discontinuation in some trials. In a

recent randomized, phase 2 study of patients >60 years, the MPV-A (HDMTX, procarbazine, vincristine, HD AraC) regimen was compared to MT (HDMTX with temozolomide). The complete response rate was 62% and 45%, respectively; the objective response rate was 82% vs 71%; and median OS was 31 vs 14 months, with comparable levels of acute toxicity.¹⁰⁸ While all of these efficacy endpoints favor the MPV-A regimen, the trial was not powered for a direct comparison and the differences did not reach statistical significance. In another recent phase 2 study, all 66 patients were treated with a dose-adjusted HDMTX-based and HD AraC-based protocol combined with liposomal AraC intrathecally; those between 66 and 75 years (n = 27) additionally received a maintenance therapy with temozolomide for 1 year or until progression.¹⁰⁹ The outcome of elderly patients was comparable with that of the younger patients, probably reflecting the benefit of maintenance therapy.

In summary, HDMTX is feasible in elderly PCNSL patients without serious comorbidities and most likely produces a better outcome than WBRT alone, which should be reserved for patients not able to receive chemotherapy. To minimize the risk of late neurotoxicity, use of WBRT after HDMTX should be avoided.

Primary Intraocular Lymphoma

The median survival of patients with isolated primary intraocular lymphoma and no CNS involvement is approximately 60 months.¹¹⁰ Local eye-dedicated therapy such as ocular radiation or intravitreal chemotherapy with MTX or immunotherapy with rituximab can be given to patients with primary intraocular lymphoma. These approaches have not been directly compared, but do not seem to differ substantially with respect to local tumor control or treatment-related visual compromise.¹¹¹

Since CNS relapse is universal in patients with primary intraocular lymphoma who undergo local treatment alone, chemotherapy regimens analogous to those used in PCNSL are employed for isolated primary intraocular lymphoma at some institutions, while others reserve systemic chemotherapy until CNS relapse.¹¹⁰ The efficacy of systemic chemotherapy depends on ocular penetration. In one study of patients treated with HDMTX (8 g/m²), anterior chamber concentrations of <10% and vitreous concentrations <1% of the corresponding plasma level were found, nonetheless achieving micromolar concentrations and producing responses in 7 of 9 patients.¹¹² With ifosfamide therapy, anterior chamber concentrations are approximately 19% to 54% of the corresponding plasma concentration.¹¹³ In a small prospective study of ifosfamide or its oral analogue as monotherapy for primary intraocular lymphoma, all 10 patients responded with a median PFS of 18 months and median OS of 32 months.¹¹⁴

A systemic HDMTX-based chemotherapy, as used in PCNSL, is the treatment of choice in patients with simultaneous ocular and CNS involvement. The role of additional local ocular therapy in this setting remains unclear. In a retrospective analysis of 221 patients with concomitant PCNSL and intraocular lymphoma, the addition of local ocular therapy in addition to PCNSL treatment was found to improve disease control but not survival.⁴³

Treatment of Immunosuppressed Patients

Patients with chronic drug-induced immunosuppression for treatment of autoimmune disorders or following organ transplantation are at risk for the development of PCNSL. The post-transplantation lymphoproliferative disorders are B-cell lymphomas developed on the basis of proliferation stimulated by Epstein-Barr virus infection. Immunosuppressive agents associated with this condition include cyclosporine, tacrolimus, and mycophenolate mofetil.

In patients on long-term immunosuppressive drugs diagnosed with PCNSL, immunosuppression is reduced when possible. In HIV-positive patients with PCNSL, immunocompetence can be achieved with antiretroviral therapy, which has been shown to prolong survival.¹¹⁵ In the largest retrospective analysis of 84 patients with post-transplant lymphoproliferative disorder (PTLD)-PCNSL, immunosuppressive medications were reduced in 93% of patients. Additional primary therapies in this patient group included HDMTX in 48%, HDARaC in 33%, WBRT in 24%, and/or rituximab in 44%. The objective response rate was 60%, but with a treatment-related mortality of 13%; 3-year PFS was 32%; and 3-year OS was 43%.¹¹⁶ These findings suggest that patients with immunosuppression-caused PCNSL can be treated similarly to immunocompetent patients, but with higher risk of serious infectious complications.

Important Ongoing Clinical Trials

Though the number of completed prospective trials for PCNSL remains small, numerous planned and ongoing trials promise to provide new insight into therapy. Some of these trials seek to optimize the use of agents already employed in the treatment of PCNSL. Others expand upon recent progress in systemic lymphoma and focus on treatments suggested to be promising in the ABC subtype of diffuse large B-cell lymphoma,¹¹⁷ which represents the vast majority of PCNSL.⁶⁴

The phase 3 HOVON 105 PCNSL/ALLG NHL 24 collaborative study (EudraCT # 2009-014722-42) will enroll 200 patients randomized to the combination of HDMTX (3 g/m²), teniposide, carmustine, and prednisone, with or without rituximab. Responders will also receive HDARaC consolidation, and patients <60 years who maintain their response status after cytarabine will then receive WBRT. Two studies, one phase 3 (NCT02531841) and one randomized phase 2 (NCT01511562), will evaluate the role of consolidation therapy with HD-ASCT by randomizing patients to HD-ASCT or consolidating conventional chemotherapy following the completion of induction chemotherapy. An additional trial aimed at maximizing the efficacy of HDMTX therapy while limiting toxicity is the randomized phase 2 trial of reduced-dose WBRT after initial therapy composed of rituximab, HDMTX, vincristine, procarbazine, and HDARaC (NCT01399372). Obinotuzumab, a novel glycoengineered type-II CD20 monoclonal antibody that proved superior to rituximab in inducing cell death is being tested in a randomized phase 2 study as maintenance therapy in patients who previously achieved complete response with primary

therapy (NCT02498951). As previously discussed, the poor blood-brain barrier penetration of most chemotherapy regimens represents a major obstacle to treatment. Though this has typically been overcome by using drugs that can cross the blood-brain barrier, therapy to disrupt the blood-brain barrier combined with rituximab, carboplatin, and MTX is being tested in an ongoing phase 1/2 study (NCT00293475).

Several ongoing trials are evaluating targeted therapy. Dysregulation of various cellular pathways (such as NF- κ B, toll-like receptor, or B-cell receptor signaling pathways) has been reported in PCNSL, and these pathways constitute potential therapeutic targets. Ibrutinib, an inhibitor of Bruton's tyrosine kinase, is currently being evaluated in combination with chemotherapy in newly diagnosed PCNSL patients (NCT02203526) and in 2 studies with relapsed/refractory patients (NCT02315326, NCT02542514). A novel dual PI3K/mTOR inhibitor, PQR309, and buparlisib (BKM120), a PIK3-inhibitor, are being tested in relapsed or refractory patients (NCT02669511 and NCT02301364). Immunomodulation is another promising therapeutic strategy in PCNSL. The thalidomide derivative pomalidomide is currently being evaluated in intraocular lymphoma and relapsed or refractory PCNSL (NCT01722305) and lenalidomide is being tested in the same indication in **combination with** rituximab (NCT01542918). The checkpoint blocker pembrolizumab is being evaluated in relapsed PCNSL (NCT02779101).

Salvage Therapy

PCNSL shows a continuing tendency to recur with longer follow-up even after intensive initial therapy.^{91,118,119} Patients generally benefit from salvage therapy after failure of primary treatment if not in a severely compromised condition.¹²⁰ Choice of salvage treatment should be driven by a patient's age, performance status, prior therapy, and duration of previous response.

WBRT is a very effective salvage treatment, with response rates of 60% to 79% among refractory and relapsed patients, and median OS of 10.9 to 16 months after progression or relapse.^{121,122} However, WBRT exposes patients to higher risk of late neurotoxicity than second-line chemotherapy. Thus, salvage chemotherapy is generally preferred, particularly in patients with good performance status and response to previous chemotherapy.

Numerous chemotherapy and immunotherapy approaches to recurrent PCNSL have been evaluated, utilizing agents such as topotecan,^{123,124} rituximab,⁸³ temozolomide with or without concurrent rituximab,¹²⁵⁻¹²⁷ bendamustine,¹²⁸ HDARaC,¹²⁹ ifosfamide-based and/or etoposide-based polychemotherapy,^{81,130,131} and yttrium-90-labeled ibritumomab tiuxetan.¹³² The median PFS figures were uniformly short at 2 to 5 months. Lenalidomide, an immunomodulatory agent, most probably acting by modifying the tumor microenvironment and activating cytotoxic T-cells and natural killer cells, induced a complete response in 2 of 6 patients with relapsed PCNSL.¹³³ A phase 2 study with the mTOR inhibitor temsirolimus is the first completed prospective trial of a targeted agent in PCNSL.¹³⁴ Complete response was seen in 5 of the 37 patients (13.5%), "complete response

unconfirmed" in 3 (8%), and partial response in 12 (32.4%), for an overall response rate (primary endpoint) of 54%. However, median PFS was only 2.6 months. Rechallenge with HDMTX is a reasonable option for patients who experienced a long-term remission after primary HDMTX therapy.^{135,136}

For younger patients who are able to tolerate intensive therapy, HD-ASCT can be considered. In a prospective trial, 43 patients with a median age of 52 years received HDARA and etoposide (CYVE) followed by thiotepa, busulfan, and cyclophosphamide and ASCT. The median PFS was 11.6 months and the 2-year OS 45%; however, 3 patients died on CYVE and 5 patients (all <60 years) developed clinically manifest late neurotoxicity.^{137,138}

Relapse or progression outside the CNS is very rare in PCNSL. Patients with isolated extra-CNS relapses are usually managed with anthracycline-based chemotherapy with or without HD-ASCT.⁴

Clinical case relevance

First-line treatment with HDMTX, temozolomide, and rituximab was initiated. Her first post-treatment MRI demonstrated excellent response to therapy (Figure 4).

Follow-up

The International Primary CNS Lymphoma Collaborative Group recommends that patients in clinical studies are reassessed every 3 months in the first 2 years after therapy completion, then every 6 months for 3 years, and then annually for at least 5 years for a total of 10 years of follow-up.⁴⁴ This schedule is also reasonable for patients not treated on clinical studies. However, very late relapses after more than 10 years have been reported in patients with PCNSL.

Routine follow-up reassessment should include history, physical examination, and gadolinium-enhanced MRI. Patients with initial CSF or eye involvement should undergo a re-evaluation of these compartments. Additional examinations should be performed at clinical suspicion; a routine search for systemic manifestations is not recommended since the vast majority of relapses are localized in the CNS. For remission status estimation, IPCG criteria⁴⁴ rather than Macdonald criteria should be used. These criteria include a response category of "complete remission unconfirmed," which allows for the presence of a small amount of contrast enhancement at the site of the initial tumor or surgery.

At relapse, pathologic confirmation of brain lesions with a typical radiomorphology is usually not performed. In rare cases, contrast enhancement may be absent, complicating the distinction between recurrent tumor and small infarctions or toxic leukoencephalopathy.¹³⁹ In these patients, a brain biopsy should be considered for definitive diagnosis.

Ideally, monitoring of late neurotoxicity should be performed. At many institutions the Mini-Mental State Examination is being used due to its simplicity and practicability. However, because its sensitivity is low, detailed psychometric testing is preferred, at least in clinical trials.⁴

Prognosis and Survivorship

Overall Survival

The prognosis of PCNSL remains poor, despite recent advances. In the G-PCNSL-SG1 study, the median OS was 35.3 months in the per-protocol population (n = 311), but only 21.5 months for the 526 patients who started treatment.⁵⁰ Moreover, while current therapeutic approaches have reduced neurotoxicity by deferring WBRT, it is not clear that survival has improved.¹⁴⁰

Older age and reduced performance status are uniformly accepted as negative prognostic factors in PCNSL, as well as in many other tumor types. The Memorial Sloan Kettering Cancer Center prognosis score based on these 2 factors divides patients into 3 risk classes with different outcomes: class 1 (age <50 years, median OS 8.5 years, median event-free survival 2 years), class 2 (age ≥50 and KPS ≥70, median OS 3.2 years, median event-free survival 1.8 years), and class 3 (age ≥50 and KPS <70, median OS 1.1 years, median event-free survival 0.6 months).¹⁰¹ The International Extranodal Lymphoma Study Group (IELSG) identified 5 variables independently associated with worse survival: age more than 60 years, ECOG performance status more than 1, elevated LDH serum level, high CSF protein concentration, and involvement of deep regions of the brain (periventricular regions, basal ganglia, brainstem, and/or cerebellum). These 5 variables were used to design a prognostic score: the 2-year OS was 80%, 48%, and 15% (P = .00001) for patients with 0 to 1, 2 to 3, and 4 to 5 unfavorable features, respectively.⁴⁵

The prognostic impact of biomarkers in PCNSL remains to be fully defined. Outcome prediction based upon the Hans algorithm as reported for systemic diffuse large B-cell lymphoma¹⁴¹ was not reproducible in a post hoc analysis of 119 patients from the G-PCNSL-SG1.¹⁴² The prognostic determination based upon individual markers from this algorithm in PCNSL is either indeterminate or of variable significance; eg, BCL6 was associated with favorable prognosis in some studies^{143,144} but with inferior prognosis in others.^{80,142,145} MYC protein expression detected by immunohistochemistry, found in 43% of 42 patients with CNS diffuse large B-cell lymphoma, identified a patient subset with worse prognosis.¹⁴⁶ The results of all these analyses, however, have to be interpreted with caution since the vast majority of them were retrospective in nature, evaluated small numbers of patients, and involved different therapeutic regimens.

Conclusion

Despite substantial progress in management, cure is still questionable in PCNSL patients and exceptional in the elderly. Multidisciplinary care including neuroradiologists, neuropathologists, neurosurgeons, neurologists, medical oncologists, radiation oncologists, and psychologists is necessary for optimal patient management.⁴ Risk-tailored treatment choice, adequate monitoring of response and side effects, and careful follow-up in experienced centers

substantially improve outcome. Initial treatment is usually based on HDMTX without WBRT, and WBRT should be deferred as long as possible to minimize the risk of delayed neurotoxicity.

Ongoing clinical trials will hopefully elucidate optimal induction and consolidation chemotherapy as well as the role of new agents. Incorporation of neuropsychologic testing into studies is to be mandated. Better understanding of tumor pathogenesis is probably essential to establish optimal therapy of this disease.

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