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European Association of Neuro-Oncology (EANO) guidelines for treatment of primary central nervous system lymphoma (PCNSL)

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Abstract

The management of primary central nervous system (PCNSL) is one of the most controversial topics in neuro-oncology because of the complexity of the disease and the limited number of controlled studies available. In 2021, given recent advances and the publication of practice-changing randomized trials, the European Association of Neuro-Oncology (EANO) created a multidisciplinary task force to update the previously published evidence-based guidelines for immunocompetent adult patients with PCNSL and added a section on immunosuppressed patients. The guideline provides consensus considerations and recommendations for the treatment of PCNSL, including intraocular manifestations and specific management of the elderly. The main changes from the previous guideline include strengthened evidence for the consolidation with ASCT in first-line treatment, prospectively assessed chemotherapy combinations for both young and elderly patients, clarification of the role of rituximab even though the

data remain inconclusive, of the role of new agents, and the incorporation of immunosuppressed patients and primary ocular lymphoma. The guideline should aid the clinicians in everyday practice and decision making and serve as a basis for future research in the field.

Keywords

chemotherapy | immunotherapy | primary CNS lymphoma | radiotherapy | treatment

Primary diffuse large B cell lymphoma (DLBCL) of the central nervous system (PCNSL) is an aggressive neoplasm confined to the brain, eyes, cranial nerves, leptomeninges, or spinal cord in the absence of disease outside the CNS. Currently, PCNSL is estimated to account for up to 1% of lymphomas, 4–6% of all extranodal lymphomas, and about 3% of all CNS tumors.[1] Immunodeficiency is the only well-known risk factor for the development of the disease, and the incidence of PCNSL rose dramatically during the peak of the acquired immune deficiency syndrome (AIDS) epidemic in the late 1980s.[2] Highly active antiretroviral therapy (HAART), which led to an immune recovery in many HIV patients, was introduced in 1996–1997, and since then many studies have indicated a dramatic decrease in the incidence of PCNSL in AIDS patients[2,3]

In contrast, the incidence continues intriguingly to rise in the elderly who consequently represent the majority of patients in the immunocompetent population in some recent studies.[4–6] In this guideline, PCNSL in immunocompetent and immunodeficient patients will be discussed separately. Although the prognosis of PCNSL remains poor, it has significantly improved over the past decades as a result of better treatment strategies with a curative aim. Treatment of PCNSL remains challenging. Despite high chemo- and radiosensitivity, remissions are frequently short-lasting. The blood brain barrier (BBB) limits the access of many drugs to the CNS and patients, especially the elderly, are at high risk of developing severe treatment related-neurotoxicity. The majority of current evidence supporting therapeutic choices still results from retrospective series or single-arm phase II studies, but the insights gained from the publication of several recent randomized trials including one phase III,[7] four phase II studies[8–13] and abstracts of 3 further randomized studies,[14–16] prompted us to update our previous recommendations.[17] The objective of this guideline is to provide clinicians with updated evidence-based recommendations and consensus expert opinions on the management of patients with PCNSL.

The task force set up in 2013 under the auspices of the EANO (European Association for Neuro-Oncology) and selected to be representative of European-based medical experts, wrote the first guideline published in 2015[17] and was partially renewed to update the guidelines and enlarge the scope to PCNSL in immunodeficient patients. The panel with specialists from 11 countries covered all fields of expertise in the management of PCNSL, ie, neurologists, hematologists, medical oncologists, neurosurgeons, pathologists, neuroradiologists, ophthalmologists, and radiation oncologists. Based on the best available evidence from the literature review, all experts were assigned to update and/or rewrite the different sections of the guidelines and grade the evidence. The revised guideline, taking into account the comments of the panelists, was resubmitted by the two chairmen (KHX, JB) to the whole task force for review and amendments three times. The final agreement was obtained in June 2022. References for this review were identified through searches of PubMed from January 1980 to May 2022 and through searches of the authors` own files. The final reference list was generated on the basis of originality and relevance to the broad scope of this review. Relevant abstracts presented at international meetings were mentioned by task force members during manuscript preparation but were not taken into account for evidence grading. As for the previous EANO guidelines, the scientific evidence of papers collected from the literature was evaluated and graded and recommendations are given according to Table 1.[17,18] The main changes from the previous guideline are the incorporation of immunosuppressed patients, a more solid basis for the consolidation with ASCT in first-line treatment and more data regarding rituximab, even though the data are still not conclusive, and development of new agents though none have become standard yet.

General Recommendations

For recommendations regarding the general approach to patients with PCNSL, including pathology and genetics, clinical presentation, diagnostic confirmation, staging, prognostic factors, and response criteria to treatment, we refer to the table in the supplemental appendix that has been built and updated on our previous guideline.[17] Similarly, updated key recommendations for treatment are summarized in Table 2.

Surgery

Resection has historically not been considered to be the standard of care for PCNSL because of i) the microscopically multifocal and infiltrative nature of PCNSL, which may extend beyond the visible border of the lesion, ii) the fact that lesions are often located deeply in the periventricular space, and iii) historical series that suggested no clear benefit in the outcome of resection when used as the only treatment compared either to supportive care (Class IIIb)[65] or with biopsy performed for patients having received post-operative chemo-and/or radiotherapy (Class IIIb).[66] In addition, early retrospective studies on combination treatment found a high complication rate of surgery without a

Table 1 Grading of evidence and recommendations[17,18]

	Grading of evidence
Class I	Prospective, randomized phase III studies
Class IIa	Prospective, randomized phase II studies
Class IIb	Phase I and II studies
Class IIIa	Prospective studies, including observational studies, cohort studies and case–control studies
Class IIIb	Retrospective studies
Class IV	Uncontrolled case series, case reports and expert opinion
Recommendations	
Level A	At least one Class I study or two consistent Class IIa studies
Level B	At least one Class IIa study or overwhelming Class IIb and III evidence
Level C	At least two consistent Class III studies
Good practice point	If insufficient evidence for Level A–C and consensus among task force

Table 2 Treatment recommendations (adapted and updated from the previous *EANO guidelines. Hoang-Xuan* et al, *Lancet Oncol 16:e322-e332, 2015*[17])

Surgery	Reference
Surgical resection may be considered in patients suffering from a large space occupying lesion with acute symptoms of brain herniation to reduce rapidly intracranial pressure (Good practice point).	
Limited and only retrospective data exist regarding surgical resection or biopsy in an unifocal and resectable lesion suspected of PCNSL. No consensus was met in the panel for a recommendation.	19–21
Induction chemotherapy, immunochemotherapy	
HD-MTX is the drug of choice in PCNSL and chemotherapy should include MTX at HD (≥3 g/m^2) both to cross the BBB and yield cytotoxic levels in the CSF. It should be delivered in 2–3 h iv infusions for a minimum of 4–6 injections and at intervals that should not exceed 2–3 weeks (level B).	22
Combination of HD-MTX with other chemotherapeutic agents improves the response and progression-free survival rates with respect to HD-MTX alone (Level B).	22
Chemotherapeutic agents to combine with HD MTX should be selected among active drugs known to cross the blood-brain-barrier, such as HD cytarabine and combinations used in large and/ or randomized prospective trials have to be preferred (Level B).	7,9,11,14,23
HD-MTX-based chemotherapy is feasible in elderly patients with adequate performance status and renal function (Level B).	8,24–26
Most combinations addressed in large clinical trials include HD-MTX associated with an alkylating agent (procarbazine, carmustine, temozolomide, and thiotepa) (Level B).	7,9,11,14,23,27
The value of IT chemotherapy is unclear. IT chemotherapy (intralumbar or preferably intraventricular through an Ommaya reservoir) can be proposed in case of documented meningeal involvement with insufficient response to iv HD MTX (>3g/m^2) based chemotherapy (Good Practice Point).	
Conflicting data exist regarding iv Rituximab combined with a chemotherapy regimen in PCNSL. No consensus was met in the panel for recommendation (Level B).	7,9,12,28
Consolidation treatment	
Radiotherapy	
WBRT and the combination of HD-MTX with WBRT expose patients to an increased risk of neurotoxicity (Level A).	29–32
The role of consolidation WBRT following HD-MTX based chemotherapy remains debated and, if considered, the optimal dose is not yet defined. Risk of neurotoxicity and alternative consolidation options (eg, ASCT) or omitting consolidation should be weighed in the individual patient (Level B).	10–13,33
Reduced dose WBRT consolidation (23.4–30 Gy in 1.8–2.0 Gy fractions) in CR patients is a therapeutic option that is currently being investigated in randomized trials. (Good Practice Point).	14
In patients with progressive or significant residual disease after primary chemotherapy, a total dose of 36–40 Gy with a 1.8–2 Gy dose/fraction appears advisable. With such doses, there is no evidence to add a focal boost on the enhancing lesions (Good Practice Point).	
In patients >60 years, the risk of delayed neurotoxicity, after WBRT especially if following HDMTX, is unacceptably high and WBRT should be avoided in these elderly patients (Level B).	29–32

Table 2 Continued

Consolidation treatment	
High dose chemotherapy with autologous stem cell transplantation (HDC/ASCT)	
HDC/ASCT as consolidation is an effective treatment for younger (age up to 65–70) patients with newly-diagnosed PCNSL, though risk of acute toxicity should be taken into account (Level B).	10–13
HDC/ASCT is an effective consolidation treatment with efficacy at least comparable to that of WBRT	10–13
High-dose thiotepa-based conditioning chemotherapy should be preferred over the BEAM regimen (Level B).	34,35
Non myeloablative chemotherapy	
The value of nonmyeloablative consolidation chemotherapy and maintenance chemotherapy is currently under investigation in clinical trials (Good Practice Point)	36,37 NCT02531841, NCT01511562 NCT03495960 NCT02313389
Primary vitreoretinal lymphoma (PVRL)	
HD-MTX-based chemotherapy seems to improve OS in PVRL (level C), though local relapses occur frequently. Whether the addition of local treatment reduces local relapses is uncertain.	38
Local treatment (intravitreal immuno/chemotherapy or ocular RT) is a valid approach for patients with systemic chemotherapy contraindications or for elderly patients with relapsing intraocular disease (Good Practice Point).	39,40
Patients with concurrent intraocular and CNS lymphoma should be treated no differently from other patients with PCNSL (Good Practice Point).	
If consolidation WBRT is proposed, it should include both eyes (Good Practice Point).	
Refractory and relapsed PVRL should be treated according to the patients' characteristics and prior treatments. Treatments include intravitreal injections of MTX, focal radiotherapy, WBRT, systemic chemotherapy, targeted treatment and HDC/ASCT (Good Practice Point).	
Salvage treatment	
Patients with relapsed/ refractory PCNSL should be enrolled into clinical trials (Good Practice Point).	
HDC/ASCT is a valid therapeutic option in patients aged <70 years with chemosensitive relapsing PCNSL especially in patients without prior ASCT (Level B).	41–43
Salvage WBRT may be proposed in radiotherapy-naïve patients; it may be preceded by induction chemotherapy (Good Practice Point).	44,45
Salvage chemotherapy can be delivered as induction therapy before WBRT or HDC/ASCT, or as exclusive treatment in patients not eligible for these therapies.	46,47
MTX re-challenge should be considered in recurrent PCNSL patients who previously responded to HD MTX (Level C).	48–50
Isolated extra-CNS relapses should be managed with anthracycline-based chemotherapy followed or not by HDC/ASCT (Good Practice Point).	
Bruton Tyrosine kinase inhibitors, imids, immune checkpoint inhibitors and CART have shown clinical activity as single agents in relapsing PCNSL and may be considered in salvage treatments.	51–57
HIV related patients	
Initiation, if not yet done, or modification of ART should be done in conjunction with the infectious disease specialist (Good Practice Point).	58,59
Patients with adequate performance status (arbitrarily defined as KPS≥60) and able to tolerate it (adequate renal function, absence of pleural or abdominal effusion) should be offered treatment with HD-MTX based chemotherapy. Polychemotherapy should be preferred to MTX monotherapy (Good Practice Point).	60–62
In HIV-related PCNSL patients the risk of delayed neurotoxicity from WBRT is significant and radiation should therefore be avoided (Good Practice Point).	
If HD-MTX based regimens cannot be considered, combination of ART with other chemotherapeutic agents or with palliative WBRT may be an alternative (Good Practice Point).	
Combinations of chemotherapy with antiviral treatments against EBV, rituximab, immune check point inhibitors or targeted therapies need further evaluation in this population (Good Practice Point).	
PCNS-post-transplant lymphoproliferative disorder (PTLD) patients	
Immunosuppression should be reduced to the lowest level possible, in close collaboration with transplant specialists (Good Practice Point). Further antitumor treatment needs to be tailored to patient's age and performance status, and transplanted organ functioning (Good Practice Point).	63,64
Extrapolated from its use in systemic PTLD, systemic chemotherapy including HD-MTX based regimens should be considered in order to increase response rates and reduce the high risk of relapse (Good Practice Point).	
On the basis of its efficacy in systemic PTLD, treatment with rituximab might also be considered when possible, especially in patients with underlying renal failure that precludes usage of HD-MTX (Good Practice Point)	
There is lack of evidence supporting treatment with antiviral agents, and other therapeutic strategies need further evaluation in this population (Good Practice Point).	

positive effect on survival (Class IIIb).[19] In contrast, recent studies suggest that resection may provide a therapeutic benefit in selected patients.[20,21,67]

In a post hoc analysis of the German PCNSL Study Group-1 trial, including 526 patients with PCNSL, 67 of whom underwent gross total resection, PFS and OS were significantly shorter in the biopsied group as compared with patients with resections even when controlled for age and KPS.[20] When controlled for the number of lesions, the difference remained statistically significant only for PFS (Class IIIa).[20] Smaller single institution retrospective analyses revealed that surgical resection for PCNSL patients is safe for patients with good performance status and a single, superficial lesion with complication rates comparable to rates for other intracranial tumors, though the clinical benefit to resection could not be concluded (Class IVb).[68,69] Data from 132 PCNSL patients cross-validated using data from 8.936 patients from two national American databases suggested that craniotomy is associated with increased survival over biopsy by 8.5 months for patients categorized in a low surgical risk, which includes lesion location and number, age and frailty (Class IIIb).[21] There have not yet been any published series prospectively assessing morbidity or survival in PCNSL patients treated with cytoreductive surgery vs biopsy; selection bias to include patients with better prognosis, that is patients with single, superficial, and small lesions in resected subgroups, cannot be excluded in these retrospective studies. No consensus was met to recommend either resection or biopsy for patients with a unifocal and resectable lesion suspected of PCNSL. In such cases, decision-making should be discussed in a multidisciplinary tumor-board.

Systemic Chemotherapy

Based on convergent results from numerous prospective and retrospective studies, high-dose intravenous (iv) methotrexate (HD-MTX), an antifolate and antimetabolite, is the most important and beneficial single agent.[22] Penetration of MTX into the CNS depends both on the total dose and rate of infusion. The optimal dose of MTX has not been determined. It has been estimated that the iv MTX dose should range between 1 g/m^2 and 8 g/m^2 to achieve sufficient drug levels within the CNS. In the absence of clear evidence for a dose-response relationship,[22] and since the rapid infusion of MTX ≥ 3 g/m^2 over 3 h achieves cytotoxic levels in the CSF, there is a growing consensus to deliver MTX according to this protocol (Class IV).[70] Since the efficacy of MTX may also depend on the duration of exposure, the MTX administration intervals in most treatment protocols range between 10 days and 3 weeks.[22] The optimal number of MTX injections to deliver has not been formally established. A minimum of 4–6 infusions is delivered in most chemotherapy regimens, especially if no consolidation treatment (radiotherapy and/or intensive chemotherapy) is scheduled in the protocol. Infusions of HD-MTX require hyperhydration, urine alkalinization, leucovorin rescue, and MTX concentration monitoring. HD-MTX has been used as monotherapy in single-arm studies though with a varying responses.[71,72] Currently, most treatment protocols combine HD-MTX with a variety of other chemotherapeutic agents to improve response rate and outcome. In the only randomized, though phase II, a study comparing HD-MTX (3 g/m^2) alone with a HD-MTX (3 g/m^2) combination regimen a significantly higher complete response (CR) rate was found in the HD-MTX + cytarabine arm (46%), compared with the HD-MTX-only control arm (18%, $P = .006$)[23] (Class IIa). In the subsequent IELSG32 phase II trial, three different HD-MTX-based induction regimens were compared for patients up to the age of 65 (ECOG ≤ 3) or 70 (ECOG ≤ 2).[9] On completion of induction chemotherapy, eligible patients underwent a second randomization and received either high-dose chemotherapy and autologous stem cell transplantation (HDC/ASCT) or WBRT as consolidation, with CR rate as a primary endpoint for induction. Patients receiving the most intensive induction regimen, consisting of HD-MTX, Ara-C, rituximab, and thiotepa (the MATRix regimen), showed a significantly higher CR rate (49%) in comparison to 23% in the least intensive regimen, consisting of HD-MTX and Ara-C, ($P = .0007$) with a 2-year OS of 69% and 42% respectively.[9] (Class IIa).

Another approach is BBB disruption (BBBD) by intra-arterial (IA) infusion of hypertonic mannitol followed by intra-arterial (IA) chemotherapy to increase the drug concentration in the CNS. BBBD with IA MTX administrated in newly diagnosed PCNSL has demonstrated a good safety profile and neurocognitive tolerance and achieved comparable outcomes to those observed with iv HD-MTX-based chemotherapy regimens (Class IIIb).[27,73,74]

In a recent meta-analysis including only prospective phase II and III trials, treatment results (CR rate, PFS, OS) were compared for HD-MTX alone with HD-MTX-based polychemotherapy including 1, 2, 3, 4, or ≥ 5 additional drugs (Class IIIa).[22] Results of this analysis suggest improved CR rates with the addition of two or three drugs in addition to the backbone of HD-MTX, but an impact on OS remains to be demonstrated in adequately powered trials. A randomized comparison of the different combinations has not been published except in elderly patients and except in the addition of agents to the same backbone. In patients who are not eligible for HD-MTX, treatment should be chosen from therapeutic regimens that have shown efficacy in PCNSL.

In summary, HD-MTX is the drug of choice for PCNSL and should be the backbone of polychemotherapy regimens that include additional substances which have been investigated in large prospective phase II and III trials (level B recommendation). Despite important advances in the induction chemotherapy of PCNSL in the past years, the complete response rate remains lower compared to that obtained in systemic DLBCL, and improving induction treatment in PCNSL to fill this gap remains an important goal.

Immunotherapy

The anti-CD20 antibody rituximab is a standard component in the treatment of B-cell non-Hodgkin lymphomas including DLBCL occurring outside the CNS. However, the high molecular weight of rituximab limits its penetration through the BBB.[75] On the other hand, BBB breakdown associated with PCNSL has been assumed to potentially

increase the rituximab concentration in the CNS to levels required for sufficient anti-neoplastic activity.[76] The effect of rituximab when used as monotherapy in PCNSL was evaluated in a single study in which 12 patients with refractory or relapsed PCNSL were treated with a weekly iv dose of 375 mg/m^2 rituximab infusion for up to eight doses (Class IV).[77] MRI responses were observed in 36% of patients.

The role of rituximab in combination with HD-MTX-based chemotherapy as initial treatment for PCNSL has been evaluated in small uncontrolled studies[36,46,51,78–83] and two prospective randomized clinical trials.[7,9] In the randomized phase II IELSG-32 study (see also above) patients with newly diagnosed PCNSL randomized for MTX—cytarabine alone had an ORR of 53% (95% CI 42–64); patients randomized for MTX-cytarabine and rituximab had an ORR of 74% (95% CI 64–84) ($P = .01$), with OS at 2 years of 42% vs 56% respectively.[9] A 2022 update showed OS at 7-years of 21% (95% CI = 4–47%) vs 37% (95% CI = 26–48%).[12] The phase II design of this study should be taken into account when considering these data supporting the use of rituximab, as well as the superior results found in patients treated with the MTX-cytarabine combination without rituximab in a previous study: an ORR of 69% and 2 year OS of just under 60%.[23] (Class IIa). The HOVON-105/ALLG-NHL-24 study was a randomized phase III study in which patients with newly diagnosed PCNSL aged 18–70 years were randomized for treatment with MBVP chemotherapy (HD-MTX, carmustine, teniposide, and prednisone) with or without rituximab.[7] Responding patients were subsequently treated with HD-cytarabine, and patients under 61 years old were additionally consolidated with low-dose (30 Gy) WBRT with an integrated boost to the tumor area if they did not achieve CR. The primary endpoint, event-free survival (EFS) at 1 year, was 49% without and 52% with rituximab, with a hazard ratio (HR) of 1.0 (95% CI 0.7–1.43), $P = .99$, thus showing no effect of rituximab on EFS. Similarly, 1-year PFS did not differ between the arms with 58% in the MBVP group and 65% in the R-MBVP group (HR 0.77, 95% CI 0.52–1.13, $P = .18$)[7] (Class I). An unplanned subgroup analysis suggested a possible effect of rituximab in patients aged up to 60 years, but given the relatively small number of patients in this analysis and the nature of such an unplanned analysis, no definitive conclusions can be drawn. A systematic review and meta-analysis investigated the influence of rituximab on outcomes in randomized prospective trials (Class IIIa).[28] The hazard ratio (HR) for death in the pooled analysis was 0.76 (95% CI, 0.52–1.12) and the HR for PFS was 0.65 (95% CI, 0.45–0.95), thus showing no statistically significant evidence for an OS benefit and low certainty for a PFS benefit of rituximab, with no evidence of increased toxicity.

In conclusion, conflicting data exist regarding the efficacy of rituximab in PCNSL and no consensus was met in the panel for a recommendation.

Intrathecal Chemotherapy

The role of intrathecal (IT) chemotherapy remains unclear because prospective trials focused on this important issue do not exist. This strategy is not used in most recent and ongoing prospective trials. Indirect evidence of the potential role of IT chemotherapy comes from long-term results of a single-arm phase II trial using the Bonn protocol which included MTX, prednisolone, and cytarabine applied via an Ommaya reservoir over six cycles in addition to HD-MTX-based polychemotherapy[74,84] and a subsequent single-arm trial using the same systemic polychemotherapy regimen but without intraventricular therapy.[85] The first version of the protocol has been associated with a 10 year OS of 53% in patients younger than 60 years, whereas the version without intraventricular chemotherapy led to inferior results. Although this seems to support the use of intraventricular chemotherapy (Class IIIa), three retrospective studies did not show benefit from the addition of intrathecal drugs (MTX, cytarabine) in patients treated with HD-MTX dosed at 3 g/m^2 that theoretically reaches cytotoxic thresholds in the CSF (Class IIIb).[86–88] Therefore, given the low level of evidence, we currently do not advocate IT chemotherapy in PCNSL patients without CSF dissemination. In the case of lymphomatous meningitis, pragmatically, IT chemotherapy may be proposed depending on the initial early assessment of the leptomeningeal response to systemic chemotherapy that should be evaluated at the latest before each scheduled intravenous HD-MTX injection.

Radiotherapy

Although recognized as an active treatment modality, discussion of the role of radiotherapy in PCNSL has become inextricably linked to concerns about neurotoxicity; in patients >60 years old this risk is considered unacceptably high and WBRT should be avoided if possible; see below.[29–32] As outcomes from systemic therapies improve and survival rates rise, avoidance of late toxicity becomes ever more critical also in younger patients. Despite high initial response rates, radiotherapy (RT) used alone provides limited survival benefit, with a median OS of 10–18 months and a 5-y survival rate of 5%[89] (Class IIb). Although never formally compared in a randomized trial, the introduction of HD-MTX followed by RT is considered to be superior to RT alone, with reported 2-4-fold increases in OS (median: 30–72 months) and more long-term survivors (5-year survival of 20–50%) for many protocols[19,90–93] (Class IIb, IIIa, and IIIb). Whether RT following induction chemotherapy could be safely omitted was investigated in the non-inferiority phase III G-PCNSL-SG 1 trial,[33] in which patients who achieved a CR received either consolidation WBRT (45 Gy in 30 × 1.5 Gy fractions) or observation. OS was similar in both arms (32.4 months in the WBRT arm, 37.4 months in the non-WBRT arm) with a non-significant trend to improved median PFS with WBRT (18.3 months vs 11.9 months) (Class I). Full interpretation has been hampered by methodological limitations, and by the fact that only 318 of 551 enrolled patients were treated per protocol. A few retrospective studies similarly suggested that omission of WBRT from first-line treatment results in shorter PFS but does not compromise OS (Class IIIb).[94–96] Nevertheless, as a result of the above-mentioned limitations and the suggested effect on PFS, the role of consolidation WBRT remains

debated. Alternative consolidation options such as reduced dose WBRT (described below) or autologous stem cell transplant (ASCT) have been explored (see ASCT section).

Changes in radiation parameters have been proposed to reduce the risk of radiotherapy-related neuro-toxicity while maintaining efficacy. Aspects to be considered include total dose, fraction size, irradiated volume, hippocampal avoidance, and the use of neuroprotective agents. The most commonly employed WBRT total dose has been 36–40 Gy shielding the orbits after 30 Gy (after 36 Gy in the case of intraocular disease). Higher doses have not demonstrated any benefit[97] (Class IIIb) and, following a phase II study demonstrating encouraging results,[78] interest now centers around the role of reduced dose WBRT, which is being evaluated in the RTOG 1114 randomized phase II study.[14] Initial data suggest that the addition of LD-WBRT (23.4 Gy in 13 × 1.8 Gy fractions) to R-MPV-A improves PFS in newly diagnosed PCNSL.[14] Neurotoxicity rates at the time of reporting were not statistically significantly increased, but further neuropsychological testing and neuro-imaging analyses are ongoing; full results need to be awaited for final interpretation, and radiation-induced neurotoxicity in PCNSL may become overt years after administration.[29–32]

The standardly employed fraction size remains 1.8 Gy/day. No trials have specifically addressed this question, but series using smaller fraction sizes and/ or twice daily hyperfractionation have not demonstrated different outcomes.[98,99] (Class IIb, Class III). The presence of multifocal disease, CSF and ocular involvement, and diffuse involvement of the brain in autopsy studies[100] imply that the traditional WBRT volume must still be advocated, with fields extending to the inferior border of C2, and covering the meninges, including the posterior 2/3 of the orbit[101,102] (Class IIIb, Class IV). A single retrospective study addressing partial brain RT demonstrated significantly more out-of-field recurrences using margins of<4cm compared to margins of >/= 4cm (83% vs 22%) (Class IIIb).[103]

Delayed radiation neurotoxicity, concerning primarily impaired psychomotor speed, executive function, attention, and memory,[104] has been found to have an incidence of 25–35%, related mortality of 30%, and typically occurs months to years after successful treatment (Class IIIb).[105–107] The risk is substantially higher in patients≥60 years (Class IIIb).[32] After reduced-dose WBRT cognitive functions remained stable at least for the first 2–3 years.[108,109] Thereafter some cognitive deterioration was found in a small series although this was not significantly more than in patients consolidated with high-dose chemotherapy and stem cell transplantation.[109]

In summary, the role of WBRT in PCNSL continues to be defined, except in older patients in whom the risk of delayed neurotoxicity is unacceptably high. Increasing response rates to induction chemotherapy may facilitate a move to the routine use of reduced dose WBRT or alternative consolidation strategies. In all settings, each patient's individualized situation and the role of RT must be considered with care, taking into account the risks and benefits of response versus late toxicity and its impact on functioning and quality of life.

Consolidation High-Dose Chemotherapy and Autologous Stem Cell Transplantation (HDC/ASCT)

Several studies have addressed the safety and efficacy of HDC/ASCT as consolidation in first-line treatment in patients with PCNSL. The first study with HDC/ASCT without WBRT used the BEAM regimen (carmustine (BCNU), etoposide, cytarabine, and melphalan) as conditioning and reported a disappointing median event-free survival of 9.3 months (Class IIIa).[110] Subsequently, encouraging studies for which WBRT had been omitted at least in patients in CR after HDC/ASCT using HD thiotepa-based conditioning regimens have been reported (Class IIIb and IV).[111–114] In these studies the selection bias—patients must meet strict criteria to be eligible for transplantation—should be taken into account. Two prospective multicentre randomized phases II studies, the IELSG-32 and the PRECIS trials have evaluated the role of consolidative HDC/ASCT as part of first-line treatment in patients with PCNSL, in parallel with a control arm with conventional, 36–40 Gy WBRT consolidation.[10,11] Both studies showed the feasibility and efficacy of thiotepa-based HDC/ASCT in first-line treatment. The per-protocol 2-year PFS was identical in the WBRT and ASCT arms (75–76%) from the date of trial registration in the IELSG study (Class IIa). The intention-to-treat 2-year PFS was 80% in the WBRT arm and 69% in the ASCT arm. In the PRECIS trial, the exploratory analysis of the per-protocol population showed a significant difference of the 2-year PFS from the time of consolidation in favor of ASCT (2-year PFS = 69% after WBRT; and 87% after ASCT; $P = .03$) (Class IIa). Both trials have reported an excess of cognitive decline in the WBRT arm and early and late lymphoma-unrelated deaths in five patients after ASCT in each study (treatment-related death rate of 9% and 11% in the IELSG and PRECIS studies, respectively). Considering all studies, although the direct comparison between conditioning regimens applied is difficult, HD thiotepa-based conditioning regimens seem more efficient than BEAM-based regimens (Class IIIa).[34,35,115] Because of its toxicity risks, the HDC/ASCT is likely to be proposed for younger patients (<60–65 years) with suitable organ functions. A retrospective European study has suggested that HDC/ASCT with a thiotepa-based conditioning regimen is also feasible and effective in PCNSL patients over the age of 65 (Class IIIb).[116]

In summary, consolidative HDC/ASCT, preferably conditioned by a thiotepa-based regimen, represents a relevant treatment option with efficacy at least comparable with WBRT despite increased acute toxicity but with less long-term deleterious neurocognitive side-effects recorded after WBRT, as confirmed in recently published long term results of the IELSG and PRECIS trials.[12,13]

Consolidation Chemotherapy without ASCT

Single-arm phase II trials have suggested that a de-escalated treatment intensity with non-myeloablative consolidation treatment, for example with cytarabine/etoposide, is feasible and effective in patients with newly-diagnosed PCNSL after induction with HD-MTX-based treatment, although with considerable risk of prolonged

grade IV neutropenia (Class IIb).[36,37] This approach is being investigated in two ongoing randomized trials that use HDC/ASCT as a control arm (NCT02531841, NCT01511562). Preliminary results of the latter, the CALGB 51101 Alliance study, have been reported as a meeting abstract. In this randomized phase II study, 113 patients with newly-diagnosed PCNSL were enrolled and randomly allocated between myeloablative (thiotepa/carmustine) or non-myeloablative (etoposide/cytarabine) consolidation after HD-MTX-based induction. Though PFS was longer after myeloablative treatment (6 years vs 2.4 years) a significant part of this difference was caused by treatment failure before initiation of consolidation and 3 year OS was similar at 83% and 72%, respectively. Initial data suggest no advantage in safety profile in patients treated with non-myeloblative consolidation. However, conclusions on feasibility, tolerability, and efficacy can be drawn only once full data are published.[16]

Salvage Treatment

The treatment of refractory or relapsed PCNSL still remains a huge therapeutic challenge since presently used treatments are of limited benefit.[48,117] About one-third of patients with PCNSL have disease refractory to the first-line treatment and half of the responders will relapse despite the high response rates seen with initial treatment.[48,117,118] Many of these patients die early due to lymphoma progression despite the use of salvage therapy, and in patients with recurrent or progressive disease, especially if combined with severe comorbidity or contraindications for chemotherapy, palliative care may be an appropriate strategy. Selection of salvage treatment should be based on results of published phase II trials and depends on performance status, comorbidities, prior treatments, and time from last treatment. After remission MTX rechallenge given as a single agent or in combination may yield a high rate of new objective response and durable remission most likely in patients who previously achieved response lasting after at least several months with HD MTX-based chemotherapy, suggesting retained chemosensitivity to MTX (Class III).[48–50,117] Alternatively, the ICE/D regimen (ifosfamide, carboplatin, etoposide, and dexamethasone),[47] the R-IE regimen (rituximab, ifosfamide, and etoposide)[46] and the ESHAP/DHAP regimen (cytarabine, cisplatin, etoposide, and methylprednisolone) have shown activity as reinduction before consolidation therapy.[119,120] In patients who had not received any consolidating treatment after HD- MTX-based induction chemotherapy, WBRT or HDC/ASCT should be considered to reduce the risk of relapse. Two retrospective studies have evaluated WBRT delivered as a single option in patients with relapsed PCNSL and reported a high rate of objective responses and a median survival of 11–16 months—quite similar to what is expected with WBRT alone as initial treatment (Class IIIb).[44,45] Delayed neurotoxicity occurred in 15%–22% and is more pronounced in patients older than 60 years of age. Therefore, if a reasonable systemic treatment-option is available it is plausible to delay or even avoid WBRT due to the high risk of significant neurotoxicity.

HDC/ASCT is an alternative option for consolidation in patients with a good performance status, preferentially offered for younger patients (aged<65 years) (Class IIb).[41–43] It has been addressed in patients with relapsed or refractory PCNSL in two multicentric phase II trials, both using thiotepa-based conditioning.[41,121] In the intention to treat the population in the French trial, median PFS and OS were 11 and 18 months.[41] However, in patients who completed the full HDC/ASCT procedure 2 and 3 year OS of 55-69% were found (Class IIIa) with treatment-related mortality of 7–12%.[41,121] Subsequent retrospective analyses have confirmed these results (Class IIIb).[42,43] However, age may be less important than overall fitness regarding toxicity, and some promising results are seen also in patients above 65 years of age (Class IIIb).[116]

Thus, consolidation HDC/ASCT following salvage induction chemotherapy may be associated with prolonged remission in a subset of fit patients (Class IIIa).[48,117,118] However, most studies were performed in patients who had not received ASCT in the first line.

Other treatment options, if the patient is not suitable for HDC/ASCT, include conventional chemotherapy. There is, however, only a limited number of prospective studies available for guidance and these have been exclusively single-arm phase II trials precluding comparison across studies (Class IIb, III, and IV for all studies in this section). Drugs used as a single agent or in combination, with or without rituximab, that have been evaluated and have demonstrated modest activity include temozolomide,[51,122] topotecan,[123] pemetrexed,[124] bendamustine,[125] the PCV regimen,[126] ifosfamide-etoposide based regimens,[46,127] HD cytarabine,[128] cisplatin-cytarabine based regimens,[120] gemcitabine-oxaliplatin based regimen,[129] rituximab.[77] See table 2.

The activity of R-CHOP, not usually used in PCNSL due to low CNS bioavailability, seems to be considerably improved by enhancing the vascular permeability and CNS access using NGR-TNF (Class IIb)[130] Further studies are underway to evaluate this approach in PCNSL. New innovative approaches using physical methods or physiological transporters to facilitate the passage of targeted therapies across the BBB are of interest to evaluate in the treatment of relapsed PCNSL. However, none of these can be recommended as a standard treatment yet.

Relapses outside the CNS account for only 3% of failures, and some studies suggest that extra-CNS relapses are associated with a better prognosis than CNS-involving relapses.[118,131] The optimal salvage treatment for this condition remains to be defined, but excellent results have been reported with anthracycline-based chemotherapy consolidated or not with HDC/ASCT.[132]

Novel Agents

BTK Inhibitors

Promising data are now available for targeted therapies in relapsed disease. Comprehensive molecular analyses of PCNSL tissue revealed a complex architecture of signaling pathways in tumor cells which may be exploited for

therapeutic targeting. The network that comprises Bruton tyrosine kinase (BTK), which acts as a central mediator of B cell receptor (BCR) and Toll-like receptor (BCR) signaling leading to NF-kappaB activation,[133] has been considered as of particular importance in PCNSL. Therefore, BTK inhibitors have gained increasing interest as novel drugs for the treatment of PCNSL. High response rates to ibrutinib were observed in patients with newly diagnosed PCNSL after treatment with the Ibrutinib-based DA-TEDDI-R regimen.[134] In two phase II trials,[52,135] single-agent ibrutinib at a dose of 560–840 md/d, resulted in a response rate of 70–77%, with a complete remission rate of 23–38%, in patients with relapsed or refractory PCNSL. A response rate of 80% was reported for the combination of ibrutinib with HD-MTX, and rituximab[53] and signs of clinical activity of tirabrutinib, a second-generation BTK inhibitor, have also been found.[136] While these findings are encouraging (Class IIb), data from randomized clinical trials are not yet available.

Imids

The thalidomide derivatives lenalidomide and pomalidomide have been investigated in a few prospective trials. Their mechanism of action involves the induction of targeted degradation of disease-relevant proteins but may also include a modulation of the tumor microenvironment.[137] Lenalidomide was used as single-agent treatment or in combination with other drugs such as rituximab resulting in an overall response rate of 68% and a median PFS of 6 months in patients with recurrent or refractory PCNSL.[54] Encouraging results were also seen in a phase 2 trial of lenalidomide in combination with rituximab in patients with recurrent or refractory PCNSL or primary intravitreal lymphoma, with an overall response rate in PCNSL patients of 65% and a median PFS of 3.9 months[55] (Class IIb). The combination of rituximab-lenalidomide-ibrutinib seems feasible and active in heavily pretreated R/R PCNSL (Class IV)[138]; a prospective study is ongoing (NCT03703167). Clinical activity was also noted with pomalidomide in patients with recurrent or refractory PCNSL.[139] (Class IIIa). The results of ongoing trials which investigate lenalidomide, pomalidomide or other targeted agents in the first line or recurrent setting need to be awaited to clarify their role in PCNSL patients.

PI3K/mTor Inhibitors

The clinical evaluation of drugs targeting the phosphoinositide 3 kinase/mammalian target of the rapamycin (PI3K/mTor) pathway is ongoing. Treatment with the mTOR inhibitor temsirolimus led to an overall response rate of 54% in a phase 2 study in patients with recurrent or refractory PCNSL but a disappointing median PFS of 2.1 months (Class IIb).[140]

Immune Checkpoint Inhibitors

Increased expression of PD1, PD-L1, and PD-L2 in PCNSL, recurrent 9p24.1 genomic alterations, and objective response to anti PD1 antibody in a small series (nivolumab) or case report (pembrolizumab) in relapsing PCNSL[141,142] (Class IV) has led to some ongoing phase II trials to better specify the therapeutic role of anti PD1 blockade (eg, NCT03012620).[143]

CAR-T

While CD19-targeted chimeric antigen receptor T-cell (CAR-T) therapy has been shown to be active in systemic DLBCL, data supporting CAR-T use in PCNSL are scarce, due to concerns related to possible severe immune effector cell-associated neurotoxicity (ICANS). Two retrospective series (class IIIB) and one phase I/II trial (class IIb), including 5, 9, and 12 highly refractory PCNSL patients respectively, converge to show that CAR-T therapy was well tolerated with manageable and reversible toxicities. In addition, 3 out of 5, 5 out of 9, and 6 out of 12 patients respectively achieved a complete response.[56,57,144]

In conclusion, patients with relapsed or refractory PCNSL should be assessed for participation in prospective trials addressing new agents, combinations or strategies. When a prospective trial is not available reinduction with HD-MTX or one of the agents studied in phase 2 studies (see Table 2) can be given with or without consolidation with HDCT/ASCT or WBRT or, alternatively, WBRT alone.

Specific Situations

Elderly Patients

As in other entities, the definition of "elderly" is not uniform. However, in the studies available which have evaluated prognostic factors, age over 60 (used by most studies as cut off) was consistently correlated with worse outcomes and found to be highly prognostic for chemoradiation-induced neurotoxicity.[32] Elderly patients represent a vulnerable treatment subgroup, due to the poor prognosis and the peculiar sensitivity to treatment side effects. Some prospective, mainly phase II, studies have been published on the treatment of elderly patients with PCNSL (Class IIb),[8,24–26,80,145,146] and seven prospective studies on patients of all ages which reported specifically on older patients (Class IIIa),.[84,89,93,98,147–149] In the RTOG phase II trial evaluating radiotherapy alone (40 Gy + 20 Gy boost), the median survival was only 7.8 months.[89] After HD-MTX-based therapy, defined as a dose of MTX ≥1 g/m^2 PFS in patients aged 60 or 65 and older is reported between 6 and 16 months and OS between 14 and 37 months (Class IIb and Class III) with OS in the majority of prospective studies under 2 years.[25,80,84,93,98,112,149–156]

Outside of retrospective studies, no direct comparisons have been made between treatment with HD-MTX-based chemotherapy and radiotherapy in this age group.[152] However, the impression from the single arm and population-based studies is that survival is at least as good and probably better after HD-MTX-based chemotherapy than after radiotherapy (Class IIIb).[157] Formal comparisons of different HD-MTX-based regimens have not been published except in a randomized phase II study, where toxicity was similar and CR rate was 53% with MPV-A (MTX,

procarbazine, vincristine, and cytarabine) vs 38% for MTX and temozolomide, although the difference was not statistically significant (Class IIa).[8] Concerning toxicity in patients aged over 60, with the exception of one study, in which an intensive multi-drug regimen was used and toxicity was exceedingly high in older patients,[93] chemotherapy with MTX doses up to 3.5 g/m^2 was well tolerated with 2–7% treatment-related mortality, less than 10% grade 3–4 nephrotoxicity and 7–10% of patients discontinuing treatment due to chemotherapy-associated toxicity, though MTX dose was reduced because of decreased renal function in 26–44% of patients.[8,24–26,42,80,145,158] Retrospective studies substantiate this view. Thus, in general, older patients tolerate treatment with HD-MTX well when adequate supportive measures are used and renal function is accurately monitored.[159]

As discussed above, the risk of delayed leukoencephalopathy is particularly high in patients older than 60 years managed with chemoradiotherapy.[32] For patients treated with HD-MTX-based chemotherapy without radiotherapy only one study reporting specifically on older patients is available,[8] but reports including neuropsychological assessment of patients of all ages show little or no cognitive decline in post-treatment evaluations (Class IIIb).[160,161] Overall, if elderly patients are considered eligible, they should receive HD-MTX-based chemotherapy including drugs that cross the BBB such as an oral alkylating agent.[162] Selected elderly patients with the good clinical condition can be considered for more intensive approaches.[163] As in other elderly cancer patients, future studies should address the role of geriatric assessment tools adapted to PCNSL patients to identify vulnerabilities to drive treatment choice in this population.[164] Prognosis in old patients with poor general condition (i.e., severe comorbidity, poor performance status lacking of autonomy) and in the very old (over 80) patients is very poor.[156] Acute morbidities and frequent admissions to hospitals associated with HD-MTX chemotherapy need to be individually weighed against the more limited survival benefits in this markedly frail population.

Primary Vitreoretinal Lymphoma

Intraocular infiltration can be the exclusive site of disease at presentation, referred to as primary vitreoretinal lymphoma (PVRL) or as a part of PCNSL with concomitant brain or meningeal disease. The optimal treatment for vitreoretinal lymphoma remains debated. Data on therapy and outcome are scarce and limited to retrospective case reports or mostly small series with heterogeneous patient populations and treatments. Up to 90% of patients with PVRL subsequently develop brain involvement over the course of the disease and dissemination to the brain is the main cause of death.[39,165]The overall median survival of isolated PVRL regardless of treatment in retrospective series is approximately 60 months.[39,166] Treatment may be focal, including ocular RT (historically, a total dose of 35–40 Gy, 2 Gy per fraction using opposed lateral beams to include both globes) (Class IV) and intravitreal drug delivery.[167–169] Uncontrolled series have reported clinical remission with repeated intravitreal MTX and more recently after rituximab injections (Class IV).[168,169] More extensive treatments, including systemic chemotherapy and WBRT have also been evaluated and intraocular responses have been reported with HD-MTX,[170] HD cytarabine,[171,172] ifosfamide, trofosfamide,[173] and temozolomide[174] used as single agent,[173] with HD-MTX-based polychemotherapy, and after HDC/ASCT (Class IV).[175] Retrospective multicenter studies have shown conflicting results regarding focal and extensive therapy for isolated PVRL in terms of disease control and survival (Class IIIb).[38–40] These and other studies failed to provide reliable predictors of brain dissemination in PVRL patients. Nevertheless, given the high risk of relapse in the CNS, and the improved OS after systemic treatment in the most recent series,[38] most experts consider that initial treatment of PVRL should not differ from that of PCNSL ie, high-dose MTX-based polychemotherapy followed, or not, by consolidation treatment to eradicate the possible concomitant microscopic disease in the brain and in the CSF in patients fit to receive such treatment. Local treatments would remain options for refractory or recurrent disease confined to the eyes and for older and frail patients. Systemic treatment with HD-MTX-based chemotherapy is associated with an increased ocular relapse rate, probably because of insufficient intraocular drug availability, which led some investigators to add local ocular treatments to improve disease control.[38] The management decision should take into account the individual risk of treatment toxicities (including those related to ocular treatment) and center expertise.[165,176] When intraocular lymphoma is concurrent with brain lesions, it has not been identified as an independent prognostic factor and the prognosis is similar to that of PCNSL without the intraocular disease (Class IIIb).[177] Accordingly, patients with concomitant intraocular and cerebral disease should be treated no differently from PCNSL. In these cases, the value of additional local ocular treatment (ie, intravitreal chemotherapy or ocular radiotherapy if WBRT has not been delivered) to systemic chemotherapy remains a matter of debate, with conflicting results in two retrospective studies (Class IIIb).[177,178] No studies, other than practice surveys, have been done to evaluate response assessment and follow-up. However, follow-up at least by fundoscopy and slit-lamp examination as well as brain MRI after treatment is recommended; the French LOC group suggests every 6 months during the first 2 years and yearly thereafter.[179]

Immunodeficiency-Related PCNSL

The pathogenesis of PCNSL in HIV-infected people and transplant recipients is strongly related to Epstein-Barr virus (EBV) reactivation, which can lead to chronic antigenic B cell stimulation and cell activity transformation.[180] There are no well-defined standard treatment regimens for immunodeficiency-associated PCNSL, including for patients with human immunodeficiency virus (HIV) infection and those receiving immunosuppressants following solid organ transplantation or for chronic autoimmune disorders. In general, the therapeutic strategy is aimed at reducing immunosuppression and administrating antitumor treatment based on existing evidence in immunocompetent patients.

HIV-Related PCNSL

PCNSL occurs generally in HIV patients with severe immunosuppression. Thus, if not yet done, initiating or modifying prior antiretroviral therapy (ART) in an attempt to reconstitute the immune system constitutes a major therapeutic intervention in these patients. The optimal ART regimen must be defined in conjunction with the infectious disease specialist, taking into account the patient's HIV genotype, previous treatments, comorbidities, and potential drug interactions. Evidence on the benefit of ART in the treatment of HIV-related PCNSL derives from observational studies that showed that early institution of ART after PCNSL diagnosis was independently associated with improved survival.[58,59,181] In a few cases, rapid immune recovery and prolonged tumor regression have been achieved with this sole approach.[182] (Class IV). In addition to enhancement of the immune system, the other mainstay of HIV-related PCNSL treatment consists of concurrent administration of systemic chemotherapy with agents with suitable CNS drug concentration, ie, HD-MTX-based regimens.[183] In general, immunocompromised patients can undergo aggressive treatments identically to immunocompetent patients, with acceptable tolerance and limited morbidity, precluded that the general indications for such therapies are respected. Regarding efficacy, OS varies widely among series and ranges from few months to up to nearly 6 years.[60–62] (Class IV) Whether the addition of rituximab to first-line chemotherapy confers a benefit in this population is not clear. Likewise, there is little or no evidence supporting the use of anti-viral agents against EBV,[184] immune checkpoint inhibitors, or other targeted therapies in HIV-related PCNSL patients, but almost no studies have investigated this. Due to historical reasons, WBRT might be still considered by some institutions as an upfront therapeutic option in HIV-associated PCNSL. However, no prospective data are available, and although radiological response rates of up to 30–50% have been described, the outcome of patients treated with WBRT alone remains poor with a median OS of around 3 months (range 1.3–7.8 months).[58,59,181] On the basis of short response durability and poor survival data, and the high risk of severe neurotoxicity in longer survivors, it is suggested to avoid or reserve palliative WBRT for patients with poor functional status who are not a candidate for chemotherapy (Class IV). For patients with morbidities that preclude safe usage of HD-MTX such as moderate or severe renal insufficiency, treatment decisions must be individualized. In this setting, and extrapolated from its use in immunocompetent patients, other agents with a more favorable toxicity profile such as temozolomide might be considered. WBRT combined with ART might be an alternative, especially for those patients with poor functional status and poor prognosis.

Post-transplant or Immune-Suppression-Related PCNSL

Evidence on the specific treatment of PCNSL in patients receiving immunosuppressants after solid organ transplantation or for a chronic autoimmune disease is lacking owing to its rarity. In consequence, patients are usually treated in a similar manner to the general population and according to the principles of management of systemic post-transplant lymphoproliferative disorders (PTLD). Few retrospective series describing the management and outcome of patients with primary CNS PTLD (PCNS-PTLD) have been published.[63,64,185–187] Patients were mostly treated with both reduction of immunosuppression and heterogeneous regimens of chemotherapy, including HD-MTX alone or in combination with other agents, or radiation therapy. Despite the unclear benefit of rituximab in PCNSL, treatment protocols based on this agent were frequently employed in these series. The high prevalence of kidney transplants and underlying renal failure in addition to the risk of nephrotoxicity related to HD-MTX might have favored this later strategy. Widely variable OS times ranging from a few months to up to 4 years were observed (Class IV). There is anecdotal evidence of the management of PCNS-PTLD by sole reduction of immunosuppression.[188] A recent series, presented as an abstract, of six patients with PCNS-PTLD treated with temozolomide revealed a complete response in three patients with an OS of 100% at 17 months of follow-up, thus illustrating the potential beneficial role of this drug particularly in patients who are not suitable for HD-MTX treatment (Class IV).[189] Single cases of response with other agents such as ibrutinib have also been recently reported.[190]

Conclusions

Guidelines reflect the state of knowledge at a given timepoint. The EANO website will inform of future updates on this guideline (https://www.eano.eu).

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