Guidelines for the Diagnosis and Management of Primary Central Nervous System Diffuse Large B-cell Lymphoma

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# Scope

This guideline is aimed at providing healthcare professionals with clear guidance on the diagnosis and management of primary central nervous system lymphoma (PCNSL), defined as diffuse large B-cell lymphoma (DLBCL) solely confined to the central nervous system (CNS): brain, spinal cord, cranial nerves, eyes and meninges. Secondary CNS lymphoma, immunodeficiency-associated lymphoma and rare forms of non-DLBCL CNS lymphoma are outside the scope of this guideline. It is not the intention of this guideline to provide treatment recommendations for all situations and clinicians are advised to make management decisions taking into account individual patient circumstances.

# Methodology

Recommendations included a systematic review of published English language literature from publication of previous BSH PCNSL guidance (1st January 2007) up to 29th May 2017. MEDLINE, EMBASE, Cochrane databases and Web of Science were searched using the preliminary search terms ‘CNS lymphoma’ and ‘intraocular lymphoma’. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) nomenclature was used to assess levels of evidence and assess the strength of recommendations (http://www.gradeworkinggroups.org).

Review of the manuscript was performed by the British Society for Haematology (BSH) Guidelines Committee Haemato-Oncology Task Force, the BSH Guidelines Committee and the Haemato-Oncology sounding board of BSH. It was posted on the members section of the BSH website for comment. It has also been reviewed by the patient focused UK charity ‘Lymphoma Action’; although these organisations do not necessarily approve or endorse the contents.

# Context

Primary central nervous system lymphoma (PCNSL) accounts for 1% of all non-Hodgkin lymphomas and 3% of all brain tumours (Rigau*, et al* 2011, Swerdlow*, et al* 2008). It is essential to minimise diagnostic delay, and clinical management requires multidisciplinary team (MDT) support. This includes haemato-oncology but, unique to haematological cancers, also requires input from specialist neurological services. Methotrexate-based protocols should only be delivered at centres experienced in intensive chemotherapy.

# Diagnosis and Imaging

PCNSL presents with a range of symptoms and signs including behavioural change, memory and language impairment, focal motor deficits, seizures, raised intracranial pressure, uveitis and neuropsychiatric symptoms (Aki*, et al* 2013, Zhang*, et al* 2010).

The diagnosis should in all cases be confirmed by specialist haematopathology review of sampled tumour tissue or fluid according to the current WHO classification (Swerdlow*, et al* 2008, Swerdlow*, et al* 2016). Stereotactic biopsy is recommended for intracerebral lesions with intraoperative rapid cytology and review of frozen sections to avoid unnecessary extensive surgery (Abrey*, et al* 2005). Cerebrospinal fluid (CSF) cytology and flow cytometry may be used in cases where a biopsy is not possible or to investigate for leptomeningeal involvement, although sensitivity is low (Schroers*, et al* 2010). At least 3-10 ml of CSF should be taken (Ferreri*, et al* 2004) and rapidly analysed (Patrick and Mohile 2015). PCR to identify clonal *IGH* gene rearrangements may improve diagnostic yield (Ekstein*, et al* 2006, Langerak*, et al* 2012).

Corticosteroids should, wherever possible, be avoided prior to biopsy as they have a substantial negative impact on diagnosis; non-diagnostic rates range from 33% after short course (<1 week) to 57% after longer course steroids (Manoj*, et al* 2014). If corticosteroids have been administered, but an enhancing lesion is still present, they should be discontinued prior to urgent biopsy (Patrick and Mohile 2015). If a suspected PCNSL lesion resolves following steroid administration, re-imaging by magnetic resonance imaging (MRI) should be performed after a short interval (e.g. 2–4 weeks) following steroid cessation. Close clinical follow-up and serial imaging thereafter is recommended, at a frequency guided by MDT advice, with urgent biopsy at lesion regrowth.

Up to 20% of PCNSL patients have intraocular involvement (Coupland*, et al* 2004), which may resemble chronic uveitis (Chan and Sen 2013, Coupland*, et al* 2004). Diagnosis can be difficult and imaging alone cannot reliably establish ocular involvement (Haldorsen*, et al* 2011). Slit lamp examination and ophthalmoscopy followed, if necessary, by vitreous biopsy are recommended. Vitreous biopsy should be combined with a sub-retinal aspirate or chorioretinal biopsy, particularly for those with visible sub-retinal deposits, as vitrectomy specimens have diagnostic failure rates up to 30% (Coupland*, et al* 2004).

Contrast-enhanced MRI of the brain is the neuroimaging modality of choice for both diagnosis and response assessment (Abrey*, et al* 2005, Coulon*, et al* 2002, Ferreri 2011). A diagnosis of PCNSL cannot be presumed on radiological appearance and/or clinical features (such as responsiveness to corticosteroids) alone, as neurosarcoidosis, multiple sclerosis, glioblastoma and vasculitis can mimic disease features (Abrey*, et al* 2005, Zaki*, et al* 2004). PCNSL can also manifest with atypical features, including variable contrast enhancement or diffusion characteristics, absence of focal masses or presence of necrosis (Tang*, et al* 2011). Use of additional imaging studies, such as 18Fdeoxyglucose positron emission tomography (18FDG-PET), or advanced MRI parameters, such as perfusion metrics, diffusion coefficients, MR spectroscopy and novel contrasts, may have the potential to improve the distinction between PCNSL and glioblastoma but none has shown sufficient evidence of specificity to allow use in routine practice (Barajas*, et al* 2009, Kawai*, et al* 2013, Valles*, et al* 2013, Wieduwilt*, et al* 2012). Leptomeningeal dissemination occurs in around 16% of cases as judged by cytology (Korfel*, et al* 2012); it can be difficult to detect on MRI (Tang*, et al* 2011).

All patients should undergo cross-sectional imaging to exclude systemic disease. 18FDG-PET combined with CT imaging (PET-CT) is a sensitive screening tool for systemic involvement at the time of diagnosis (Mohile*, et al* 2008). A bone marrow biopsy is not essential in the context of typical histology if PET-CT has excluded systemic disease, full blood count parameters are normal and there is no detectable serum monoclonal protein to suggest a concurrent low grade lymphoma. There is insufficient evidence that PET-CT has sufficient sensitivity to exclude testicular involvement therefore testicular ultrasound should be performed. Serum lactate dehydrogenase (LDH), performance status (PS) and CSF protein levels form part of established prognostic scores (see Appendix 1) and should be measured, where feasible (Ferreri*, et al* 2003). The International PCNSL Collaborative Group (IPCG) guidelines on standardised evaluation of patients with newly diagnosed or suspected PCNSL (Abrey*, et al* 2005) are summarised in Table 1.

## *Recommendations*

1. **Patients with suspected PCNSL should be discussed with a PCNSL specialist early in their pathway to minimise delays. (1C)**
2. **A histological or cytological diagnosis is required to confirm PCNSL; MRI findings alone are insufficient. The diagnosis should always be confirmed by specialist haematopathology review. (1B)**
3. **Corticosteroids should be avoided prior to biopsy (1A)**
4. **Where steroids have been administered and an enhancing lesion is still present, steroids should be discontinued prior to urgent biopsy to improve diagnostic yield. (1B)**
5. **If a suspected PCNSL lesion resolves following steroid administration, re-imaging with MRI should be performed after a short interval with a view to urgent biopsy at lesion regrowth (1B)**
6. **Stereotactic biopsy of a brain lesion is the recommended approach for histological diagnosis. Intra-operative rapid diagnosis using cytology and frozen sections is recommended to avoid unnecessary surgical resection. (1B)**
7. **Vitreous biopsy should ideally be combined with a sub-retinal aspirate or chorioretinal biopsy to establish a diagnosis of primary intraocular lymphoma (PIOL). (1B)**
8. **Where biopsy is not possible, a diagnosis of PCNSL may be supported by the combined assessment of characteristic MRI findings, clinical features AND demonstration of large clonal B cells in the CSF or vitreous fluid by multi-parameter flow cytometry and/or PCR for *IGHV* gene rearrangements. (1B)**
9. **Contrast-enhanced MRI (including diffusion sequences) is the recommended imaging modality pre-treatment and for response assessment. Neuroaxis imaging (brain and entire spinal cord) should be reviewed by a specialist neuroradiologist. (1B)**
10. **Thorough ophthalmological assessment including slit lamp examination should be performed in all patients to exclude intraocular involvement. (1B)**
11. **All patients should undergo cross-sectional imaging to exclude systemic disease. (1A)**
12. **PET-CT is recommended. Contrast-enhanced CT of neck/chest/abdomen/pelvis should be performed if PET-CT is not possible. (1B)**
13. **Men should undergo testicular ultrasonography. (1B)**
14. **All confirmed PCNSL cases should be discussed at a lymphoma MDT. Patients should receive definitive treatment as soon as possible, ideally within 14 days of diagnosis, at an established centre with multidisciplinary PCNSL expertise. (1B)**

# Treatment of Primary CNS Lymphoma

Optimal therapy of PCNSL incorporates two phases of treatment; remission induction followed by consolidation. This concept largely relates to challenges in delivering sufficient dose intensity across the blood brain barrier and the high rates of PCNSL relapse when consolidation therapy is not delivered (Ferreri 2011).

Fitness for chemotherapy should be determined by physiological fitness (organ function and comorbidities) rather than chronological age. In particular, cardiac and renal function should be adequate for delivery of high-dose methotrexate protocols (i.e. left ventricular ejection fraction >45% and creatinine clearance > 50 ml/min) (Roth*, et al* 2012, Welch*, et al* 2012, Zhu*, et al* 2009).

Performance status is frequently impaired at diagnosis of PCNSL and should not preclude intensive induction therapy. PS often improves following initial therapy which may allow subsequent intensification of therapy. Moreover, both intensive multi-agent induction and high dose therapy with autologous stem cell transplant (HDT-ASCT) approaches are feasible in selected older patients, including some >70 years (Schorb*, et al* 2017a). No validated comorbidity assessment exists to guide treatment choices. High-dose methotrexate (HD-MTX)-based protocols require adequate renal, hepatic and cardiac function and may require dose adjustment in line with institutional and manufacturer’s guidance if impaired.

In practical terms, PCNSL patients may be delineated into 3 treatment fitness groups:

* 1. Eligible for intensive combination immuno-chemotherapy incorporating high dose methotrexate (HD-MTX)
	2. Eligible for HD-MTX-based immuno-chemotherapy but ineligible for intensive combination chemotherapy
	3. Ineligible for HD-MTX-based therapy: palliative treatment (a minority of patients)

Outcomes for PCNSL patients have improved significantly over the past decade, largely as a result of alterations in management based on evidence emerging from prospective clinical trials. Patients should be offered entry into a clinical trial wherever available.

# Remission Induction

## *1. Intensive Methotrexate-Based Induction Immunochemotherapy*

Combination chemotherapy regimens incorporating HD-MTX are considered the standard of care for newly diagnosed PCNSL, resulting in high rates of initial response when combined with other agents (Ferreri*, et al* 2016, Hoang-Xuan*, et al* 2015). Penetration of MTX into the CNS is influenced by the total dose and rate of infusion. Most studies employ doses of between 3 and 8 g/m2 (Ferreri*, et al* 2016, Glass*, et al* 2016, Rubenstein*, et al* 2013) although the optimal dose has not been established. It is crucial that MTX is administered as a rapid infusion (2–4 hours) at a dose of at least 3 g/m2 to maximise therapeutic CSF concentrations, at an interval of 10–21 days, as part of an established protocol.Modern protocols typically employ 4–8 cycles of HD-MTX-based therapy. The optimal number of treatment cycles is likely to be influenced by partner chemotherapy agents, dose intensity of the regimen and intended consolidation approach, but comparative data are not available.

The IELSG20 study demonstrated the value of combining HD-MTX with partner cytotoxic agents: the addition of cytarabine (4 doses of 2 g/m2) significantly improved rates of complete response (CR) and progression free survival (PFS) as compared to HD-MTX alone (Ferreri*, et al* 2009). The randomised phase 2 IELSG32 trial subsequently demonstrated that the addition of 8 doses of rituximab (375 mg/m2) to HD-MTX/cytarabine improved response rates. Importantly, the addition of both thiotepa and rituximab to HD-MTX/cytarabine as a 4 drug regimen (MATRix; see Appendix 2) resulted in a clear improvement in overall survival (OS) over HD-MTX/cytarabine alone, with a 2-year OS rate of 69% (95% confidence interval (CI) 64–74) vs 42% (95% CI 36–48), respectively. Patients with stable disease or better after 4 cycles of MATRix were subsequently randomised to receive consolidation with whole brain radiotherapy (WBRT) or HDT-ASCT. Peripheral blood stem cells (PBSC) were successfully collected in 96% patients after 2 cycles of MATRix (Ferreri*, et al* 2016). PBSC collection after MATRix should be attempted but may be less successful if deferred beyond cycle 2 (*experience of writing group, unpublished data).*

Treatment-related mortality is around 4–7% with MATRix, with most treatment-related deaths occurring during the first treatment cycle (Ferreri*, et al* 2016, Schorb*, et al* 2017b). Within the IELSG32 study (median age 57 years), the relative dose intensity of cytarabine and thiotepa during remission induction was 78% and 76% respectively, with protocol-defined reductions predominantly for haematological toxicity. In a recent real world study of outcomes with MATRix chemotherapy (median age 61 years), 23 of 88 included patients would not have met IELSG32 eligibility criteria due to age, performance status or co-morbidities (Schorb*, et al* 2017b). Consequently, chemotherapy modifications were more frequent (40-50%) but survival rates were similar to those in IELSG32, with 2-year OS of 64%. Severe infectious complications and intensive care support were more common during cycle 1 (16%) than cycle 4 (5%). Thus, for patients considered at risk of increased toxicity (any of: ECOG PS ≥2, co-morbid conditions or age >65 years) we recommend dose reducing the myelotoxic agents in MATRix (cytarabine and thiotepa) for the initial cycle, with dynamic review cycle by cycle. In practice, a 25% reduction of cytarabine (achieved by omitting the 4th dose in the cycle) with or without a 25% dose reduction of thiotepa is a reasonable strategy. Granulocyte colony stimulating factor (G-CSF) and anti-infection prophylaxis (against herpes simplex and *Pneumocytis jirovecii* as a minimum) are recommended.

A number of alternative remission-induction regimens have been assessed in non-randomised trials, limiting reliable comparisons. Promising results have been reported with HD-MTX, temozolomide and rituximab (MT-R), with a variety of consolidation strategies (2-year PFS of 57–64%) (Glass*, et al* 2016, Rubenstein*, et al* 2013). The R-MPV regimen (HD-MTX, procarbazine, vincristine and rituximab) has also been associated with encouraging results in a number of small, non-comparative phase 2 studies (Morris*, et al* 2013, Omuro*, et al* 2015a, Omuro*, et al* 2015b). R-MBVP induction chemotherapy (rituximab, HD-MTX, BCNU (carmustine), prednisolone, etoposide) followed by either WBRT or HDT-ASCT resulted in a 2-year OS of 86% in the PRECIS trial (Houillier*, et al* 2016). A recent randomised study failed to demonstrate that adding rituximab to the same MBVP regimen improves outcomes (hazard ratio for PFS: 0.77 (95% CI 0.52-1.13, p=0.18) (Bromberg*, et al* 2017). However, a post hoc analysis showed evidence of a PFS benefit in patients aged <60 years, and those aged ≥60 years did not receive consolidation therapy; the full study publication is awaited.

Whilst rituximab and HD-MTX are internationally accepted as standard of care (Hoang-Xuan*, et al* 2015), the optimal induction regimen remains uncertain. Although a number of published protocols are associated with promising outcomes, MATRix is recommended given the higher level of randomised evidence demonstrating clear survival advantages over comparator arms.

The additional value of concurrent intrathecal chemotherapy is unproven, with conflicting data from published series (Ferreri*, et al* 2002b, Khan*, et al* 2002, Pels*, et al* 2009, Sierra Del Rio*, et al* 2012). In view of the risks and potential morbidity associated with repeated lumbar punctures, low level of available evidence, and improved efficacy of systemic therapy, we do not advocate concurrent intrathecal chemotherapy.

Surgical intervention has a very limited role in PCNSL therapy. Although a retrospective analysis of the G-PCNSL-SG-1 trial suggested that patients with subtotal or total resections had improved outcomes (Weller*, et al* 2012), this finding is likely to be influenced by patient selection bias; resection was more commonly performed for superficial lesions associated with a better prognosis (Ferreri*, et al* 2003). These findings remain controversial and have not been adopted by consensus (Hoang-Xuan et al. 2015). Given that PCNSL is considered a whole brain disease (Lai, Rosenblum, and DeAngelis 2002), therapeutic resection of PCNSL lesions should be restricted to critical circumstances where urgent surgical reduction of intracranial pressure is essential.

## *2. Less Intensive Methotrexate-Based Remission Induction*

Historically, clinical studies for PCNSL have defined ‘elderly’ patients as >60 years of age, although this cut-off has been empirically adopted without a modern evidence-base. It is clear that chronological age is not a barrier to safe delivery of HD-MTX (>3 g/m2) if physiological fitness (particularly cardiac and renal function) is deemed adequate (e.g. left ventricular ejection fraction >45% and creatinine clearance > 50 ml/min) (Roth*, et al* 2012, Welch*, et al* 2012, Zhu*, et al* 2009).

A number of phase 2 studies have focused on less myelotoxic induction regimens in patients ≥60 years, typically combining HD-MTX with orally administered alkylating agents, without WBRT consolidation (Fritsch*, et al* 2011, Hoang-Xuan*, et al* 2003, Illerhaus*, et al* 2009). Recently, the PRIMAIN study assessed HD-MTX with rituximab, procarbazine and lomustine, followed by procarbazine maintenance in patients ≥65 years (median age 73 years). The study was amended to omit lomustine due to excessive toxicity, without any clear loss of efficacy. The 2-year OS with and without lomustine was 47.9% (95% CI 30.4–65.3) and 46% (95% CI 34.1–57.8), respectively (Fritsch*, et al* 2017). A Nordic study used a modified Bonn protocol (Pels*, et al* 2003) in patients aged 65–75 years(median age 70 years), incorporating reduced dose HD-MTX-based polychemotherapy with temozolomide, followed by maintenance temozolomide for 1 year. Estimated 2-year OS was 55.6% (95% CI 35.3–71.8), which was similar to a younger cohort receiving a more intensive version of the same regimen (2-year OS 60.7%, 95% CI 43.3–74.2) (Pulczynski*, et al* 2015). The only randomised phase 2 study in patients >60 years (median age 72 years) compared HD-MTX, procarbazine, vincristine and cytarabine (MPV-A) to HD-MTX and temozolomide (MT), without rituximab. No significant difference between arms could be demonstrated with a 1-year PFS of 36% in both arms (Omuro*, et al* 2015a).

A meta-analysis evaluated individual patient data from 20 prospective and retrospective studies in PCNSL patients aged >60 years. HD-MTX-based therapy was associated with improved OS, although there was no discernible survival benefit to using intensive intravenous treatment protocols over HD-MTX combined with oral alkylating agents (Kasenda*, et al* 2015).

## *3. Palliative Therapy*

For patients considered unfit for MTX-based therapy there remains a paucity of good quality data to inform treatment decisions. WBRT, corticosteroids and oral chemotherapy are common approaches. A small retrospective study of single agent temozolomide in elderly patients with co-morbidities (n=19) showed a complete response (CR) rate of 47%, with prolonged responses (>12 months) in 29.4%, median PFS 5 months and median OS 21 months (Kurzwelly*, et al* 2010). A number of novel agents have shown promise as single agent therapy in relapsed/refractory PCNSL (see below) but there are currently insufficient data to recommend the use of these, as yet unlicensed, agents for those unfit for MTX-based therapy. In patients ≥60 years, WBRT alone (40 Gy + 20 Gy boost) gave a median survival of only 7.6 months (Nelson*, et al* 1992). Lower doses and shorter treatment durations (20–30 Gy in 1.8–4 Gy fractions) may be a more pragmatic approach as long term neurotoxicity is not the primary clinical concern. Fatigue is the most common side effect of palliative WBRT and may take several months to improve. Performance status, life expectancy and quality of life are important factors to take into consideration when discussing treatment options, including best supportive care. Key in this context are good communication and input from palliative care specialists if required; expectations of patients and their families should be carefully managed.

## *Response Assessment*

Response should be assessed by contrast-enhanced MRI with neuroradiology review according to international guidelines, as summarised in Table 2 (Abrey*, et al* 2005). The role of interim MRI has not been clearly defined, although early achievement of CR after 2 cycles of chemotherapy (of 6) appears to be associated with improved OS (Pels*, et al* 2010). Early response assessment after 1–2 cycles may also facilitate decisions regarding PBSC harvest and allow detection of early disease progression in the 8–29% who progress during first-line chemotherapy (Ferreri*, et al* 2016, Langner-Lemercier*, et al* 2016). Patients with non-progressive disease (stable disease or better) following induction therapy should be considered for consolidation therapy (Illerhaus*, et al* 2016, Soussain*, et al* 2008).

## *Recommendations*

1. **Fitness for chemotherapy should be determined by physiological fitness rather than chronological age. (1A)**
2. **Patients should be offered a clinical trial wherever possible. (1A)**
3. **For patients eligible for HD-MTX-based regimens:**
	1. **If fit for intensive therapy, offer treatment with 4 cycles of MATRix immuno-chemotherapy. (1A)**
		1. **Dose reductions should be considered for those with impaired performance status at presentation, co-morbid conditions and/or who experience significant toxicity from MATRix. (2C)**
		2. **G-CSF and prophylaxis against opportunistic infections should be employed (2C)**
		3. **For patients where HDT-ASCT is planned, PBSC collection should be attempted following cycle 2 if practicable. (1B)**
	2. **If unfit for intensive therapy, offer treatment incorporating HD-MTX, rituximab and an orally administered alkylating agent within an established protocol (e.g. R-MP, see Appendix 3). (1B)**
	3. **HD-MTX should be delivered at doses of at least 3 g/m2 with an infusion time of 2–4 hours, for a minimum of four cycles at 2–3 week intervals. (1B)**
	4. **Rituximab should be delivered at 375 mg/m2 for 8 doses (i.e. 2 doses per cycle with MATRix) (1A)**
4. **For patients ineligible for HD-MTX, consider one, or a combination, of the following treatments. (2C)**
	1. **Oral chemotherapy (such as temozolomide)**
	2. **Whole-brain radiotherapy (20–30 Gy in 1.8–4 Gy fractions according to performance status, therapeutic aims and life expectancy) +/- orbital radiotherapy if co-existing ocular involvement**
	3. **Corticosteroids (dexamethasone is typically used)**
5. **Intrathecal chemotherapy is not recommended alongside systemic CNS-directed therapy (1A) but may be considered for symptomatic control of leptomeningeal disease in patients unfit for systemic therapy. (2C)**
6. **Response assessment should be performed with contrast-enhanced MRI:**
	1. **Consider performing after cycle 1 to inform timing of PBSC collection. (2C)**
	2. **Routinely perform every 2 cycles of HD-MTX-based therapy and at the end of remission induction therapy. (1B)**

# Consolidation treatment

## *Timing of consolidation therapy*

Given the inherent difficulty in delivering optimal dose intensity across the blood brain barrier, the risk of early relapse, and the important role of consolidation in the management of PCNSL, we recommend that clinicians plan to commence consolidation therapy within 6–8 weeks of the first day of the final induction chemotherapy cycle. This is a judgement for individual clinicians and assumes that the patient’s performance status is reasonable and any significant toxicities have sufficiently resolved.

## *Radiotherapy consolidation*

The diffuse multifocal nature of PCNSL necessitates whole brain rather than targeted radiotherapy. Most protocols empirically use a WBRT dose of 30–45 Gy although it should be emphasised that the optimal total dose and role of a ‘boost’ remains uncertain, particularly in the era of more intensive remission induction protocols. WBRT has traditionally been used as consolidation following response to first-line chemotherapy (DeAngelis*, et al* 2002), but its role in the context of modern immuno-chemotherapy is less clear. A randomised phase 3 trial compared WBRT (45 Gy) with no further treatment in patients achieving CR following MTX-based chemotherapy (Korfel*, et al* 2015, Thiel*, et al* 2010). The design and conduct of this study have been criticised; only 58% patients received protocol treatment and the trial failed to meet its non-inferiority end point. Therefore it remains unclear whether WBRT consolidation can be safely omitted for patients in CR (Thiel*, et al* 2010).

Irreversible, and sometimes disabling, neurocognitive dysfunction is a well-recognised consequence of WBRT, particularly in those >60 years. Indeed, a systematic meta-analysis found no clear overall benefit, in terms of quality-adjusted life years, for WBRT in first remission in patients >60 years (Prica*, et al* 2012). In an attempt to mitigate this risk, trial strategies have investigated hyper-fractionated or lower radiation doses (Correa*, et al* 2009, Doolittle*, et al* 2013, Ferreri*, et al* 2016, Glass*, et al* 2016). Use of reduced dose radiotherapy (23.4 Gy) as consolidation for patients in CR has been explored by Morris *et al* in a non-randomised phase 2 study. In this subset of patients (n=12), survival and neurocognitive outcomes were encouraging, but the number of evaluable patients was small and definitive conclusions cannot be drawn (Morris*, et al* 2013). Randomised studies are needed to validate this approach.

Any decision to employ WBRT as consolidation should be based on high quality MRI imaging reviewed by a neuroradiologist or, ideally, following neuroradiology consensus opinion through MDT structures.

## *Chemotherapy consolidation*

Encouraging results from early studies with HDT-ASCT consolidation in PCNSL have challenged the role of WBRT as the favoured first line consolidation strategy (Illerhaus*, et al* 2006, Soussain*, et al* 2001). On an intention-to-treat basis, prospective trials of thiotepa/carmustine-conditioned ASCT after intensive induction chemotherapy have reported 3–5 year OS rates of 70–81%, where 79–92% received planned HDT-ASCT (Illerhaus*, et al* 2016, Kasenda*, et al* 2012). In the study by Illerhaus *et al* only a minority (14%) received additional WBRT. Broadly similar results have also been achieved with thiotepa, busulfan and cyclophosphamide conditioning (Houillier*, et al* 2016, Omuro*, et al* 2015b, Soussain*, et al* 2012), although no formal comparison of conditioning regimens has been conducted. Historical results with the BEAM regimen were disappointing (Abrey*, et al* 2003). In the IELSG32 study, 24 of 28 patients with partial response or stable disease after induction therapy achieved complete response following HDT-ASCT (Ferreri*, et al* 2017). Long-term survival rates, however, are lower in chemorefractory patients who fail to achieve partial remission to induction therapy (Schorb*, et al* 2013, Soussain*, et al* 2012). Survival outcomes from the prospective studies have been mirrored by a ‘real world’ UK retrospective study recently published (Kassam *et al*, BMT 2017).

Importantly, results of the first randomised trials comparing WBRT consolidation with HDT-ASCT have recently been reported. Interim analysis of the PRECIS trial reported a 2-year PFS of 63.2% (95% CI 49.5–80.5) for WBRT consolidation vs 86.8% (95% CI 76.6–98.3) after HDT-ASCT, with identical 2-year OS between the 2 arms (Houillier*, et al* 2016). The IELSG32 trial reported no significant difference in PFS or OS between WBRT and HDT-ASCT consolidation on intention-to-treat analysis (2-year OS 80% (95% CI 70–90) vs 69%, respectively (95% CI 59–79)) (Ferreri*, et al* 2017). Although longer follow up and neurocognitive results are awaited, a reduced incidence of delayed neurotoxicity is likely to favour HDT-ASCT as consolidation therapy. Notably, feasibility of consolidation with HDT-ASCT has been demonstrated in selected older patients (>65 years) by a recent European collaborative study (Schorb*, et al* 2017a).

A non-myeloablative chemotherapy consolidation approach has been investigated as an alternative to HDT-ASCT. A single arm trial of intensive EA consolidation (etoposide/cytarabine) after MT-R induction (HD-MTX/temozolomide/rituximab) reported a 4-year OS of 65%. Notwithstanding a relatively high rate of early disease progression, long-term disease control using this strategy appears broadly comparable to chemo-radiation protocols (Rubenstein*, et al* 2013). Randomised trials are ongoing to ascertain whether non-myeloablative chemotherapy approaches, such as EA or DeVIC (dexamethasone, etoposide, ifosfamide and carboplatin) (Motomura*, et al* 2011) are comparable to HDT-ASCT consolidation (NCT01511562).

## *Recommendations*

1. **Consolidation therapy should be considered for all patients with non-progressive disease following induction chemotherapy. This decision should be informed by comorbidities, performance status, neurocognitive function and patient wishes. (1B)**
2. **High-dose thiotepa-based chemotherapy with ASCT as first-line consolidation should be considered for all eligible patients. (1B)**
	1. **Patients with PCNSL achieving at least stable disease following HD-MTX-based first-line therapy should be considered for HDT-ASCT. (1B)**
	2. **BEAM should not be used as HDT-ASCT conditioning for PCNSL. (1A)**
3. **Radiotherapy consolidation**
	1. **WBRT +/- boost should be considered for:**
4. **Patients ineligible for HDT-ASCT with residual disease following induction immunochemotherapy (1B).**
5. **Patients with residual disease after thiotepa-based ASCT. (1B)**
	1. **Patients with concurrent ocular involvement should also be considered for bilateral ocular radiotherapy (see PIOL section) if ineligible for HDT-ASCT, *or* not in CR following thiotepa-based ASCT. (2B)**
	2. **For HDT-ASCT-ineligible patients in CR after HD MTX-regimens, WBRT consolidation is contentious.**
		1. **Potential improvement in PFS should be carefully balanced against risks of neurocognitive toxicity for individual patients. (1B)**
		2. **For patients ≥60 years in CR after HD MTX, either WBRT should be omitted, or lower dose WBRT consolidation may be considered given the higher risk of neurocognitive toxicity. (2B)**
	3. **Where WBRT is offered, the following dosing schedules are recommended depending on age, comorbidities and induction treatment received.**
		1. **36 Gy in 20 fractions (1B).**
			1. **Consider a 9 Gy boost with a 1–2 cm margin (total dose 45 Gy/25 fractions) to residual enhancing lesion(s) at the time of WBRT.**
			2. **Orbits should be shielded after 30 Gy (36 Gy if previously documented intraocular disease).**
		2. **Reduced dose (23.4 Gy in 1.8 or 2 Gy fractions) for selected cases at higher risk of neurotoxicity. (2C)**

# Follow-up

Around 6–25% of all relapses are asymptomatic and detected on follow-up imaging (Fossard*, et al* 2017, Langner-Lemercier*, et al* 2016, Mylam*, et al* 2017). In a large population-based retrospective study, asymptomatic patients had better performance status, which may have facilitated delivery of intensive salvage therapy, and was associated with improved outcomes. On multivariable analysis, performance status at relapse was one of the factors most strongly associated with overall survival (Langner-Lemercier*, et al* 2016). Smaller studies have not shown a clear benefit for surveillance imaging, but this may relate to the frequency and timing of surveillance (Fossard*, et al* 2017, Mylam*, et al* 2017). Prospective data are lacking. A recommended schedule for disease monitoring has been outlined in international consensus guidelines (Abrey*, et al* 2005).

## *Recommendations*

1. **Response assessment with contrast-enhanced MRI should be performed 1–2 months after completion of consolidation therapy. (1B)**
2. **Follow-up imaging with contrast-enhanced MRI may be considered, particularly in the first 2 years following treatment, in patients eligible for salvage therapies. A suggested schedule is every 3–4 months for 2 years following completion of therapy. Further surveillance MRI imaging should be judged on an individual patient basis. (2B)**

# ***Primary Intraocular Lymphoma (PIOL)***

PIOL is classified as a variant of PCNSL with its own therapeutic considerations. The optimal treatment for intraocular disease remains controversial as evidence is largely limited to retrospective and small prospective case series.

Given that CNS lymphoma is the principal cause of death in PIOL (Grimm*, et al* 2007), the potential coexistence of CNS disease should be proactively addressed within PIOL treatment algorithms. Chemotherapy agents that penetrate the blood brain barrier, particularly HD-MTX and cytarabine, also cross the blood-ocular barrier (Batchelor*, et al* 2003, Baumann*, et al* 1986, Siegel*, et al* 1989), resulting in ocular responses and persistent remissions (Grimm*, et al* 2007, Riemens*, et al* 2015). Single agent ifosfamide and trofosfamide have also been shown to have some efficacy in a small prospective study (n=10) (Jahnke*, et al* 2009). The optimal combination of these drugs is yet to be determined.

Intravitreal chemotherapy alone, usually MTX +/- rituximab (Frenkel*, et al* 2008, Larkin*, et al* 2014) can achieve remission in a proportion of patients. However, CNS relapse occurs in 33–58% patients, and ocular toxicity is reported in 26–36% (Grimm*, et al* 2007, Riemens*, et al* 2015), hence, systemic PCNSL regimens should be employed. A limited number of small retrospective and single arm studies have reported promising outcomes with a combined intravitreal and systemic approach (Ma*, et al* 2016). However, randomised data are absent and given the potential for additional ocular toxicity this approach cannot be routinely recommended.

Irrespective of treatment modality used, relapse rates remain high (Grimm*, et al* 2007, Nguyen*, et al* 2016, Riemens*, et al* 2015) therefore consolidation therapy is recommended. Both ocular radiotherapy (usually incorporating both globes +/- WBRT) (Ferreri*, et al* 2002a) and HDT-ASCT (Soussain*, et al* 2001) can induce durable remissions in PIOL. At present there are insufficient data to recommend one consolidation strategy over another.

## *Recommendations*

1. **PIOL should be treated with systemic HD-MTX based combination chemotherapy with rituximab. For fit patients, consider using evidence-based PCNSL induction protocols such as the MATRix regimen. (1C)**
2. **Intravitreal MTX (administered by a specialist ophthalmologist) can be considered for elderly patients with isolated PIOL who are unfit for systemic therapy. (2C)**
3. **Concurrent intravitreal therapy, for patients receiving a systemic HD-MTX regimen, cannot be routinely recommended. (2C)**
4. **For PIOL patients who have responded to intensive systemic chemotherapy, the following consolidation options should be considered:**
	1. **For eligible patients, high-dose thiotepa-based chemotherapy with ASCT**
	2. **Bilateral orbital radiotherapy (up to 36 Gy in 1.8–2 Gy fractions). WBRT (23.4–30 Gy in 1.8–2 Gy fractions) should be considered but needs to be carefully balanced against risks of neurocognitive toxicity for individual patients. (2B)**

# Relapsed and refractory PCNSL

Treatment of relapsed and refractory (R/R) PCNSL remains a major area of unmet clinical need. The prognosis of R/R PCNSL is very poor with a median OS of 3.5 months (Langner-Lemercier*, et al* 2016). Published studies of salvage therapy for R/R PCNSL comprise small, non-randomised and often retrospective analyses, with low quality evidence and thus no established standard of care. Studies of non-myeloablative chemotherapy, either single-agent or combination approaches, typically report dismal outcomes with response rates of 30–55% and median PFS of 2–11 months (Grommes and DeAngelis 2017). Consequently, patients should be offered clinical trial entry wherever available.

Ifosfamide-based salvage regimens, usually in combination with etoposide +/- carboplatin and rituximab (R-IE and R-ICE), have resulted in overall response rates of 41–95% in predominantly chemorefractory or heavily treated patient cohorts (Choi*, et al* 2013, Choquet*, et al* 2015, Langner-Lemercier*, et al* 2016, Mappa*, et al* 2013, Motomura*, et al* 2011). For patients who experience durable first remissions following HD-MTX-based protocols, re-treatment with HD-MTX-based regimens may be effective, although the effectiveness of this approach is much more uncertain in the modern-era of intensified MTX-containing regimens. Two retrospective studies described a median PFS of 16 and 25.8 months after re-treatment with HD-MTX at relapse, usually as part of multi-agent salvage regimens, in patients who had experienced as median duration of response to first-line HD-MTX of 24.4 and 26 months (Pentsova*, et al* 2014, Plotkin*, et al* 2004). This may be particularly relevant for MTX-experienced, but rituximab- and thiotepa-naïve, patients for whom the more intensive MATRix protocol may be an option, although it should be noted that currently no published data exist for MATRix in R/R PCNSL. Encouraging results have been achieved with a number of novel agents, with response rates >50% observed with single agent ibrutinib (Chamoun*, et al* 2017, Grommes*, et al* 2017, Lionakis*, et al* 2017) and nivolumab (Nayak*, et al* 2017). Lenalidomide also crosses the blood brain barrier and appears to have activity in PCNSL when combined with rituximab (Ghesquieres*, et al* 2016, Rubenstein*, et al* 2016). However, these agents are not yet licensed for this indication and survival data are immature.

For eligible, chemosensitive patients, available data support the use of thiotepa-based HDT-ASCT in R/R PCNSL, with a median PFS of 24-41 months reported (Kasenda*, et al* 2017, Soussain*, et al* 2012, Soussain*, et al* 2008). Either HDT-ASCT or WBRT should be considered in second remission if not undertaken as first-line consolidation therapy. WBRT alone (median dose 36–40 Gy) can result in CR rates of 37–58% and a median survival of 10–16 months in radiotherapy-naïve patients who are refractory to, or relapse after, HD-MTX therapy (Hottinger*, et al* 2007, Khimani*, et al* 2011, Nguyen*, et al* 2005).

## *Recommendations*

1. **All patients with suspected PCNSL relapse should be reviewed urgently within regional MDT meetings. The primary treating Haemato-oncology team should be promptly informed. (1C)**
2. **Re-biopsy at relapse is recommended in the context of atypical MRI appearances, or for new brain lesions occurring beyond 2 yearsfrom initial therapy, particularly if intensive salvage therapy is planned. (2C)**
3. **Patients with a confirmed diagnosis of relapsed PCNSL should undergo complete re-staging if further therapy is planned. Re-staging is not usually necessary for PCNSL refractory to first-line therapy. (1C)**
4. **Wherever possible, patients should be offered participation in a clinical trial. (1C)**
5. **Outside of clinical trials, potential treatment options should be individualised (1C), taking account of:**
	* 1. **Physiological fitness, performance status and neurocognitive function**
		2. **Previous therapy and duration of response**
		3. **Patient choice**
6. **For patients eligible for intensive treatment: (see figure 1)**
	* 1. **Consider ifosfamide-based immunochemotherapy, particularly for refractory disease or early relapse after MTX-based immunochemotherapy. (2B)**
		2. **Consider HD-MTX-based immunochemotherapy if the duration of first remission to HD-MTX-based therapy was >2 years. (2B)**
7. **Consolidation following salvage chemotherapy:**
	1. **Patients who have not previously undergone HDT-ASCT should be considered for thiotepa-based HDT-ASCT in second or subsequent response (1B)**
	2. **WBRT-naive patients who are ineligible for, or have previously undergone, HDT-ASCT should be considered for WBRT (23.4–36 Gy in 1.8–2 Gy fractions), either alone or following salvage chemotherapy. (2C)**
8. **Patients ineligible for intensive treatment:**
	1. **Palliative treatment should be offered, which may include WBRT (23.4–36 Gy in 1.8–2 Gy fractions), corticosteroids and/or oral temozolomide. (2C)**
	2. **Patients should receive best supportive care and, where appropriate, palliative care input. (1B)**

# Neuropsychological Assessments

Cognitive impairment is a feature of PCNSL, with inevitable heterogeneity in neuropsychological deficits being associated with different tumour locations. In some patients there may also be unilateral weakness affecting motor function and/or behavioural syndromes such as disinhibition or apathy, which may influence test selection or approach during assessments.

Elucidating the cognitive effects of disease versus treatment is difficult due to methodological limitations of published studies, including lack of baseline cognitive assessments and control groups, and variable disease status. The type of treatment and age are important considerations. In a review of 17 studies, cognitive impairment was found in most PCNSL patients treated with WBRT plus chemotherapy whereas patients treated with chemotherapy alone had either stable or improved cognitive performance (Correa*, et al* 2007). In the longest observational study of 80 PCNSL survivors in CR, patients receiving WBRT had lower mean scores in attention/executive function, motor skills and overall neuropsychological composite score compared with those treated without WBRT (Doolittle*, et al* 2013). Treatment-related cognitive morbidity is also associated with a lower quality of life and poor prognosis (Doolittle*, et al* 2013, Prica*, et al* 2012).

There is no consensus on the optimal neurocognitive test battery for PCNSL patients, or on the interval at which follow-up neurocognitive assessments should be performed. Baseline and serial mini mental state examination has been suggested as a minimum requirement (Abrey*, et al* 2005). Table 3 shows the proposed minimum core battery for the assessment of neuropsychological functions and quality of life in PCNSL patients recommended by Correa *et al* and proposed alternative measures for UK patients. The battery can be completed within 30–40 minutes and has been incorporated into prospective trials (Correa*, et al* 2007).

Given the cognitive, psychological and physical effects of both CNS lymphoma and its treatment, it is important that holistic needs are addressed during treatment and throughout the recovery period. Early referral to support services and specialist therapies should be considered according to individual patient need.

## *Recommendations*

1. **Cognitive and quality of life outcomes should be assessed in all patients with PCNSL before and after treatment, with ongoing long-term monitoring.**
2. **As a minimum, all patients receiving treatment for PCNSL should be assessed on cognitive domains of attention, processing speed, motor speed, executive function and memory before and after treatment.**

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# Review Process

Members of the writing group will inform the writing group Chair if any new pertinent evidence becomes available that would alter the strength of the recommendations made in this document or render it obsolete. The document will be archived and removed from the BSH current guidelines website if it becomes obsolete. If new recommendations are made an addendum will be published on the BSH guidelines website (https://b-s-h.org.uk/guidelines/).

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While the advice and information in this guidance is believed to be true and accurate at the time of going to press, neither the authors, the BSH nor the publishers accept any legal responsibility for the content of this guidance.

# Author Contributions

All authors reviewed the literature and contributed to the drafting and editing of this manuscript

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**Figure 1. Relapsed/refractory PCNSL algorithmAbbreviations:** ASCT, autologous stem cell transplant; CR, complete response; MTX, high dose methotrexate; PD, progressive disease; PR, partial response; PS, performance status; SD, stable disease; WBRT, whole brain radiotherapy

**YES**

**YES**

**NO**

**NO**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Histology** | **Imaging** | **Clinical evaluation** | **Laboratory evaluation** | **CSF analysis\*** |
| **Essential** | Tissue diagnosis: | Gadolinium enhanced MRI brain\* | Physical examination including full neurological assessment | Renal and liver function |  |
| a) Stereotactic or surgical biopsyb) Vitrectomy specimen (if PIOL suspected)c) CSF (if no other diagnostic material) | Systemic cross-sectional imaging (PET-CT preferred but contrast-enhanced CT of neck to pelvis acceptable) | Full medical history and drug history, including corticosteroid use | Serum LDH |
| Testicular ultrasound | Performance status | Creatinine clearance |
| Gadolinium-enhanced MRI spine | Ophthalmological examination with fundoscopy and slit-lamp examination | HIV, hepatitis B (including core Ab) and C serology |
| Baseline MMSE |
|  |
| **Desirable** | Bone marrow trephine and aspirate§ | Whole body FDG-PET§ | Formal neuropsychological assessment (see Table 2) |  | CSF protein |
| Assessment of LVEF if indicated | Cytology assessment |

**Table 1: Pre-Treatment Investigations and Staging for PCNSL**

\*unless contraindicated. §strongly encouraged unless likely to cause treatment delay

Abbreviations: Ab, antibody; CSF, cerebrospinal fluid; CT, computed tomography; FDG, fluorodeoxyglucose; HIV, human immunodeficiency virus; LDH, lactate dehydrogenase; LVEF, left ventricular ejection fraction; MMSE, mini mental state evaluation; MRI, magnetic resonance imaging; PET, positron emission tomography.

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

**Table 2: Response Criteria for Primary CNS Lymphoma.** Adapted from the Report of an International Workshop to Standardize Baseline Evaluation and Response Criteria for Primary CNS Lymphoma (Abrey*, et al* 2005)

Abbreviations: CNS, central nervous system; CR, complete response; CRu, unconfirmed complete response; CSF, cerebrospinal fluid; PR, partial response; PD, progressive disease; RPE, retinal pigment epithelium; SD, stable disease.

|  |  |  |
| --- | --- | --- |
| **Domain** | **Tests recommended by Correa *et al* (Correa*, et al* 2007)** | **Tests recommended for use with UK patients** |
| Premorbid IQ Estimation  | Barona Index (1)  | National Adult Reading Test-Revised (8) ***or*** Test of Premorbid Functioning (9) |
| Attention/Executive  | WAIS-III (2) Digits Forward and Backward Span; Trail Making Test (Parts A and B) (3) | WAIS-IV Digits Forward, Backward Span and Sequencing Span (10); Trail Making Test (Parts A and B) |
| Verbal Memory | Hopkins Verbal Learning Test-Revised (4) | Hopkins Verbal Learning Test-Revised orCalifornia Verbal Learning Test Standard Form  |
| Motor | Grooved Pegboard Test (5) | Grooved Pegboard Test  |
| Quality of life | EORTC-QLQ-C30 (6)BCM 20 (7) | EORTC-QLQ-C30BCM 20 |

**Table 3: Proposed Baseline and Follow-Up Neuropsychological Evaluations in PCNSL**

EORTC-QLQ-C30, The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C-30; BCM 20, Brain Cancer Module 20; IQ, intelligence quotient; WAIS-III, Wechsler Adult Intelligence Scale Third Edition; WAIS-IV, Wechsler Adult Intelligence Scale Fourth Edition

1. (Barona*, et al* 1984),
2. (Wechsler 1997)
3. (Reitan and Wolfson 1985)
4. (Benedict*, et al* 1998)
5. (Russell and Starkey 1993)
6. (Aaronson*, et al* 1993)
7. (Osoba*, et al* 1996)
8. (Nelson and Willison 1991)
9. (Wechsler 2011)
10. (Wechsler 2008)
11. (Delis*, et al* 2000)