Challenges in the Treatment of Newly Diagnosed and Recurrent Primary Central Nervous System Lymphoma

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ABSTRACT

Primary central nervous system lymphomas (PCNSLs) are rare cancers of the central nervous system (CNS) and are predominantly diffuse large B-cell lymphomas of the activated B-cell (ABC) subtype. They typically present in the sixth and seventh decade of life, with the highest incidence among patients aged >75 years. Although many different regimens have demonstrated efficacy in newly diagnosed and relapsed or refractory PCNSL, there have been few randomized prospective trials, and most recommendations and treatment decisions are based on single-arm phase II trials or even retrospective studies. High-dose methotrexate (HD-MTX; 3–8 g/m²) is the backbone of preferred standard induction regimens. Various effective regimens with different toxicity profiles can be considered that combine other chemotherapies and/or rituximab with HD-MTX, but there is currently no consensus for a single preferred regimen. There is controversy about the role of various consolidation therapies for patients who respond to HD-MTX-based induction therapy. For patients with relapsed or refractory PCNSL who previously experienced response to HD-MTX, repeat treatment with HD-MTX-based therapy can be considered depending on the timing of recurrence. Other more novel and less toxic regimens have been developed that show efficacy in recurrent disease, including ibrutinib, or lenalidomide ± rituximab. There is uniform agreement to delay or avoid whole-brain radiation therapy due to concerns for significant neurotoxicity if a reasonable systemic treatment option exists. This article aims to provide a clinically practical approach to PCNSL, including special considerations for older patients and those with impaired renal function. The benefits and risks of HD-MTX or high-dose chemotherapy with autologous stem cell transplantation versus other, better tolerated strategies are also discussed. In all settings, the preferred treatment is always enrollment in a clinical trial if one is available.

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Primary central nervous system lymphomas (PCNSLs) are predominantly diffuse large B-cell lymphomas (DLBCLs) that involve the brain, eyes, leptomeninges, or spinal cord without evidence of systemic involvement. Molecular and gene expression profiling studies demonstrate that most PCNSLs are of the activated B-cell type of DLBCL and often carry mutations in *MYD88*^{L265P} and *CD79B*.^{1–5} With an estimated incidence of 1,500 cases per year in the United States, they account for 6% of all newly diagnosed primary malignancies in the CNS. The incidence of PCNSL in immunocompetent patients has been increasing, with the highest increase in those of advanced age.^{6–8}

Many different regimens, predominantly with a high-dose methotrexate (HD-MTX) backbone, have demonstrated efficacy in the treatment of newly diagnosed and relapsed or refractory (R/R) PCNSL, but currently there is no consensus on the optimal treatment of these patients. Very few prospective randomized controlled studies have been conducted, and most recommendations and decisions are based on single-arm phase II trials or retrospective studies. This is in part due to the rarity of this disease, as well as different personal and institutional experiences favoring one specific HD-MTX regimen. More aggressive, potentially more effective therapies have been investigated that include high-dose chemotherapy (HDC) with or without autologous stem cell transplant (ASCT); however, these regimens are limited to fitter, and often younger, patients. Treatment options that are more suitable for elderly or frail patients exist, and there is increasing evidence that these treatments can be effective.⁹

This review aims to provide a structured overview of currently available, evidence-based approaches for the treatment of newly diagnosed and R/R PCNSL. Treatment options are discussed in relationship to the eligibility of patients to tolerate the respective regimens. The 3 main eligibility groups, both for newly diagnosed and R/R PCNSL, used in this review are patients who are (1) candidates for HD-MTX-based treatment followed by HDC and ASCT; (2) candidates for HD-MTX-based therapy, but not for HDC and ASCT; and (3) not suitable

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for HD-MTX or other more aggressive treatments. The predominant theme throughout this discussion is the lack of consensus regarding a best regimen in most settings, and we strongly urge clinicians to consider clinical trials for these patients if one is available.

Treatment of Newly Diagnosed PCNSL

The formal diagnosis of PCNSL requires comprehensive workup and staging. In addition to imaging of the brain and entire spine using MRI with contrast, cerebrospinal fluid analysis (CSF) and ophthalmologic examination to rule out ocular involvement are necessary. Brain biopsy is typically required to make the diagnosis of lymphoma unless CSF or vitreoretinal cytopathology and flow cytometry are diagnostic. In addition to CNS staging as described earlier, patients with confirmed diagnosis of PCNSL should undergo systemic staging to rule out systemic lymphoma. Although clinical practices vary, most institutions would recommend CT of the chest, abdomen, and pelvis; body PET/CT; testicular ultrasound in older men (aged >65 years); and, in rare situations, bone marrow biopsy. Serologic studies include testing for HIV, because PCNSL in immunosuppressed patients requires specific considerations and initiation of antiretroviral therapy, as well as for hepatitis B and C virus, because these may be reactivated in the context of therapy (Figure 1).¹⁰

Once the diagnosis is confirmed, treatment must begin expeditiously because PCNSL can progress rapidly. HD-MTX-based therapies (MTX dose of 3–8 g/m²) are the standard for induction therapy in patients considered able to tolerate this therapy. Although age and performance status are known prognostic factors and are

considered when deciding treatment, the key criterion for distinguishing patients who can tolerate high-dose MTX from those who cannot is renal function; patients with creatinine clearance of ≥ 40 mL/min should be considered for treatment with HD-MTX-based therapy. However, appropriate dose reductions must be applied.^{11,12} It should be emphasized that even some patients with poor performance status at diagnosis, if this status is due to the CNS lymphoma, can dramatically improve with HD-MTX-based therapy and achieve long-term remissions. Similarly, elderly patients also may benefit substantially from HD-MTX-based therapy and should not be excluded from treatment solely on the basis of age. Patients experiencing MTX-associated renal failure may be reconsidered for treatment with HD-MTX if their renal function recovers. At that time, using a lower dose of MTX should be considered before returning to full dosing.

There are institutional differences regarding the choice of additional antineoplastic medications to combine with HD-MTX, and patient comorbidities may guide the clinician to select the most suitable regimen for an individual patient. Frequently used additions to HD-MTX include rituximab, procarbazine, and vincristine, and rituximab and temozolomide (Table 1). Based on available literature and evidence, no one regimen is clearly the most effective. Some of the more aggressive regimens that include polychemotherapy, HDC, or HDC/ASCT as consolidation have shown favorable results. It must be acknowledged that these studies typically included younger and healthier patients, and that more frail, elderly patients would not have been included in these comparatively promising datasets. The most common

Figure 1. Overview of diagnostic workup and treatment considerations for patients with primary central nervous system lymphoma at time of initial diagnosis, first recurrence, and additional recurrences.

Abbreviations: Ara-C, cytarabine; CSF, cerebrospinal fluid; HBV, hepatitis B virus; HCT/ASCT, high-dose chemotherapy and autologous stem cell transplant; HCV, hepatitis C virus; MTX, methotrexate; WBRT, whole-brain radiation therapy.

Table 1. Possible Treatment Regimens for Patients With Newly Diagnosed PCNSL

Strategies With Consolidation for Fit Patients			Strategies Without Consolidation, Including for Elderly or Frail Patients	
Induction	Consolidation	References	Induction/Maintenance	References
MTX, TMZ, rituximab	Ara-C + VP-16	Rubenstein et al, 2013 ²³	MTX (if can tolerate) ± rituximab	Batchelor et al, 2003 ¹¹ ; Zhu et al, 2009 ⁴⁸ ; Holdhoff et al, 2014 ⁴⁹
MTX, TMZ, rituximab	Low-dose WBRT + TMZ	Glass et al, 2016 ⁵⁰	Rituximab, MTX (if can tolerate), PCZ, lomustine	Fritsch et al, 2011 ⁵¹
MTX, PCZ, VCR, rituximab	Low-dose WBRT	Morris et al, 2013 ⁵²	TMZ + MTX (if can tolerate)	Omuro et al, 2007 ¹⁴
MTX, Ara-C, thiopeta, rituximab	WBRT or HDC/ASCT	Ferreri et al, 2016 ⁵³	TMZ + rituximab	Nayak et al, 2013 ¹⁵
MTX, PCZ, VCR, rituximab	HDC/ASCT (age <65 y)	Omuro et al, 2015 ²⁵	TMZ	Kurzweil et al, 2010 ¹⁶
MTX, carmustine, teniposide, prednisone ± rituximab	HiDAC (+ low-dose WBRT in patients aged ≤60 y)	Bromberg et al, 2019 ⁵⁴		

Abbreviations: Ara-C, cytarabine; ASCT, autologous stem cell transplantation; HDC, high-dose chemotherapy; HiDAC, high-dose cytarabine; MTX, methotrexate; PCNSL, primary central nervous system lymphoma; PCZ, procarbazine; TMZ, temozolomide; VCR, vincristine; VP-16, etoposide; WBRT, whole-brain radiation therapy.

criterion for HDC/ASCT eligibility is age, although there is no absolute cutoff. Generally, patients aged <60 years are more often considered for this modality; however, those aged 60 to 70 years can also benefit.¹³

For patients who are not eligible for HD-MTX, there is no clear best standard treatment, and selection of the most appropriate regimen should at least in part be based on patient comorbidities and physician expertise. Often referral to a center with expertise in the management of PCNSL should be considered. Regimens considered in this setting include temozolomide and rituximab, often used in combination,^{14–16} or other agents typically reserved for treatment of recurrence tried in the first line in this patient population. For example, ibrutinib and lenalidomide have demonstrated efficacy in the recurrent setting,¹⁷ but can be considered as first-line treatment in patients for whom HD-MTX is not feasible. Moreover, clinical trials using novel agents may allow enrollment of patients with newly diagnosed PCNSL who are too frail for conventional MTX chemotherapy.

Whole-brain radiation therapy (WBRT) offers high response rates in PCNSL, but unfortunately the responses are not durable. Additionally, the significant neurotoxicity of WBRT at the doses administered for upfront therapy makes this modality unattractive for older patients. Therefore, WBRT is not recommended as first-line treatment in newly diagnosed patients.

Role of Consolidation Therapy in Newly Diagnosed PCNSL

Multiple consolidation therapies are in use today, but similar to the induction regimens described earlier, no clear consensus exists on the optimal choice for consolidation. In addition, the question of the added value of consolidation versus observation after remission has never been conclusively addressed in prospective clinical

trials. The main goal of consolidation is to significantly improve progression-free survival (PFS) and delay relapses. The 3 main modalities used for consolidation in PCNSL include nonmyeloablative chemotherapy, HDC/ASCT, and WBRT. Historically, WBRT was commonly used as an effective method of consolidation following chemotherapy-based induction regimens.^{18,19} Although WBRT can generate rapid radiographic responses, they are not always durable. In addition, radiographic response assessment can be affected when WBRT is added after systemic induction. Moreover, significant neurotoxicity and lack of coverage for CSF-disseminated disease make full-dose RT less than ideal. Although combined treatment modalities using HD-MTX followed by WBRT at a reduced dose²⁰ may mitigate the neurotoxicity, newer approaches such as dose-intensive chemotherapy and HDC/ASCT have emerged as viable options.

Nonmyeloablative chemotherapy strategies have been studied and may offer a reasonable alternative to WBRT or ASCT in some patients, although again, no consensus exists on the best approach. The value of consolidative high-dose cytarabine (HiDAC) after HD-MTX has been investigated in a prospective phase II study in elderly patients (age >60 years),²¹ and a PFS advantage has been demonstrated for consolidative HiDAC after HD-MTX in a randomized phase II trial.²² Additionally, intensified conventional chemotherapy was studied in a prospective ALLIANCE phase II trial.²³

Several studies investigating HDC followed by ASCT as part of initial therapy have demonstrated high complete response and 2-year PFS rates.^{24,25} Currently 2 clinical trials are investigating whether there are significant differences in outcomes between HDC followed by ASCT and consolidative conventional-dose chemotherapy (NCT01511562).²⁶ Trials examining consolidative conventional-dose chemotherapy and consolidative

full-dose WBRT have shown similar 2-year PFS in randomized phase II trials; however, the toxicity profiles of these therapies differ, and longitudinal neurocognitive assessment showed persistent and significant neurocognitive impairment in the patients who received consolidative WBRT but not in the HDC group.^{13,27} Reduced-dose WBRT has recently been shown in a randomized study to improve PFS (ClinicalTrials.gov identifier: NCT01399372), although long-term neurocognitive studies are pending. It is important to note that patient selection in the HDC trials may have played a role in these favorable outcomes.

Treatment of R/R PCNSL

More than 25 different regimens have been published for patients with R/R PCNSL in several prospective, but mostly retrospective, reports.²⁸ However, no prospective randomized trials have been published in this setting. Patients with refractory disease or early recurrence need to be differentiated from those who had remained in prolonged remission after initial HD-MTX-based therapy. What defines a meaningful minimum time in remission to consider repeat treatment with HD-MTX remains controversial. The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for CNS Cancers²⁹ currently use a 12-month interval as a cutoff; however, other factors may influence how to define a meaningful time for an individual patient (eg, adequate dosing and frequency of HD-MTX cycles). For patients who are good candidates for rechallenge with HD-MTX-based therapy, this may be a reasonable first option.^{17,30,31} Select chemosensitive and fit patients may then be candidates for HDC/ASCT if they have not received this therapy previously.^{32–34}

Patients with R/R PCNSL who are not candidates for HD-MTX regimens or HDC/ASCT may be candidates for several single-agent and combination therapy regimens that have also demonstrated activity in this setting (Table 2). Mechanisms of action of the drugs used in the different published regimens encompass a broad spectrum, from chemotherapy and immunochemotherapy to antiangiogenesis and targeted strategies, as well as combinations of different strategies. Selection of the most appropriate therapy for an individual patient requires consideration of potential side effects, preference for administration route, and comfort and expertise of the treating physician. For example, treatment with ibrutinib alone or in combination with MTX and rituximab, or lenalidomide $\pm$ rituximab may be more suitable for patients with compromised bone marrow reserve, whereas pemetrexed, which is predominantly renally cleared, will pose the same hurdles as HD-MTX for patients with significant renal impairment. Due to small patient numbers and lack of randomized trials, there is no clear evidence showing which of these

strategies is most effective. Often, several treatment options appear reasonable for an individual patient. Participation in a clinical trial, if available, should therefore be strongly considered. Outside of a clinical trial, treatment with ibrutinib, lenalidomide $\pm$ rituximab, or temozolomide is often considered a reasonable choice (Table 2) if no suitable clinical trial is available. However, responses are typically short-lived and measured in several months.

WBRT is an option for patients with multiple relapses or rapid disease progression if no better systemic therapy is available, but significant neurocognitive complications need to be carefully considered when choosing this treatment option. Given the growing portfolio of systemic options with often acceptable side effect profiles and reasonable response rates, WBRT is increasingly considered as a salvage option for patients with no systemic options. In very selected circumstances, stereotactic radiotherapy can be considered as an initial salvage therapy followed by one of the chemotherapy regimens discussed earlier.³⁵

Novel Approaches and Targeted Therapies

Insights into the molecular mechanisms of PCNSL pathophysiology have led to the introduction of novel agents, including targeted and immune-based therapies for the treatment of patients with R/R PCNSL. In particular, therapeutic agents targeting the B-cell receptor (BCR) and Toll-like receptor (TLR) signaling pathways with Bruton tyrosine kinase (BTK) inhibitors, PI3K/mTOR pathway with targeted agents, tumor microenvironment with immunomodulatory drugs (IMiDs), mechanisms of immune evasion with checkpoint inhibitors, and CD19 with cellular therapies have entered into phase I and II clinical trials.³⁶

Two agents, ibrutinib (BTK inhibitor) and lenalidomide (IMiD), have data available from multiple studies and are included in the NCCN Guidelines for consideration as salvage therapies.²⁹

A phase II multicenter study of single-agent ibrutinib at 560 mg/d orally in 52 patients with R/R PCNSL and primary vitreoretinal lymphoma (PVRL) yielded a disease control rate (including complete response, partial response, and stable disease) of 62% with a median PFS of 3.3 months in the intent-to-treat population. In patients presenting with brain and spinal cord disease at presentation (ie, excluding those with PVRL), the disease control rate was 52% and median PFS was 2 months.³⁷ Results from phase I single-institution studies of ibrutinib at 840 mg/d orally as a single agent and in combination with chemotherapy demonstrated a higher overall response rate (ORR) at 77% to 86%.^{5,17,38} Ibrutinib was also shown to be effective and safe when combined with rituximab and MTX.^{5,28} These studies also demonstrated longer duration of response compared with single-agent ibrutinib, although not in a randomized setting. Phase I and II studies of rituximab and lenalidomide in

Table 2. Prospective Trials in Relapsed or Refractory PCNSL

Regimen	Dose and Schedule	Patients, N	Median Age (y)	Complete Response n (%)	Partial Response n (%)	mPFS (mo)	mOS (mo)	Reference
Topotecan	1.5 mg/m ² days 1–5 every 3 weeks	27	51	5 (19)	4 (15)	2	8.4	Fischer et al, 2006 ⁵⁵
TMZ	150 mg/m ² × 5 days every 28 days	36	60	9 (25)	2 (6)	2.8	3.9	Reni et al, 2007 ⁵⁶
Topotecan	1.5 mg/m ² days 1–5 every 3 weeks	15	56	3 (20)	3 (20)	2	32.2	Voloschin et al, 2008 ⁵⁷
Rituximab	375 mg/m ² IV weekly × 8	12	64	3 (25)	1 (8)	57 days	20.9	Batchelor et al, 2011 ⁵⁸
Pemetrexed, dexamethasone	Pemetrexed, 900 mg/m ² every 21 days + low-dose dexamethasone	11	70	4 (36)	2 (18)	5.7	10.1	Raizer et al, 2012 ⁵⁹
Rituximab, TMZ	Rituximab, 750 mg/m ² on days 1, 8, 15, and 22 + TMZ, 100–200 mg/m ² days 1–7 and 15–21	16	63	2 (13)	3 (19)	7 weeks	Not reached	Nayak et al, 2013 ¹⁵
Pemetrexed, rituximab	Pemetrexed, 900 mg/m ² every 21 days; rituximab, 375 mg/m ² on day 0	27	53	6 (22)	11 (41)	6.9	11.2	Zhao et al, 2015 ⁶⁰
Temsirolimus	25 or 75 mg IV weekly	37	70	CR: 5 (14) CRu: 3 (8)	12 (32)	2.1	3.7	Korfel et al, 2016 ⁶¹
Ibrutinib	560, 700, or 840 mg orally daily	13	69	5 (39)	5 (39)	4.6	15	Grommes et al, 2017 ⁵
Pomalidomide, dexamethasone	Pomalidomide, 3, 5, 7, or 10 mg days 1–21 per 28-day cycle, and dexamethasone, 40 mg every week × 8 weeks; then pomalidomide alone	25	Not reported	8 (32) 6 CR, 2 CRu	3 (16)	5.3	Not reported	Tun et al, 2018 ⁶²
Lenalidomide, rituximab	Lenalidomide, 20 mg/d days 1–21 for cycle 1; 25 mg/d days 1–21 for subsequent cycles; rituximab, 375 mg/m ² on day 1 of each 28-day cycle; maintenance phase: lenalidomide alone, 10 mg/d for up to 12 28-day cycles	45	69	12 CR/CRu (29)	3 (7)	7.8 mo	17.7 mo	Ghesquieres et al ⁴⁰
Ibrutinib	560 mg by mouth daily	52	69	10 (19)	17 (33)	4.8	19.2	Soussain et al, 2019 ³⁷
HD-MTX, ibrutinib	HD-MTX, 3.5 g/m ² and ibrutinib, 560–840 mg daily	15 (9 PCNSL, 6 SCNSL)	62	8 (53)	4 (27)	9.2	Not reached	Grommes et al, 2019 ¹⁷
Pemetrexed	600–1,200 mg/m ² every 2 weeks (MTD: 900 mg/m ² every 2 weeks)	17 (14 evaluable for response)	64	3 (21)	5 (36)	42	44.5	Dietrich et al, 2020 ⁶³

Abbreviations: CR, complete response; CRu, complete response unconfirmed; HD-MTX, high-dose methotrexate; IV, intravenous; mOS, median overall survival; mPFS, median progression-free survival; MTD, maximum tolerated dose; PCNSL, primary central nervous system lymphoma; SCNSL, secondary central nervous system lymphoma; TMZ, temozolomide.

combination demonstrated similar results, with an ORR of 64% to 67% and median PFS of 6 to 7.8 months.^{39,40} Current ongoing clinical trials are investigating single-agent checkpoint inhibitors (pembrolizumab and nivolumab), various combinations of targeted agents and checkpoint inhibitors, and CD19-directed CAR T-cell therapies (ClinicalTrials.gov identifiers: NCT02779101, NCT04022980, NCT04401774). Early results from most of these studies appear promising, but caution should be exercised when considering any of these new therapies.

Despite high response rates, both ibrutinib and lenalidomide have a relatively short duration of response, and one disadvantage of using these drugs at first

recurrence is that it may restrict potential trial opportunities. Both drugs are now used in combination therapy trials; moreover, newer-generation agents are also being considered, which may present better options for patients. Additionally, they may pose unique toxicities in patients with PCNSL (ie, risk of aspergillosis with ibrutinib). In general, use of novel agents is recommended in the context of clinical trial enrollment. However, in carefully selected patients, these 2 agents can be considered for patients with R/R PCNSL if clinical trials are not feasible, while closely monitoring for side effects. As such, we discourage off-label use of other novel agents in routine clinical practice for R/R PCNSL. Additionally,

we do not recommend off-label use of any novel agents in the upfront setting or consolidation due to lack of definitive data.

Borderline Candidates for HD-MTX Treatment

Elderly patients have been classified as those older than 50 or 60 years, although most prospective studies have included patients older than 60 or 65 years. Although this age threshold remains essential when considering therapies such as WBRT, clinical trials have demonstrated that older patients do tolerate treatment with HD-MTX and that the critical factor is renal function rather than age itself. A single-institution retrospective study demonstrated that patients aged ≥ 80 years could be successfully treated with HD-MTX.⁴¹ In general, patients with a creatinine clearance of >40 mL/min typically tolerate a flat dose of 3.5 g/m².¹² Dose reduction is recommended in patients with reduced renal function and poor creatinine clearance. For HD-MTX dosing schedule of 8 g/m², the dose is reduced based on the percent reduction of the creatinine clearance below 100 mL/min.¹¹ It is important to note that doses of HD-MTX as low as 1 g/m² yield brain parenchymal responses, although doses of at least 3 g/m² are recommended for adequate CSF penetration and are also associated with improved survival.^{42–44}

Challenges in Response Assessment

PCNSL response assessment includes evaluation of brain and spinal cord with contrast MRI (contrast CT, if MRI is not possible), CSF, and eyes (detailed ophthalmologic examination), with a focus on corticosteroid use per International PCNSL Collaborative Group (IPCG) guidelines.⁴⁵ We recommend making every effort to complete extent-of-disease evaluation in all patients before starting any therapy to adequately assess response, particularly when patients are neurologically stable. Although initiation of treatment in a timely fashion is important for neurologic recovery and improved survival, it is essential to avoid delays in obtaining all necessary tests.²³ If significant delays are expected in patients with significant neurologic symptoms, treatment should be initiated as soon as the diagnosis is obtained, and other evaluations can occur concurrently. Every effort should be made to taper off corticosteroids once therapy is initiated to adequately assess response and prevent side effects. Minimal residual enhancement can be seen in patients who have otherwise met criteria for a complete response, which is a diagnostic challenge. These changes could be related to biopsy or focal hemorrhage and may not represent residual lymphoma. These types of responses are often classified as “complete response unconfirmed.” If these changes do not change or if they slowly involute over several follow-up scans in absence of corticosteroid

use, it is reasonable to consider the patient as having a complete response.⁴⁵ Patients who have involvement of CSF or eyes should undergo follow-up ophthalmologic examinations to confirm response. These tests do not need to be repeated if negative at baseline as long as patients do not develop new symptoms to indicate involvement of the intraocular or sub-arachnoid space.

One of the major challenges with therapy for PCNSL has been development of posttreatment neurocognitive decline. This risk is higher in patients aged >60 years as well as long-term survivors.⁴⁶ Many recent clinical trials have incorporated formal neuropsychiatric testing or the IPCG cognitive battery to follow patients; however, this is not routinely practiced in the general outpatient clinic setting.⁴⁷ Comprehensive neuropsychiatric evaluation may be considered if feasible and available to follow routine patients after upfront treatment. At a minimum, the Mini Mental Status Examination (MMSE) should be performed serially during follow-up of patients, as indicated in IPCG guidelines.

Conclusions

PCNSL is in most cases a highly treatable disease, with many patients achieving long-term remission and possibly cure. Patients with appropriate renal function, independent of chronologic age and performance status and if no other contraindications are present, should be considered for HD-MTX–based therapy with curative intent. Consolidation therapy can be considered for fit patients who are well enough to tolerate HDC and/or ASCT. For patients with R/R PCNSL, HD-MTX–based therapies are often the most reasonable first option to try to reach a complete response. If systemic treatment options are available, WBRT should be avoided due to concerns about limited long-term control and significant neurocognitive complications. Enrollment in clinical trials should be considered in all treatment settings, as currently no uniform consensus exists regarding a standard of care, which is especially the case in R/R PCNSL and in patients not eligible for HD-MTX therapy.

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