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POSITION PAPER

Diagnosis and management of primary central nervous system lymphoma: a consensus practice statement from the Australasian Lymphoma Alliance

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Abstract

Primary central nervous system lymphoma is a clinicopathological disease entity that accounts for 1% of all non-Hodgkin lymphoma (NHL). Advanced patient age, adverse disease biology and complexities of diagnosis and treatment render outcomes markedly inferior to systemic NHL. Despite this, an increasing evidence base, including limited randomised controlled clinical trial data, is informing optimal therapeutic strategies with methotrexate-based induction chemotherapy schedules and intensified consolidation in selected patients. This practice statement represents an evidence-based review of the literature and has been devised to assist healthcare professionals in the diagnosis and management of this disease.

Introduction

Primary central nervous system lymphoma (PCNSL) is a rare clinicopathological disease entity that represents 1% of all NHL and 3% of all brain tumours.[1] It is a complex disease, requiring multidisciplinary team support, including neurosurgical, neurology, ophthalmology, radiology, radiotherapy and haematology/oncology specialists. The complex nature of current standard of care treatment protocols and supportive care requires therapy to be undertaken in centres experienced in delivering intensive chemotherapy.

Methodology

This consensus practice statement was undertaken by a panel of lymphoma experts with particular interest in PCNSL under the auspices of the Australasian Lymphoma Alliance in accordance with the Australasian Lymphoma Alliance (ALA) policy for Consensus Practice Statement development. The authors performed a systematic review of all available literature pertaining to PCNSL as of August 2020.

Relevant literature was selected by the expert authors following a survey of current literature and international guidelines. The statement was drafted by the authors and guidance was developed through an iterative consensus approach both to the opinions provided and the grading of certainty. This practice statement does not represent the treatment policies of the individual institutions where the authors are employed. A summary of recommendations is shown after each section. Levels of evidence and grades of recommendation have been applied using the NHMRC levels of evidence (Supporting Information Tables S1, S2)[2] and are mentioned at the end of each section. Statements without grading were considered an

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acceptable standard clinical practice by the experts, ALA members and key stakeholders.

The subsequent recommendations pertain to diffuse large B-cell lymphoma (DLBCL) of the central nervous system (CNS) (which accounts for 95% of CNS lymphoma); other disease entities, such as non-DLBCL CNS lymphoma and secondary CNS involvement, human immunodeficiency virus-related PCNSL and PCNSL occurring in the post-transplant setting, are beyond the scope of this review. This guideline aims to provide an evidence base to support therapeutic decision-making within the context of individual patient circumstances and treatment goals.

Clinical presentation

Clinical presentation and neurological sequelae are dictated by the location of lesions, which may arise in the brain, leptomeninges, spinal cord or eye. Symptoms can include focal neurologic deficits, neuropsychiatric symptoms, loss of higher cognitive functions (such as memory impairment), visual disturbances and back pain.[3] Leptomeningeal infiltration occurs in approximately 40% of cases, although in isolation in less than 10%.[4] Spinal cord involvement is uncommon (<1%) and is often associated with delayed diagnosis.[5] Isolated involvement of eye tissue (vitreous matter or uvea) is termed primary intraocular lymphoma.

Diagnosis

PCNSL is a histological diagnosis. Stereotactic biopsies may be required given the frequent deep location of cerebral lesions; however, small biopsies and any preceding steroid administration can hinder diagnosis. Steroids should be avoided prior to biopsy where possible. Cerebrospinal fluid (CSF) or vitreous fluid may demonstrate malignant lymphocytes and in conjunction with flow cytometry demonstrating B-cell monoclonality can aid diagnosis.[6]

PCNSL (of DLBCL type) expresses CD20/CD79B/BCL6/MUM1(IRF4) and is Ki-67 high. Lesions are frequently located in a perivascular distribution.[7] Activated B-cell (ABC) subtype of DLBCL is found in the majority (70–90%) of cases compared with systemic DLBCL (approximately 30%).[8] Epstein–Barr virus (EBV) status of the tumour should be assessed given the significant association with immunosuppression and EBV positivity.

Mutation testing is not routinely performed in clinical practice but has an emerging role in clinical trial and research settings. Somatic mutations affecting the B-cell receptor signalling pathway are prevalent, including *MYD88* (>60%) and *CD79B* (>60%).[8–10] As a target of somatic hypermutation, *PIM1* is mutated in the majority of cases.[10] *CARD11*, *TOX*, *ETV6*, *TBL1XR1* and *BTG2* are also commonly mutated as well as biallelic deletion of *CDKN2A*. PD-L1/PD-L2 amplifications have been demonstrated in several PCNSL cases, although their role in pathobiology remains incompletely understood.[11,12]

Table 1 International Extranodal Lymphoma Study Group prognostic scoring system

Total score	2-year overall survival
0–1	80%
2–3	57%
4–5	24%

Staging

The International PCNSL collaborative group (IPCG) has developed guidelines on the work up of newly diagnosed patients.[13] Contrast-enhanced magnetic resonance imaging (MRI) is the best modality for diagnosis and response assessment. Systemic imaging (preferably ^{18}F deoxyglucose positron emission tomography (FDG-PET) combined with computed tomography (CT)) is required to exclude synchronous systemic DLBCL, particularly sites of known high risk of CNS involvement (e.g. testis, breast, kidney and adrenal gland). Testicular ultrasound should be considered in male patients. CSF examination (protein concentration, cytology and flow cytometry) should be performed where possible. Ophthalmological examination using a slit-lamp is essential to exclude occult involvement. Standard blood testing as for systemic DLBCL (full blood count, liver, renal, lactate dehydrogenase (LDH), viral serologies) should be performed. Bone marrow biopsy omission can be considered for PET-negative patients in the absence of other indications (e.g. unexplained cytopenias).

Prognostic factors

Patients with PCNSL have poorer prognosis than systemic DLBCL with 5-year overall survival (OS) of 30–40%.[14,15] A prognostic scoring system proposed by the International Extranodal Lymphoma Study Group (IELSG) assigns age >60 years, Eastern Cooperative Oncology Group performance status >1, elevated LDH, elevated CSF protein concentration and involvement of deep regions of the brain a score of 1 each. Score-associated 2-year overall survival is reported in Table 1.[16]

Recommendations:

1 Tissue biopsy is required for the diagnosis of PCNSL using the least invasive approach available (I,B).
2 Steroids should be avoided prior to diagnostic biopsy (I,B).
3 MRI of the brain is the preferred modality for assessment of disease and response (I,B).
4 Whole-body FDG-PET CT should be performed to exclude systemic DLBCL involvement (I,B).
5 Full ophthalmological examination is required (I,B).
6 Examination of CSF should include protein concentration, flow cytometry and cytology (I,B).

Management

General principles

Variation in treatment reflects institutional experience and limited prospective clinical trial data. Patients should be enrolled in clinical trials where possible. High-dose CNS-penetrant chemotherapy (e.g. high-dose methotrexate (HDMTx)) is required to cross the blood–brain barrier. Poor performance status at diagnosis is common, although initial low-intensity therapy, including prephase corticosteroids, may overcome this and facilitate subsequent treatment intensification. Frequent review to upgrade or uptitrate therapy intensity is critical to ensure the maximal delivery of therapy, balanced by toxicity burden. Physical fitness rather than age should be the main criterion for selection of patients for intensive HDMTx-based induction regimens.

Induction therapy should be followed by consolidation in patients who have achieved an objective response and remain eligible for further treatment, although this may not be feasible for many patients. Due to treatment intensity and infection risk, infective prophylaxis and granulocyte colony-stimulating factor (G-CSF) support should be considered per protocols and local guidelines. Patients with PCNSL should be advised not to drive until formal reassessments have been performed after completion of therapy. An approach to the treatment of newly diagnosed patients is provided in Figure 1.

First-line therapy of PCNSL

Systemic methotrexate. Intravenous HDMTx is the mainstay of treatment.[17–19] Doses above 3 g/m^2 have been correlated with adequate CNS drug levels, and rapid infusions (e.g. 3–4 h) facilitate optimal CNS drug concentration.[20–25] HDMTx-containing regimens have been demonstrated to improve response rates and result in superior survival in patients with PCNSL, especially in combination with high-dose cytarabine.[19,26–31] Although combination regimens are more effective than HDMTx monotherapy, they are associated with increased toxicity.[19]

Complete remission rates up to 60% have been reported for patients treated with combination HDMTx regimens.[32–34] Given the absence of randomised clinical trial (RCT) data showing superiority for a particular regimen, the choice of induction therapy is often based on physician or institutional preference and patient factors. Two commonly used regimens are R-MPV (rituximab, HDMTx, procarbazine, vincristine) followed by high-dose cytarabine[35] and MATRix (HDMTx, cytarabine, thiotepa, rituximab).[36] HDMTx-based combination chemoimmunotherapy, such as either R-MPV or MATRix, is recommended over HDMTx monotherapy, provided patient eligibility for more intensive treatment (i.e. adequate renal function). HDMTx, carmustine, teniposide and prednisolone (MBVP) are not currently deliverable in Australia due to lack of availability of teniposide.

Maintenance of HDMTx dose intensity has been demonstrated to associate with outcome; hence, strict review to avoid interacting concomitant medications and compliance with protocols to prevent nephrotoxicity are essential. Data on dose reductions in older patients or patients with renal impairment are limited and where possible published protocols or evidence-based reference benchmarked (e.g. eviQ) guidance should be followed. Empiric dose reductions in older/frail patients should still take into consideration pharmacokinetic properties risking insufficient CNS and parenchymal drug concentrations. One cited example used is of percentage dose reduction relative to reduction in eGFR (i.e. 30 mL/min equating to 100–30 = 70% dose reduction).[37]

Cytarabine. Cytarabine is the most common adjunct chemotherapy agent utilised in HDMTx regimens. Efficacy of cytarabine (four doses of 2 g/m^2) and HDMTx compared with HDMTx alone was demonstrated in a randomised phase II study where the combination significantly improved overall response rate (69% vs 40%; $P = 0.009$) and failure-free survival (38% vs 21% at 3 years; $P = 0.01$), although OS was not statistically significantly different (46% vs 32% at 30 months; $P = 0.07$).[19] Most patients received whole brain radiotherapy (WBRT) as consolidation, so the added benefit of cytarabine appears independent of radiotherapy.

Increased haematological toxicity (particularly thrombocytopenia and neutropenia) associated with cytarabine is typically manageable.[24] Due to neurotoxicity risks,

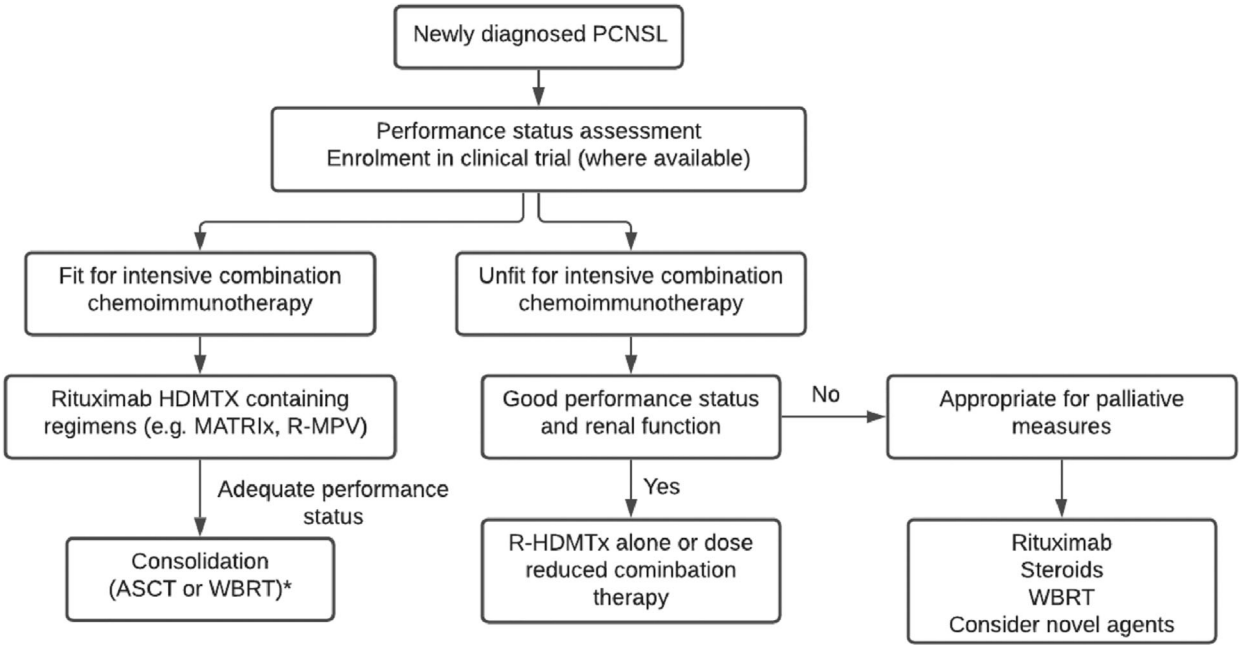

Figure 1 Approach to newly diagnosed patients with PCNSL. *See text for discussion.

dose reduction in patients aged >65 years is recommended, and toxicity is usually prohibitive for frail or elderly patients.[3] However, for young and fit patients, HDMTx/cytarabine regimens are standard of care.

Rituximab. Rituximab has been assessed in two RCT. The first randomisation of the IELSG32 (MATRix) trial compared the addition of rituximab or rituximab plus thiotepa with four cycles of induction chemotherapy with HDMTx and cytarabine.[36] The primary end-point of complete remission rate was not significant for the addition of rituximab only but was significant for rituximab plus thiotepa (OR 3.32; 95% CI 1.64–6.72; $P = 0.00083$). Furthermore, there was a trend towards improved progression-free survival (PFS) (HR 0.52 (95% CI 0.32–0.86); $P = 0{\cdot}051$) and OS (HR 0.63 (95% CI 0.42–1.02); $P = 0{\cdot}095$) between the R-HDMTx/cytarabine arm versus HDMTx/cytarabine alone, even after secondary randomisation to consolidative ASCT or radiotherapy. Addition of thiotepa and rituximab to HDMTx/cytarabine was clearly superior to HDMTx/cytarabine alone for PFS (HR 0·38 (95% CI 0.24–0.61); $P = 0{\cdot}00089$) and OS (HR 0.41 (95% CI 0.25–0.68); $P = 0{\cdot}0015$) respectively.

The HOVON 105/ALLG NHL24 trial randomised addition of rituximab to chemotherapy with MBVP, consolidated by cytarabine in responders then radiotherapy in subjects aged ≤60 years. The primary end-point of improvement in EFS was not met (HR 1.00; 95% CI 0.70–1.43; $P = 0.99$), although there was a trend to improved EFS in subjects aged ≤60 years from addition of rituximab (HR 0.56 (95% CI 0.31–1.01); $P = 0.054$).[38] As a result of the conflicting data from these two RCT, but the larger sample size and standard concurrent chemotherapy within MATRix, rituximab is generally recommended for use in patients with PCNSL.

Intrathecal chemotherapy. There are insufficient data to provide definitive guidance on the use of intrathecal chemotherapy in PCNSL and it is not routinely a part of commonly used induction regimens. Some protocols include intrathecal administration until disease clearance from the CSF, which typically occurs rapidly on commencement of CNS-penetrant systemic chemotherapies.

Considerations for patients unsuitable for intensive upfront therapies. For patients who are ineligible for standard intensified strategies, the prognosis is very poor. Therapeutic options include palliative radiotherapy, steroids, novel agents and/or dose-reduced chemotherapy (although sufficient CNS-penetrating doses are still required to achieve any meaningful response). For patients who are not candidates for chemotherapy, WBRT as the main treatment modality to a dose of 40–50 Gy (1.5–1.8 Gy/fraction) can be considered. Palliative WBRT 30–36 Gy in 10–15 fractions would also be a reasonable option considering the poor prognosis of the patients.

Recommendations:

1 Consider enrolment in a clinical trial whenever possible for treatment of PCNSL (I,A).
2 HDMTx-based regimens are preferred first-line therapy. Dose should be at least 3 g/m^2 given rapidly, every 2–3 weeks for at least four cycles if tolerated. Exact dosing and frequency will be guided by the regimen chosen (I,B).
3 HDMTx-containing combination chemotherapy such as MATRix/R-MPV (or similar) regimens are favoured first line treatments for eligible patients (I,A).
4 Adjustments may need to be made for older patients but wherever possible if performance status and renal function allow then HDMTx-based regimens should be considered (I,B).
5 There is insufficient evidence to advise on utility of intrathecal chemotherapy in the front-line setting.
6 Due to treatment intensity and infection risk, infective prophylaxis and G-CSF support should be considered per protocols and local guidelines (II,C)

Consolidation therapy

Radiotherapy consolidation. The primary role of radiotherapy in PCNSL is consolidation following chemotherapy.[39] WBRT (40–45 Gy) alone achieves highly effective local response but disappointing survival outcomes and delayed neurotoxicity, most notable in patients older than 60 years.[40,41] Trials examining HDMTx-combination chemotherapy with lower radiation doses demonstrated improvement in survival and reduced radiotherapy-related toxicity, leading to widespread adoption of a lower dose range of 30–36 Gy.[42–44] Further dose reduction, including phase II trial data from 52 patients with induction R-MPV and utilising 23.4 Gy for patients achieving complete response (CR), demonstrated highly effective outcomes with no significant RT-related toxicity even in elderly patients,[35] but it should be noted that the number of evaluable patients for neurocognitive testing in this study was small. This approach is being evaluated further in a trial by the RTOG (NCT01399372). International guidelines support low-dose WBRT to a dose of 23.4 Gy in 1.8 Gy fractions following CR to chemotherapy.[45] For less than CR or recurrent disease, WBRT to a dose of 36–45 Gy (1.5–1.8 Gy/fraction) is recommended, and the role of a boost to residual or recurrent disease remains controversial.

Autologous stem cell transplantation consolidation. There is a growing number of prospective single-arm studies of ASCT in patients with newly diagnosed PCNSL, as well as trials comparing ASCT with WBRT as consolidation.[30,46–53] ASCT provides encouraging disease control and less neurotoxicity than WBRT. In the second phase of the IELSG32 trial, 122 patients who had responsive or stable disease after HDMTx/cytarabine-based induction therapy were randomised to either thiotepa-carmustine ASCT or WBRT. Outcomes were similar for both 2-year PFS (69 vs 80% for HCT vs WBRT; HR 1.5; 95% CI 0.83–2.71) and 2-year OS (71 vs 85%; HR 1.67; 95% CI 0.86–3.23).[51] In the PRECIS phase II trial, 140 patients were treated with induction chemotherapy (R-MBVP × two cycles, then R-cytarabine × two cycles) then randomised to receive either thiotepa/busulphan/cyclophosphamide ASCT or WBRT. Outcomes were again similar for both 2-year PFS (70% and 58%) and 2-year OS (66% and 75%) for HCT and WBRT respectively.[53] Mean test scores of executive function tend to decline over time with WBRT but improve or remain stable in ASCT.[52] The optimal conditioning regimen for HCT in patients with PCNSL has not been defined, but BEAM (carmustine, etoposide, cytarabine and melphalan) is considered inadequate. Options include thiotepa, busulfan, cyclophosphamide [TBC][49,50] or thiotepa/carmustine.[51]

Recommendations:

1 Consolidation therapy is recommended for all eligible patients without progression following induction chemotherapy. The optimal consolidation strategy remains to be determined. Consideration should be given to expected tolerability. Long- and short-term toxicity of consolidative strategies should be considered and the patient should be fully informed of these (I,B).
2 ASCT and WBRT demonstrate similar survival outcomes but long-term neurotoxicity remains a concern when WBRT is delivered as consolidation therapy for patients aged >60 years (I,B).
3 ASCT requires a high-dose thiotepa-based approach. BEAM is not appropriate in the setting of PCNSL (I,B).
4 If WBRT consolidation is administered, the evidence supports a dose of 23.4 Gy (II,C) if in CR or 36–45 Gy if not in CR (I,B).

Relapsed PCNSL

Relapsed/refractory PCNSL (rrPCNSL) is associated with extremely poor prognosis and therapy is guided by assessment of fitness for salvage therapy and ASCT (if not already performed). Palliative treatment is appropriate for older/frail patients ineligible for intensified salvage strategies.

Internal Medicine Journal **52** (2022) 1624–1632

Retreatment with HDMTx-based chemotherapy schedules. Despite limited evidence, there is potential benefit of repeat therapy with HDMTx-based chemotherapy in patients who had durable initial responses and late relapse. However, shorter duration of second remission would be expected and hence consolidation strategies are required for patients where curative response is intended. Alternative chemotherapy schedules published as part of salvage/autograft protocols should be considered as discussed below.

Autologous stem cell transplantation at relapse. There are limited data on the efficacy of ASCT in patients with rrPCNSL. A multicentre phase 2 study examined the use of two cycles of high-dose cytarabine and etoposide as salvage followed by TBC ASCT in 43 patients and showed 2-year OS and PFS rates of 45% and 43% respectively.[54] A single-centre study of ASCT in 10 patients showed a CR rate of 40%, 20% treatment-related mortality and 2-year RFS and OS rates of 37% and 40% respectively.[55] In a single-arm multicentre study where 39 patients received two cycles of induction with rituximab, high-dose cytarabine and thiotepa then consolidation with rituximab, carmustine and thiotepa ASCT and WBRT in those who did not achieve CR post ASCT, 56.4% achieved CR after HCT-ASCT with 2-year PFS and OS rates of 46.0% and 56.4% respectively.[56] We recommend patients are enrolled in clinical trials and outside of this context ASCT is a reasonable option.

Radiotherapy at relapse. There are no prospective trials on WBRT in rrPCNSL, but retrospective studies demonstrate a 70–79% response rate with 15–22% neurotoxicity, 10 months PFS and 11–19 months OS.[57,58] Neurocognitive toxicity risk is a challenging issue. WBRT may be considered in those patients who have not received it as part of the initial therapy.

Bruton tyrosine kinase inhibition. The molecular pathogenesis of PCNSL includes somatic mutations in *MYD88*, *CD79B* and other BCR pathway components.[59] The BTK inhibitor ibrutinib has been shown to have activity in patients with rrPCNSL as a single agent[60–63] and in combination with HDMTx[64] with ongoing larger prospective studies. Multiple studies have also demonstrated detectable levels of ibrutinib in CSF proving CNS penetrance.[60,62,64]

A prospective multicentre study treated 52 patients with rrPCNSL or primary intravitreal lymphoma with daily ibrutinib (560 mg) until disease progression or toxicity.[60] Among 44 patients assessable for response, the disease control rate at 2 months was 70%, including 10 CR and 17 PR. The median PFS and OS were 4.8 and 19.2 months respectively. In a phase Ib study, 15 patients with rrPCNSL or secondary CNS lymphoma were treated with HDMTx, rituximab and ibrutinib.[64] The objective response rate was 80%, and median PFS was 9.2 months (not yet reached in the subgroup with PCNSL). Adverse events observed include invasive fungal infections, such as aspergillosis.[61] Based on the observed benefit from limited clinical trial data, ibrutinib can be considered as a treatment option but remains investigational.

Novel approaches. Refer to Supporting Information Appendix S1.

Intraocular lymphoma. Refer to Appendix S1.

Recommendations:

1 Relapsed PCNSL should be staged as per diagnosis (I,C).
2 Clinical trials should be considered for all patients with relapsed PCNSL (I,C).
3 Therapy at relapse is guided by performance status, treatment goals and prior therapy (I,C).
4 Patients eligible for ASCT should undergo intensive chemotherapy at relapse with a view to ASCT if not already performed (I,B).
5 Patients who obtained durable initial remissions with HDMTx may be considered for repeat dosing while those with short remission or refractory disease may be considered for alternative chemotherapy salvage (II,B).
6 Patients may be considered for consolidative or salvage WBRT particularly if radiation naïve (II,C).
7 Palliative radiation, temozolomide and/or steroids can be given in the palliative setting (II,C).
8 Bruton tyrosine kinase inhibition is not approved for use in PCNSL but off-label use can be considered in appropriate clinical situations (III,C).
9 There is currently insufficient evidence to support use of novel therapies, such as checkpoint inhibitors or CAR-T cell therapy outside of a clinical trial setting. (See Appendix S1 for guidelines on selected novel agents.)

Response assessment and follow up

For parenchymal PCNSL, MRI of the brain with contrast should be used, but is limited due to its inability to discern viable lymphoma versus residual signal in responding areas. Prospective clinical trials commonly include MRI scans 3rd monthly for 2 years then 6–12 monthly to 5 years due to the ongoing risk of relapse,

although in clinical practice most institutions do not perform routine surveillance scans and only image on suspicion of relapse. Follow up should include directed history to screen for new CNS or systemic symptoms of lymphoma relapse, physical examination, including full neurological examination where able, and rational use of blood tests if indicated. In practice, most patients are followed in acute care clinics due to late relapse risk, but this can be included in Survivorship follow up where offered.

Conclusion

Combination chemoimmunotherapy protocols containing HDMTx, cytarabine and rituximab have improved the initial response rates and overall outcomes for patients with PCNSL. Consolidation strategies in eligible patients with radiotherapy or ASCT remain standard of care, balancing benefit of disease control against short- and long-term toxicities of therapy. Due to rarity of disease, patients should be enrolled into clinical trials whenever possible.

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Supporting Information

Additional supporting information may be found in the online version of this article at the publisher's web-site:

Appendix S1. Other approaches.
Table S1. Levels of evidence.
Table S2. Grades of recommendation.