# BHS guidelines for primary central nervous system lymphoma

V. De Wilde, MD, PhD[1], D. Dierickx, MD, PhD[2], W. Schroyens, MD, PhD[3], E. Van Den Neste, MD, PhD[4], C. Bonnet, MD, PhD[5], M. Andre, MD[6], A. Janssens, MD, PhD[2], V. Van Hende, MD[7], A. Van Hoof, MD[8]

**Primary central nervous system lymphoma is a rare form of extranodal B cell lymphoma of the brain, the eyes, the meninges or the spinal cord in the absence of systemic lymphoma. The management of primary central nervous system lymphoma remains controversial, which is related to the rarity of the cases and the small number of controlled studies available. The present consensus report provides the guidelines proposed by the Belgian Hematology Society Lymphoproliferative Working Party for treating immuno-competent adult patients with primary central nervous system lymphoma.**

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## Introduction

Primary central nervous system lymphoma (PCNSL) is a rare extranodal form of Non-Hodgkin Lymphoma (NHL) localised in brain, meninges, eyes and/or spinal cord, without systemic involvement at the time of diagnosis. It represents 2-4% of all intracranial neoplasms and 4-6% of extra-nodal lymphomas, with a yearly incidence of five cases per 1,000,000 people.[1,2]
Immunodeficiency (congenital or acquired) is associated with an increased risk of the development of PCNSL. In immunocompetent patients, the median age at diagnosis is around 60 years.

## Clinical picture

Patients with PCNSL may present various clinical symptoms and signs. The extent of symptoms such as personality changes, headaches, cognitive disturbances or focal neurological defects depend on tumour size and localisation and on the peritumoral oedema. B symptoms are rare. Intraocular invasion may cause blurred vision, floaters, visual field defects and decreased visual acuity.[3] Intraocular involvement is observed in 10-20% of patients while only half of them experience visual complaints, which at times can be the only symptom of primary intraocular lymphoma, possibly followed weeks or months later by the onset of brain lesions.

## Diagnosis

*Histology, flow cytometry, biochemical analysis*

All PCNSL patients should have had histopathological confirmation, including immunophenotyping. Whenever possible, steroid treatment should be avoided before tissue biopsy, as such treatment could interfere with the histopathological assessment. If, however, steroids have been used before diagnosis, the biopsy should be performed after a steroid-free interval of 7-10 days, if clinically safe, to prevent a possible false-negative result. The choice diagnostic procedure for PCNSL is stereotactic needle biopsy. Surgical resection is not recommended.[4] Only one retrospective study suggests subtotal or gross total resection may improve PFS, in case of a single lesion.[5] If there is evidence of

[1]Department of Haematology, Université Libre de Bruxelles, LB Hospital Erasme, Brussels, Belgium, [2]Department of Haematology, University Hospitals Leuven, Leuven, Belgium, [3]Department of Haematology, University Hospital Antwerp, Antwerp, Belgium, [4]Department of Haematology, Cliniques Universitaires St Luc, UCL, Brussels, Belgium, [5]Department of Haematology, Centre Hospitalier Universitaire, Liege, Belgium, [6]Department of Haematology, Cliniques Universitaires Mont Godinne, UCL, Belgium, [7]Department of Haematology, University Hospital Gent, Gent, Belgium, [8]Department of Haematology, AZ St. Jan, Brugge, Belgium.

*Please send all correspondence to:* V. De Wilde, MD, PhD, ULB Hôpital Erasme, Department of Haematology, Route de Lennik 808, 1070 Brussels, Belgium, tel: +32 2 555 57 07, email: virginie.de.wilde@erasme.ulb.ac.be.

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ocular or cerebrospinal fluid (CSF) involvement, vitrectomy or CSF flow cytometry may establish the diagnosis. Raised IL10 (above 50 pg/ml) and an IL10/IL6 ratio above one are highly suggestive of ocular lymphoma and may contribute to establishing the diagnosis in case of poor cellularity in an aqueous or vitreous sample.[6] The detection of MYD88 mutations on a vitrectomy specimen may also improve diagnosis.[7] About 90-95% of PCNSLs are diffuse large B cell lymphomas (DLBCL), histological diagnosis of lymphomas other than DLBCL (including Burkitt's lymphoma, lymphoblastic, marginal zone lymphoma or T cell lymphoma) will be made less often.[8,9] PCNSL has to be distinguished from dural-based marginal zone lymphoma's: these do not disseminate in the brain parenchyma and mimic meningioma.[9] Dealing with those rare entities is beyond the scope of the present guidelines.

Neoplastic B lymphocytes usually form classical perivascular cuffs, and phenotypically express pan-B-cell markers (CD20, CD19, CD22, CD79a), markers of germinal centre B cells (bcl-6 in 60–80% of cases) and markers of late germinal centre B cells (IRF4/MUM1; 90%), while they are rarely positive for CD10 (<10%). Therefore, the majority of PCNSLs are of an activated B cell immunophenotype. The proliferation index is usually high.[10,11] A mutation activating MYD88 has been demonstrated in 40-94% of all cases.[12,13] However, there are currently insufficient data to recommend the routine use of specific histopathological, immunohistochemical or genetic features for an individual prediction of prognosis or a treatment adaptation.

*Magnetic resonance imaging (MRI)*

Contrast-enhanced brain MRI provides superior lesion characterisation and localisation, compared to CT, and is recommended in all suspected cases. MRI sequences should include: T1 weighted sequences before and after contrast, perfusion, diffusion, FLAIR and spectroscopy sequences. Contrast enhanced CT scans may be substituted only if MRI is medically contraindicated. Characteristic brain images are homogeneously enhanced mass lesions with restricted diffusion signals (typically in the periventricular regions, in deep grey matter structures and in the corpus callosum). Stereoscopy shows typical choline and lipids pics. Although the radiological appearances of PCNSL may be distinctive, there is considerable overlap with other aggressive intracranial neoplasms such as high grade gliomas, metastases, inflammatory or infectious conditions. Thus, histological confirmation is mandatory. Because of the complex imaging, an expert review of all neuroradiological images is highly recommended.

*Baseline clinical evaluation*

The baseline evaluation of a newly diagnosed patient with PCNSL should include a comprehensive physical and neurological examination. Particular attention should be paid to peripheral lymph nodes and scrotum. Age and performance status (ECOG performance scale) are the two most widely documented prognostic variables and must be recorded for every patient. The evaluation of the cognitive function is important, at baseline and during follow-up, to gauge the benefit of therapy as well as to monitor for a possible treatment-related neurocognitive decline. Neuropsychological testing should include at least a Mini-Mental State Examination (MMSE), and use the Instrumental Activities of Daily Living scale (IADL).

*Laboratory evaluation*

Baseline laboratory evaluation should include peripheral blood count, serum lactate dehydrogenase (LDH) level, hepatic and renal functions and HIV, Hepatitis B and C virus serology.

## Staging

Determining the full extent of the disease is critical before initiating a therapy. All patients should have, if possible, a lumbar puncture for cytology, immunophenotyping, PCR of the rearranged immunoglobulin heavy-chain genes, and total protein level assessment.[14] Meningeal involvement, often asymptomatic, is detected by conventional CSF cytology, and is present in 16% of patients. Isolated leptomeningeal lymphoma, in the absence of a parenchymal mass, represents <5% of all PCNSLs.[15] A detailed ophthalmological fundus examination with dilated pupils and slit lamp examination should be performed to exclude vitreous, retinal or optic nerve involvement. Fluorescein angiography may be helpful to confirm lymphomatous involvement of the retina.

Involvement of the spinal cord parenchyma is rare, and gadolinium-enhanced MRI of the total spine is only warranted in patients with spinal symptoms.

Occult systemic disease has been reported in up to 8% of patients initially thought to have isolated PCNSL.[16,17] As a result, complete systemic staging is warranted in every patient. This is done by CT-scan or positron

**Table 1.** Response criteria for Primary Central Nervous System Lymphoma.

| Response | Brain Imaging | Corticosteroid Dose | Eye Examination | CSF Cytology |
|---|---|---|---|---|
| CR | No contrast enhancement | None | Normal | Negative |
| CRu | No contrast enhancement | Any | Normal | Negative |
| | Minimal abnormality | Any | Minor RPE abnormality | Negative |
| PR | 50% decrease in enhancing tumour | Irrelevant | Minor RPE abnormality or Normal | Negative |
| | No contrast enhancement | Irrelevant | Decrease in vitreous cells or retinal infiltrate | Persistent or suspicious |
| PD | 25% increase lesion | Irrelevant | Recurrent or new ocular disease | Recurrent or positive |

*Abbreviations: CR, complete response; Cru, unconfirmed complete response; PR, partial response; PD, progressive disease; RPE retinal pigment epithelium.*

emission tomography (PET)-CT scan imaging and bone marrow biopsy. The role of brain PET is a matter of debate and is not routinely recommended.[18-20]

## Prognostic scores

Various prognostic scores have been proposed in PCNSL. Scores are important for comparing studies and for predicting the outcome in individual patients. However, these prognostic indexes require prospective confirmation. The International Extranodal Lymphoma Study Group (IELSG) prognostic score is based on age, performance status, elevated lactate dehydrogenase (LDH), CSF protein levels and the involvement of 'deep brain structures' (periventricular space, basal lymph nodes, cerebellum and brainstem). This score, applied retrospectively, establishes three risk groups in the presence of these predictors: 0–1 (low), 2–3 (intermediate) or 4–5 (high risk). Two-year overall survival rates were 80%, 48% and 15%, respectively.[21] The Nottingham/Barcelona scoring system is based on the following: age >60 years, ECOG performance status >2 and extent of disease (multifocal versus unifocal). This scoring system examined retrospectively has shown median survivals of 55, 41, 32 and one month for scores of 0, 1, 2, and 3, respectively.[22] The Memorial Sloan-Kettering Cancer Centre prognostic model score (MSKCC score) identified age <50 years and Karnofsky performance score [KPS] <70 as independent risk factors and distinguished three prognostic classes. Class 1 (patients <50 years), class 2 (patients ≥50; Karnofsky performance score [KPS] ≥70) and class 3 (patients ≥50; KPS < 70). Median survival where 8.5 years, 3.2 years and 1.1 years, respectively.[23]

## Response criteria

Standardised response assessment criteria have been published and are summarised in *Table 1*.[24] It should be noted that at the time a CR is determined, the patient should have discontinued use of all corticosteroids for at least two weeks. Rare exceptions may be made for those patients receiving corticosteroids for another diagnosis (e.g. panhypopituitarism). Repeat ophthalmologic evaluation is not required for patients without evidence of ocular lymphoma at baseline or interval development of ocular symptoms. Patients without significant CSF abnormalities at baseline do not require repeat CSF evaluation provided they have not developed interval symptoms that suggest leptomeningeal dissemination.

## Treatment

*First line treatment: induction and consolidation*

The optimal management of patients with PCNSL remains to be established. Historically, radiotherapy (RT) was the standard treatment for PCNSL with response rates of 60-97%. But despite the high CR rates, almost all patients only treated with RT relapse after a few months with a median survival of fourteen months, and a 5-year survival of only 3-26%.[25,26] Chemotherapy plays a central role in the management of PCNSL, although drug efficacy is limited by the blood–brain barrier (BBB), resulting in the establishment of chemo

**Table 2.** Commonly used chemotherapy combinations (for abbreviations see text).

| | | |
|---|---|---|
| **R-MPV** | Rituximab 375/m² d1 | **4 cycles q 28 d, more if PR** |
| | MTX 3.5 g/m² d1 and d15 | |
| | Vincristine 1.4 mg/m² d1 and d15 | |
| | Procarbazine 100 mg/m² d1 to d7 | |
| | Ara-C 3 g/m² d1 and 2 | **1 cycle 14 days after last MTX** |
| **R-MTX-AraC (IELSG)** | Rituximab 375/m² d1 | **4 – 6 cycles q14-21d** |
| | MTX 3.5 g/m² d1 | |
| | Ara-C 2 x 2 g/m² d2 and d3 | |
| **R-MTX-AraC-Thiotepa (MATrix, IELSG)** | Rituximab 375/m² d0 and d5 | **4 cycles q21 days** |
| | MTX 3.5 g/m² d1 | |
| | Ara-C 2 x 2 g/m² d2 and d3 | |
| | Thiotepa 30 mg/m² d4 | |
| **R-MBVP (Precis, LYSA)** | Rituximab 375/m² d1 | **2 cycles followed by 2 cycles of R-AraC** |
| | MTX 3 g/m² d1 and d15 | |
| | Etoposide 100 mg/m² d2 | |
| | Carmustine 100 mg/m² d3 | |
| | Prednisone 60 mg/m² d1 to d5 | |
| | Rituximab 375/m² | **2 cycles** |
| | Ara-C 3 g/m² d1 and d2 | |

therapy sanctuaries, like CSF, meninges and eyes, where tumour cells may grow undisturbed. So, the capability of crossing the BBB and achieving therapeutic concentrations in the CNS should be taken into account when selecting drugs to treat patients with PCNSL. Useful drugs can be divided in two groups: 1) drugs exhibiting moderate capability to cross the BBB that can be safely administered at high doses to obtain therapeutic concentrations in the CNS (methotrexate-MTX and cytarabine-AraC) and 2) drugs able to cross the BBB and to reach therapeutic concentrations in the CNS even when administered at conventional doses (i.e. steroids and some alkylating agents like thiotepa, ifosfamide, and temozolomide). Initial improvements in response rates were achieved with the combination of MTX-based chemotherapy and WBRT.[27] Unfortunately this combined strategy is often associated with severe neurotoxicity, especially among elderly patients. Therefore, the dilemma in PCNSL treatment is the choice between (1) strategies designed to intensify therapy (induction and consolidation with or without radiotherapy) to improve cure rate and (2) de-escalation strategies to avoid neurotoxicity. Individualised strategy will mainly depend on age and response to induction treatment.

*Induction treatment: methotrexate backbone*

Numerous studies including large retrospective multicentre surveys have shown that High Dose methotrexate (HD-MTX) is the most efficient cytostatic agent in this pathology.[15,28,29] Penetration of methotrexate into the

CNS is poor when given at conventional doses. Patients treated with less than 3 g/m$^2$ do not reliably achieve cytotoxic concentrations in the CSF. Additional rapid infusion over three hours is needed to ensure a correct CSF diffusion, whereas this is not reliably obtained with a 24 hour continuous infusion of 8 g/m$^2$.[30,31] A MTX dose of 3.5 g/m$^2$ seems to be the best compromise between safety and efficacy for combination regimens. Addition of high dose cytarabine (HD-AraC) to MTX has been explored in small noncomparative studies, suggesting a survival advantage. One randomised trial has compared MTX alone (3.5 g/m$^2$) with MTX (3.5 g/m$^2$) plus high-dose Ara-C (four cycles of 2 g/m$^2$) followed by WBRT as consolidation treatment in both arms.[32] Addition of HD-AraC has resulted in significantly improved CRR (46% versus 18%) and a trend towards prolonged survival (three year OS 46% versus 32%) compared with MTX alone. The disappointingly and exceptionally poor results of the single agent MTX in this trial are likely due to the fact that MTX was administered only every three weeks rather than the usual every two weeks, leading to insufficient dose intensity. A recent study also showed that AraC doses <2 g/m$^2$ result in a less beneficial effect (OS two year of 26%).[33] Today, the MTX-AraC combination every two to three weeks for a minimum of four to six cycles is the backbone of most standard chemotherapeutic approaches for first line therapy of PCNSL, since it is supported by the highest level of evidence available. Other agents such as BCNU, procarbazine, vinca alkaloids, temozolomide and thiotepa have also been added to MTX-AraC showing promising remission rates and acceptable toxicity profiles. However, the optimal combination of chemotherapeutic agents remains unclear. The combination of HD-MTX, HD-ARAC, thiotepa and rituximab was associated with an ORR of 87% and a 2-year PFS of 62% and is the only one tested in a randomised trial.[67]

In summary, the first line treatment should be combination chemotherapy including HD-MTX, preferably in combination with HD-AraC and/or an alkylating agent. The treatment should be based on established protocols and discussed on an individual basis. Combinations commonly used in first line therapy are listed in *Table 2*.

*Other active drugs or combinations*

Temozolomide

Temozolomide is an oral alkylating agent with an excellent tolerability, used in other cerebral tumours like glioma. As upfront monotherapy in elderly patients with PCNSL, temozolomide was associated with a CRR of 47%, and a median OS of 21 months. The drug can be safely combined with MTX, also in elderly patients.[34] A combination of HD-MTX, rituximab and temozolomide has been associated with a 66% CRR, and a 2-year PFS of 59% in first line therapy.[35] Temozolomide is not reimbursed in Belgium and thus is currently not used in first line therapy outside clinical trials.

Thiotepa

Thiotepa (TT) is an alkylating agent with a high CNS bioavailability. TT containing regimens have revealed promising responses and survival rates. For example, a single-arm phase II trial assessing a chemotherapy combination including TT was associated with an ORR of 72%, a 5-year OS of 42% and a persisting plateau in the long term survival curve.[36] Recently, a phase II randomised trial (IESLG#32) has shown that adding TT to a rituximab-MTX–AraC regimen results in a significantly improved response (2-year OS 58% versus 66%).[67] This drug is not reimbursed in Belgium.

Rituximab

The use of rituximab is supported by its efficacy in extra-CNS DLBCL patients. However, some doubts about its capacity to cross the BBB remain: the rituximab level in the CSF has been shown to be <1-2% of the serum level.[37,38] Favourable effects of rituximab monotherapy were reported as salvage therapy or anecdotal first line therapy in pregnant women.[39-42] This may reflect the partially disrupted BBB in PCNSL. Retrospective series or small prospective trials looking at the efficacy of rituximab when added to a MTX-based regimen or a salvage regimen also suggest a certain activity in PCNSL.[35,40,43-45] This was associated with increased CR levels, without additional toxicity (*Table 2*). Addition of rituximab to a regimen that includes HDC/ASCT has been recently reported in two prospective phase II trials with excellent results (2-year PFS 81% and OS 93%; 2-year PFS 79% and OS 81%).[12,46] Recently, a phase II randomised trial (IESLG trial NCT01011920) has shown that adding rituximab to a MTX-AraC based regimen significantly improves FFS and OS (2-year FFS 52% versus 62%; 2-year OS 58% versus 66%).[67] The role of rituximab in PCNSL is currently being investigated in another randomised trial (Hovon trial NTR2427).

Intraventricular administration of rituximab has been assessed in a small cohort of PCNSL patients. The drug

was well tolerated but its potentially beneficial effects need further investigation.[47]

In conclusion, although there is a lack of large randomised trials supporting rituximab for the treatment of PCNSL, because of its excellent tolerability and given the good results obtained in prospective trials, its use in frontline treatment and in the occurrence of a relapse is favoured by several haematologists.

Ibrutinib

Ibrutinib can cross the BBB and initial clinical results are favorable.[48] Ibrutinib has been incorporated in a DA-TEDDI-R regimen.[68]

Intrathecal/intraventricular chemotherapy

Intrathecal/intraventricular chemotherapy has not been studied prospectively. However, two large retrospective studies have been conducted that did not demonstrate benefits when adding the drugs intrathecally in patients treated with HD-MTX.[3,49] Therefore, intrathecal/intraventricular chemotherapy is not routinely recommended. However, in the presence of a meningeal involvement not responding to systemic HD-MTX intrathecal therapy can be considered.

DA-TEDDI-R

Based on an established DA-EPOCH-R chemotherapy, a novel combination has been developed using drugs that are known to penetrate the BBB: temozolomide, etoposide, liposomal adriamycin (Doxil®), dexamethasone, ibrutinib and rituximab. Preliminary data were presented at the ASH 2015 meeting and are promising.

*Consolidation treatment*

Consolidation treatment should be considered for all patients in CR or PR after induction. Patients with either stabilised or progressive disease should receive a second line therapy. Modalities of consolidation may include radiotherapy, non-myeloablative consolidation chemotherapy and high dose chemotherapy with autologous stem cell transplantation (HDCASCT).

Radiation therapy

Numerous uncontrolled phase II studies have demonstrated the beneficial role of radiation therapy in consolidation after chemotherapy. Variable response rates and survival data have been reported, but cannot be compared to each other because of different designs.[27,50-52] Because of the diffuse infiltrative nature of PCNSL, the whole brain should be irradiated 20 to 30 days after chemotherapy. The optimal dose of radiotherapy has never been explored in a randomised way. In protocols the doses can differ from 20 to 50 gray (Gy), with or without a boost on the target lesion. Most protocols use a total dose of 40-45 Gy without a boost.

Radiotherapy at standard dose (40-50 Gy WBRT) is associated with considerable late chronic neurotoxicity, particularly in elderly patients (usually defined as age >60). This complication consists of progressive leukoencephalopathy with cognitive deterioration, associated with a significant decrease in quality of life.[25,53]
Strategies have been explored to minimise neurotoxicity. The first strategy is to avoid WBRT in patients who are in CR after primary chemotherapy. This was explored through two randomised phase III trials. In the first one, consolidation WBRT in MTX-based chemotherapy resulted in prolonged PFS (eighteen months for the WBRT group compared to twelve months in patients who did not receive WBRT) but without a difference in OS (32 and 37 months, respectively).[54] Unfortunately, this trial is fraught with design flaws: no distinction between young and elderly patients resulted in interpretation difficulties. More recently, another randomised phase III study also suggested a prolongation of PFS (median: 18,2 versus 11,9 months) after radiotherapy, however without OS prolongation.[48]

Another strategy is the reduction of the RT doses. This has been explored retrospectively and prospectively in small studies.[45,55,56] In a multicentric phase II study, patients already in CR after chemotherapy were treated with low dose WBRT (23.4 Gy). Compared to the use of higher doses (historical data), the outcome was similar, but apparently there was better neurotolerability. Median OS was not reached (median follow-up for survivors: 5.9 years) and 3-year OS was 87%.[45] But owing to the lack of a control group in this trial, the benefit of the consolidation treatment with low dose radiotherapy could not be determined.

Ongoing studies investigate chemotherapy induction with and without reduced doses of WBRT. They will provide data on the relevance of consolidation treatments in newly diagnosed PCNSL.

In conclusion, frontline WBRT in consolidation remains standard in patients under 60 because it provides better disease control. If the dose of radiotherapy should be

**Table 3.** Radiotherapy recommendations by different treatment groups.

| |
|---|
| **• if complete remission after chemotherapy:** |
| 26-30 Gy WBRT (fraction of 1,8-2 Gy/day) (French Network for oculocerebral lymphoma - LOC 2014-2015) |
| 36 Gy WBRT (IESLG32 protocol) |
| 24-36 Gy WBRT (NCCN guidelines 2014) |
| **• If partial remission after chemotherapy:** |
| 40 Gy WBRT (fraction of 1,8-2 Gy/day) (LOC 2014-2015 ) |
| 36-40 Gy +/- boost of 9 Gy on target lesion (IESLG 32 protocol) |
| 24-36 Gy WBRT + limited involved field RT to 45 Gy (NCCN 2014 guidelines) |

adapted to the response after chemotherapy remains a matter of debate. Because of increased neurotoxicity, RT consolidation is not recommended in patients over 60 in CR. *Table 3* shows the various recommendations for radiotherapy.

High dose chemotherapy and autologous stem cell transplantation (HDC/ASCT)

The role of high-dose chemotherapy followed by autologous stem cell transplant (HDTASCT) was first investigated in relapsed or refractory PCNSL. It revealed promising responses and survival rates.[57,58] These encouraging results prompted several groups to include ASCT in first-line PCNSL treatment.[12,39,59-61] Conditioning with a thiotepa-based combination should be preferred.[60] A BCNU-thiotepa regimen seems to be the best compromise between safety and effectiveness. However, no randomised trials demonstrating a benefit of this concept over conventional combination chemotherapy have been published and the impact on neurocognitive functions remains obscure. A comparison between WBRT and HDC/ASCT is underway in randomised trials (NCT01011920 IESLG; NCT00863460 LOC/Precis), which will establish the most effective and better-tolerated strategy for consolidating primary chemotherapy. Today, HDC/ASCT as part of first-line therapy remains an experimental approach, however, it can be considered on an individual basis.

Guidelines from the European Association of Neuro-Oncology consider upfront HDC/ASCT as an experimental treatment in PCNSL, whereas the NCCN guidelines refer to HDC/ASCT as an alternative to WBRT in patients who achieve CR after an HD-MTX-containing induction. *Table 4* list some conditioning regimens used in patients with newly diagnosed PCNSL.

**Table 4.** Conditioning regimens used in patients with newly diagnosed PCNSL (references Ferreri A and Illerhaus G, 2016).

| | |
|---|---|
| **Regimen without Thiotepa** | |
| **BUCYE** | Busulfan 3.2 mg/kg days -7 to -5 |
| | Cyclophosphamide 50 mg/kg days -3 and -2 |
| | Etoposide 200 mg/m$^2$ days -5 and -4 |
| **LEED** | Cyclophosphamide 60 mg/kg days -4 and -3 |
| | Etoposide 250 mg/m$^2$ every 12 h days -4 to -2 |
| | Melphalan 130 mg/m$^2$ day -1 |
| | Dexamethasone 48 mg/d days -4 to -1 |
| **Regimen with Thiotepa** | |
| **Busulfan-thiotepa** | Busulfan 4 mg/kg po days -8 to -5 |
| | Thiotepa 5 mg/kg days -4 and -3 |
| **BCNU-thiotepa** | BCNU 400 mg/m$^2$ day -6 |
| | Thiotepa 5 mg/kg days -5 and -4 |
| **BCNU-thiotepa 10** | BCNU 400 mg/m$^2$ day -6 |
| | Thiotepa 2 x 5 mg/kg days -5 and -4 |

Consolidation with chemotherapy

Concerns regarding neurocognitive toxicity of WBRT and possibly also from ASCT have led to the development of alternative, dose-intensive chemotherapeutic strategies for consolidation in PCNSL. Induction with polychemotherapy (MTX, temozolomide and rituximab) followed by consolidation with etoposide and HD-AraC in patients with stabilised or improved disease after induction has been assessed. The association was evaluated in a highly selected population in a multicentre phase II study. Results were encouraging. Median OS had not yet been reached after a median follow-up of 4.9 years. The results indicate that polychemotherapy alone can result in excellent long-term survival.[35] However,

the potential benefit of prolonged polychemotherapy compared to standard treatment involving WBRT or ASCT needs to be confirmed in randomised trials (such as the ongoing IESLG43 trial NCT02531841 comparing BCNU/thiotepa ASCT to conventional ifosfamide-based chemotherapy). The American Alliance/CALGB Intergroup is conducting a randomised phase II trial that compares BCNU/thiotepa ASCT to a non-myeloablative combination of etoposide and HD-AraC in patients <70 years (NCT01511562).

*Elderly patients*

Patients over 60 years represent half of all patients with PCNSL; 20% are over 80. In this population, neurotoxicity of the radiochemotherapy combination is particularly high, dementia, ataxia, and incontinence being major sources of late morbidity. A large retrospective analysis of 783 patients aged >60 suggests that whole brain radiotherapy is associated with neurological side effects in about 20% of patients. Therefore, WBRT is best avoided in patients achieving CR with induction chemotherapy who can have consolidation with additional cycles of HD-MTX. If radiotherapy is used, reduced doses should be considered.

For elderly patients in otherwise good health the choice treatment is MTX-based chemotherapy. Few data are available concerning the use of a standard MTX/AraC-combination in the elderly. However, even in elderly patients HD-MTX can be well-tolerated in the absence of renal dysfunction. Most authors suggest a dosage between 3.5 and 8 gr/m$^2$. A recent retrospective analysis suggests that the addition of procarbazine could be useful.[6] MD Anderson published results from a cohort of 22 patients aged 80–90: only two needed a dose reduction. The median OS survival was 7.9 months, the two-year OS was 33%. Seventy seven percent of the patients received MTX at a dosage of 3.5 g/m$^2$; 5/22 received MTX between 1 and 2.5 g/m$^2$. The most important toxicity was myelosuppression.

In elderly patients the best prognostic indicator is the Karnofsky Performance Score (KPS). A KPS of >70 is associated with improved survival. In unfit patients, WBRT offers a good palliative treatment.

*HIV patients*

HIV positive patients presenting with PCNS lymphoma should undergo the same investigations as those who are HIV negative. HIV+ patients should receive optimal HAART therapy in addition to the same therapy as HIV- patients.

*Conclusion: treatment advice for first line treatment (see algorithm Figure 1)*

Young patients

Induction with a combination based on a rituximab + HDMTX/HDAraC backbone for at least four cycles. Better results can possibly be obtained by adding thiotepa or procarbazine. If the remission is only partial, more cycles of chemotherapy should be added.

Consolidation will best use WBRT (at low dose in case of CR and at standard dose in case of PR) or autologous SCT. Consolidation by chemotherapy instead of WBRT or ASCT can be discussed on an individual basis.

Elderly (>60)

**Fit patients:** a combination of rituximab + high dose MTX/AraC and/or procarbazine/thiotepa regimen is preferred. Radiotherapy consolidation will not be used.

**Unfit patients:** palliative care, WBRT.

## Treatment of relapse

Relapses are mostly seen within the first few years after diagnosis. Late relapses are rare (4% of the relapses occur after five years). There are no clear guidelines for treatment of relapsed PCNSL. Patients with a relapse after >1 year can be treated again with the MTX/AraC combination. Patients not responding during their first line treatment or whose disease progresses rapidly can be treated with WBRT or salvage chemotherapy, followed by auto-SCT if feasible. Possible second line treatments are Ara-C/etoposide, Ara-C or ifosfamide/etoposide, while dexamethasone can be used for short term palliation.

*Radiotherapy*

WBRT is an active treatment for patients with recurrent or refractory PCNSL who did not receive RT during their first line treatment. A retrospective study on 48 patients demonstrated an overall response rate of 79% and a median OS of sixteen months in recurrent or refractory PCNSL.[62]

*ASCT at relapse*

High dose chemotherapy and auto-SCT is an efficient option at relapse. It should be offered to patients who have a disease sensitive to second line chemotherapy and who can tolerate an intensive treatment. ASCT conditioning with BEAM regimen, which is widely used for other aggressive lymphomas is less effective in PCNSL, resulting in a median EFS of 9.3 months.[63] Therefore, conditioning regimens containing thiotepa

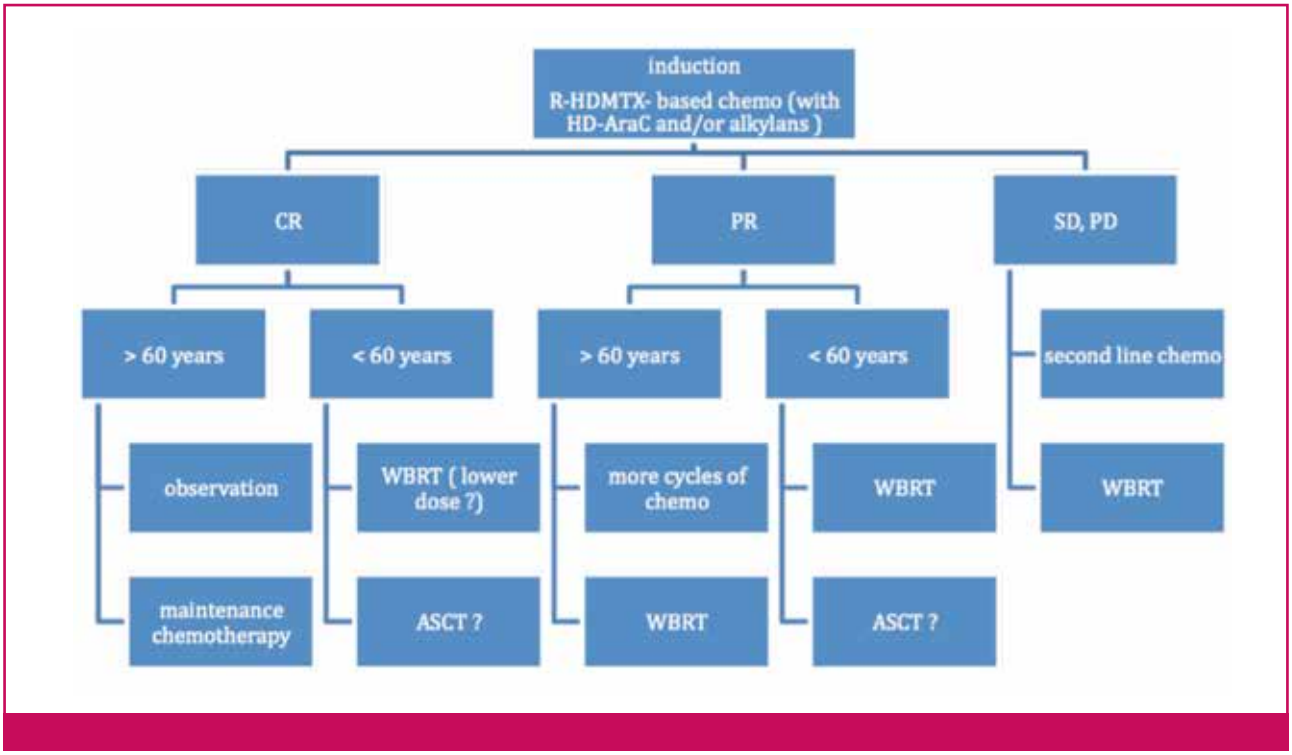


**Figure 1.** PCNSL treatment algorithm for patients eligible for HD-MTX-AraC based treatment.

should be preferred (busulfan–thiotepa-cyclophosphamide).[57] However, while those regimens seem to be more effective they are also more toxic. In particular, the busulfan-thiotepa association is associated with a 13% treatment-related mortality.[57]

## Novel agents

Although clear progress in the treatment of PCNSL has been made during the last decades, prognosis remains poor compared to classical DLBCL, making further attempts to improve survival rates warranted, particularly for refractory cases, and in elderly patients not tolerating current treatment strategies.

New insights in the pathogeny of neoplastic diseases have led to improved (molecular-based) classifications of tumours in general and of lymphoid malignancies in particular. It also resulted in the development of specifically targeted therapies. However, the use of targeted therapy in PCNSL is restricted and challenged by its ability to pass the BBB and to maintain effective concentrations in the CNS. Currently, the use of new agents in PCNSL is very limited.

Houillier et al. recently described a series of six elderly patients with relapsed PCNSL treated with lenalidomide monotherapy at a dose of 25 mg/day on days 1-21 of a 28-day cycle. Three patients experienced progressive disease during the first or second cycle, whereas the remaining patients obtained a partial (n=1) or even a complete (n=2) response. One of these latter patients received nine cycles of lenalidomide, resulting in a long-lasting remission of more than 24 months, with excellent treatment tolerance.[64] A phase II trial combining rituximab and lenalidomide for recurrent PCNSL is ongoing in France (NCT01956695).

Other trials are currently ongoing that examine the use of targeted therapies for PCNSL. Since this disease has a high incidence of MYD88 mutations, the use of drugs targeting BCR signal looks promising. Three such studies are (1) ibrutinib: dose-escalation, phase I/II study with ibrutinib monotherapy for patients with relapsed/refractory PCNSL and secondary CNSL (NCT02315326), (2) phase I study of Ibrutinib in combination with immunochemotherapy for patients with PCNSL (NCT02203526), and (3) buparlisib: phase II trial with the pan-PI3K inhibitor buparlisib (BKM120) for patients with relapsed/refractory PCNSL and secondary CNSL (NCT02301364).

## Primary Intraocular Lymphoma (PIOL)

PIOL is uncommon. It manifests itself first in the retina or in the vitreous body of one or both eyes. Central nervous system lymphoma develops in about 55-85% of these patients, which will determine their survival. The median survival is about 58 months. PIOL differs from primary uveal lymphoma (choroidal, iridal and

## Key messages for clinical practice

1. If possible, biopsy should be done before steroids are started.
2. Chemotherapy should include high-dose methotrexate at doses of at least 3.5 g/m², given over 2-3 hours, at intervals of maximum 2-3 weeks, no more, for a minimum of 4-6 cycles.
3. Combination with alkylantia and/or Ara-C improves response.
4. Consolidation WBRT should be discussed with young patients in CR; reduced dosage is an option. In PR, consolidation with 40-45 Gy without boost is advisable. In patients >60, WBRT should be avoided during first line treatment.
5. High dose chemotherapy (thiotepa-based) with autologous stem cell support in first line remains experimental and should be discussed on an individual basis, and only used in experienced centres.
6. Salvage treatment depends on age, performance status, and type(s) of previous treatment(s).

ciliary body lymphomas) which are usually extranodal marginal zone lymphomas with no propensity for CNS infiltration.

There are two distinct treatment strategies for PIOL. For local treatment, ocular radiotherapy and intravitreal injections of MTX or rituximab may be effective, but this is entails high risks for the eyes and/or relapses in the CNS. External radiotherapy is favoured in case of bilateral eye disease while intravitreal injections of MTX or rituximab are preferred in unilateral disease. In fit patients, systemic chemotherapy is the preferred initial therapy. Systemic treatment is based on the presumption that subclinical involvement of the CNS is present at diagnosis. Administration of HDMTX and HDAraC can ensure therapeutic levels of the drugs in the intraocular fluids. Clinical responses have been documented.[64] However, drug concentrations in the vitreous fluid are unpredictable and intraocular relapse is common. Thus, additional irradiation of both globes has been proposed.[65] Nevertheless, as with PCNSL without ocular involvement, the beneficial effects of consolidation radiotherapy of the eyes needs to be carefully balanced against the risk of radiation-related toxicity. Another possibility is to use intravitreal methotrexate in conjunction with intravenous MTX. Proof of superiority of intraocular chemotherapy versus radiotherapy is lacking. A recent large retrospective study showed no difference in outcome between local and systemic treatment and challenges the use of systemic chemotherapy in patients with isolated eye involvement.[66]

*Conclusion: treatment advice for PIOL*

In the presence of eye and CNS involvement: treat as CNS lymphoma and add RT to both ocular globes.
If only one eye is involved and there is no CNS infiltration: treat locally using intravitreal injection of MTX.
If both eyes are involved without CNS infiltration: treat locally or consider systemic treatment.

## Follow up

The benefit of surveillance studies aimed at the detection of early relapse is controversial. No studies have examined this in PCNSL. International working group recommendations suggest that minimum testing includes anamnesis, physical examination, MMSE, and a gadolinium-enhanced MRI scan of the brain.[24] Patients should be reassessed, after completion of therapy, every three months for two years, then every six months for three years, and later annually for at least five years. Patients with initial involvement of the eyes or the spinal fluid should undergo repeat ophthalmologic or CSF evaluation, as clinically indicated. Additional blood tests or imaging studies may be added as appropriate, considering the clinical situation.

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For the complete list of references we refer to the electronic version of this article which can be downloaded from www.ariez.com.

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