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Guidelines on the diagnosis and management of adult patients with primary CNS lymphoma (PCNSL) and primary intra-ocular lymphoma (PIOL)

British Committee for Standards in Haematology

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Introduction

The guideline group was selected to be representative of UK based medical experts and patients representatives. MEDLINE and EMBASE were searched systematically for publications in English from 1950 - April 2007 using key words: CNS and intraocular lymphoma. The writing group produced the draft guideline, which was subsequently revised by consensus by members of the Haemato-Oncology Task Force of the British Committee for Standards in Haematology. The guideline was then reviewed by a sounding board of approximately 60 UK haematologists, the BCSH (British Committee for Standards in Haematology) the British Society for Haematology Committee and the NCRI Lymphoma Clinical Studies Group comments incorporated where appropriate. Criteria used to quote levels and grades of evidence are as outlined in appendix 3 of the Procedure for Guidelines Commissioned by the BCSH

(<http://www.bcsguidelines.com/process1.asp#App3>)

The objective of this guideline is to provide healthcare professionals with clear guidance on the management of adult patients with primary CNS and intra-ocular lymphoma. The guidance may not be appropriate to all patients and individual patient circumstances may dictate an alternative approach.

Summary of key recommendations

- 1. Diagnosis of PCNSL should always be confirmed histologically. When PCNSL is suspected, stereotactic biopsy is the preferred surgical procedure. Surgical resection has no role to play in the treatment of PCNSL. Biopsy samples for PCNSL and PIOL should be subjected to central pathological review. Every effort should be made to avoid corticosteroid therapy prior to biopsy (grade C, level IV).**
- 2. Staging should include CT scanning of chest, abdomen and pelvis; testicular ultrasonography in elderly males; lumbar puncture for CSF protein/glucose quantification, cytology, flow cytometric analysis and immunoglobulin gene rearrangement studies; and examination of the anterior chamber of the eye, vitreous and ocular fundus. Intraocular lesions should be biopsied, and HIV infection should be confirmed or excluded in all patients (grade C, level IV).**

- 3. A prognostic score should be calculated based upon age >60 years, performance status >1, raised LDH, raised CSF protein and involvement of deep brain matter (grade C, level IV)**
- 4. Patients and relatives should be warned of the risk of neurocognitive deterioration when consent for treatment is being obtained (grade C, level IV)**
- 5. Dexamethasone is the treatment of choice for short-term palliation but should be avoided before biopsy (grade C, level IV)**
- 6. Whole brain radiotherapy can provide effective palliation but should not be used as first-line therapy in patients who are sufficiently fit to receive chemotherapy (grade B, level III)**
- 7. There is no role for CHOP-like chemotherapy in the treatment of primary CNS lymphoma (grade A, level 1b)**
- 8. All patients should be offered chemotherapy as first line treatment if they are sufficiently fit. Chemotherapy should consist of a regimen that includes HD-MTX (3-5 doses of $\geq 3\text{g/m}^2$ delivered over a maximum of 2-3 hours at intervals of not more than 2-3 weeks). The efficacy of HD-MTX may be improved by using it in combination with other CNS-penetrating chemotherapeutic agents such as cytarabine but such treatment should be based on established protocols and should ideally be given within the framework of a clinical trial (grade B, level IIa)**
- 9. Consolidation WBRT should be considered in patients who achieve CR with MTX-based chemotherapy. In patients under 60 years of age, WBRT should be offered to patients unless there is a significant neurocognitive deficit following chemotherapy. In patients aged 60 years or over, neurocognitive side-effects are more likely to outweigh potential benefits (grade B, level IIa)**
- 10. There is no evidence supporting a role for intrathecal chemotherapy as an adjunct to high-dose intravenous MTX in patients with PCNSL (grade B, level III)**

- 11. First line treatment with high-dose chemotherapy and autologous stem cell transplantation remains experimental and should not be conducted outside clinical trials (grade B, level III):**
- 12. Rituximab administered via the intrathecal or intraventricular route should not be used in the routine treatment of PCNSL except in a clinical trial (grade B, level III):**
- 13. Pharmacological disruption of the blood-brain barrier should not be performed as part of the treatment of PCNSL unless as part of a clinical trial (grade B, level IIb):**
- 14. Relapsed or refractory disease should be treated with salvage radiotherapy in patients who have not previously received WBRT. Dexamethasone should be considered for short-term palliation. Alternative chemotherapeutic regimens such as temozolomide or high-dose chemotherapy with autologous stem cell transplantation show promise but require further evaluation in clinical trials (grade B, level III)**
- 15. Concurrent intraocular and CNS lymphoma should be treated with systemic HD-MTX-based chemotherapy followed by radiation to both globes and possibly also the brain if the patient is less than 60 years old. Isolated intraocular disease should be treated in the same way. Intravitreal MTX is an effective treatment option for patients with recurrent disease confined to the eyes (grade B, level III)**

1. Background

Primary central nervous system lymphoma (PCNSL) is an aggressive form of non-Hodgkin's lymphoma (NHL) arising in and confined to the brain, spinal cord, leptomeninges, retina, vitreous humour and, occasionally, optic nerve (Batchelor, 2004). The ocular manifestation of PCNSL is termed primary intraocular lymphoma (PIOL). PIOL is a variant of PCNSL that can appear prior to, concurrent with, or subsequent to other PCNSL. Although rare, the incidence of both PCNSL and PIOL seems to be increasing. Over the last three decades survival has improved, thanks to the introduction of methotrexate (MTX)-based combination chemotherapy; however, long-term treatment-related neurological toxicity remains a major problem. The role of consolidation radiotherapy is controversial. These guidelines attempt to provide an evidence-based approach to the management of PCNSL, including its ocular component.

2. Epidemiology

The incidence of PCNSL has trebled over the last 30 years and in the USA is now 4.8 per million population per year. This disease accounts for approximately 5% of all primary brain tumours (Olson et al, 2000). Most series show a slight male preponderance with most patients aged 60 years or more. A recent European study suggests an incidence of 2.7 per million population (Van der Sanden et al, 2002) and this was supported by a recent UK study, which reported an incidence of 2.8 per million population per year (Hodson et al, 2005). The increase in the incidence of PCNSL cannot be explained solely by improved diagnostic technology because the incidence of other cerebral tumours has not shown a similar increase. Neither can it be explained by the human immunodeficiency virus (HIV) epidemic since the trend is also observed in populations with a low prevalence of HIV, and it far outpaces the increase seen in other HIV-related malignancies, such as Kaposi's sarcoma (Olson et al, 2000). Nevertheless, within the HIV+ population, NHL is the second most common malignancy, and PCNSL accounts for 20% of such cases (Knowles, 2003). Prior to the advent of highly active anti-retroviral treatment, it was estimated that individuals with HIV infection were 3600 times more likely to develop PCNSL than the general population (Cote et al, 1996).

3. Diagnosis

PCNSL is an aggressive high-grade malignant lymphoma, and patients usually present with neurological symptoms developing over a few weeks. A large survey of 248 patients presenting with PCNSL showed that 70% had focal neurological defects, 33% raised intracranial pressure, 14% seizures, and 4% ocular symptoms (Bataille et al, 2000). Headache is a rare complaint, whereas behavioural changes are common. Up to 20% of patients with PCNSL present with ocular involvement, which masquerades as steroid-resistant posterior uveitis. This is usually bilateral, and is often associated with painless loss of vision and/or vitreous “floaters” (Coupland et al. 2004).

Radiology usually reveals a mass lesion, which is multifocal in over a third of cases. Contrast enhancement is a feature in 80-90% of patients by computerised tomography (CT) scanning and in nearly all patients by magnetic resonance imaging (MRI) (Kuker et al, 2005). The frontal lobe is the most common site of involvement but PCNSL also has a predilection for the corpus callosum, basal ganglia and deep periventricular structures. Diffuse brain abnormality with no mass lesion has also been described. PCNSL is frequently not suspected on the basis of its radiological appearance, which may closely mimic other CNS tumours (Heckmann et al, 2000).

Diagnosis of PCNSL requires morphological, immunohistochemical and, possibly, molecular genetic studies. Tissue is preferentially acquired through stereotactic brain biopsy rather than surgical resection. Treatment with surgery alone is associated with a very short survival of 1-4 months (Henry et al, 1974; Murray et al, 1986; Bellinzona et al, 2005). In about 90% of cases, PCNSL can be sub-typed as a diffuse large B-cell lymphoma (DLBCL), according to the WHO Lymphoma Classification. The remainder are a mixture of Burkitt's lymphoma, T-cell rich B-cell lymphoma, peripheral T-cell lymphoma and rarely 'low-grade' B-cell lymphoma (Miller et al, 1994; Jahnke et al., 2005a). Leucocyte common antigen (CD45) is useful in distinguishing PCNSL from high-grade glioma and metastatic carcinoma. The immunophenotype of PCNSL of DLBCL sub-type is

the following: CD79a+, CD20+, PAX-5+, BCL-2+, MUM1/IRF4+, BCL-6+/- and CD10-/+ , with the tumour cells having a high growth fraction (Ki-67, circa 90%) (Coupland et al., 2005a). BCL-6 expression was associated with improved survival in patients with PCNSL in one series (Braaten et al, 2003). A high frequency of somatic mutation of the variable region of the immunoglobulin gene (V_H) has been reported in PCNSL and its intraocular counterpart, with a limited germline V_H gene usage (e.g. V_H4-34) being apparent (Montesinos-Rongen et al., 1999; Coupland et al., 2005b). The high frequency of somatic mutations in the V_H genes, together with the tumour-cell immunophenotype (as above), suggests that PCNSL is derived from mature B cells that have undergone a prolonged interaction with the germinal centre microenvironment and are either at the late germinal centre stage of differentiation or the early post-germinal centre stage.

Should the ocular manifestation of PCNSL occur prior to detection of cerebral involvement, the diagnosis is achieved by performing a vitreous biopsy, preferably combined with a sub-retinal aspirate or a chorioretinal biopsy. The vitrectomy specimens are notoriously paucicellular and “difficult”, so that diagnostic failure rates up to 30% have been reported. These specimens, which should be sent rapidly in cytofixatives, are examined for morphology, immunophenotype and rearrangements of the immunoglobulin and/or T-cell receptor genes using the polymerase chain reaction (IgH and/or TCR-PCR, respectively), depending on the amount of material available for examination (Coupland et al. 2004). In patients with visible subretinal deposits, taking additional chorioretinal biopsies and aspirates improves diagnostic accuracy (Coupland et al. 2004).

Because of the rarity of PCNSL and the scanty diagnostic material usually obtained, biopsy samples in suspected PCNSL and PIOL should be subjected to central pathological review. These should be sent as rapidly as possible to the examining laboratory. Steroid therapy should be avoided prior to biopsy, unless there is rapid neurological deterioration when they should be used for a short a period as possible since such treatment may induce rapid transient tumour regression and increase cellular fragility, thereby rendering the biopsy samples difficult to process and to interpret.

Recommendation (grade C, level IV): Diagnosis of PCNSL should always be confirmed histologically. When PCNSL is suspected, stereotactic biopsy is the preferred surgical procedure. Surgical resection has no role to play in the treatment of PCNSL. Biopsy samples for PCNSL and PIOL should be subjected to central pathological review. Every effort should be made to avoid corticosteroid therapy prior to biopsy.

4. Staging and other investigations

The International PCNSL Collaborative Group (IPCG) has recently published guidelines on standardized baseline evaluation of patients with newly diagnosed PCNSL (Abrey et al, 2005). Staging has two purposes: to define the extent of central nervous system (CNS) involvement and to exclude disease outside the CNS. By definition, systemic disease is not a feature of PCNSL. However, up to 12.5% of patients presenting with disease apparently confined to the CNS are found to have extra-neural involvement (O'Neill et al, 1995; Ferreri et al, 1996; Loeffler et al, 1985). A full body CT scan is, therefore, mandatory together with a bone marrow aspirate and trephine biopsy. Elderly males should also undergo testicular ultrasound examination, because testicular lymphoma has a high risk of CNS involvement.

Given the tendency of PCNSL to involve the leptomeninges, a lumbar puncture should be performed unless contraindicated due to the risk of coning. The cerebrospinal fluid (CSF) should be analysed cytologically and by flow cytometry, protein and glucose concentrations should be measured and IgH-PCR should be performed. Typical CSF abnormalities include a raised protein concentration, a reduced glucose concentration and a raised white cell count. Cytology reveals abnormal, pleomorphic lymphocytes in 15–31% of cases (Fitzsimmons et al, 2005; Balmaceda et al, 1995), although the frequency is much higher at autopsy (Onda et al, 1999). The finding of a clonal B lymphocytosis in the CSF in conjunction with typical radiology is strongly suggestive of a diagnosis of PCNSL

but does not obviate the need for a brain biopsy. Consideration should also be given to a single instillation of intrathecal methotrexate at this time

Ophthalmic involvement should be sought by non-invasive procedures such as slit lamp examination and ophthalmoscopy, and confirmed by invasive procedures, including vitreous biopsy, subretinal aspiration and/or chorioretinal biopsy, as outlined above (Coupland et al. 2004). Given the strong association with HIV infection, it is important to bear in mind the possibility that intraocular lesions in a patient with PCNSL might be due to opportunistic infection rather than PIOL. Intraocular biopsy is indicated also when a patient is suspected to have primary or recurrent intraocular lymphoma.

In view of the strong association between PCNSL and HIV infection, HIV serology should also be performed in all patients. Table 1 summarises the baseline investigations recommended by the IPCG.

Recommendation (grade C, level IV): Staging should include CT scanning of chest, abdomen and pelvis; testicular ultrasonography in elderly males; lumbar puncture for CSF protein/glucose quantification, cytology, flow cytometric analysis and immunoglobulin gene rearrangement studies; and examination of the anterior chamber of the eye, vitreous and ocular fundus. Intraocular lesions should be biopsied, and HIV infection should be confirmed or excluded in all patients.

5. Prognostic scoring systems

The prognosis of patients with PCNSL varies markedly between different reported series. Patients considered unfit for chemotherapy have a median survival of just six weeks (Hodson 2005). Those treated with radiotherapy alone have a median survival of about 12 months while the most successful chemotherapy regimens achieve a median survival of up to 60 months (De Angelis et al, 2000). Much of this variability in prognosis is probably

caused by selection bias. To compare different studies and to predict the outcome for individual patients, some form of prognostic scoring stratification is required.

The International Prognostic Index (IPI) used for systemic lymphoma is of limited use in PCNSL because two variables – stage and number of extranodal sites - will by definition be constant in all cases. Bessell et al (2004) proposed the Nottingham/Barcelona scoring system to generate a score between 0 and 3 based on the following:-

- *age >60 years*
- *ECOG performance status >2*
- *extent of disease (multifocal versus unifocal)*

This scoring system was examined retrospectively in 77 patients with PCNSL treated with either BVAM (carmustine, vincristine, cytarabine and MTX) or CHOD (cyclophosphamide, doxorubicin, vincristine, dexamethasone)/BVAM and whole brain radiotherapy (WBRT). Poor survival correlated with a higher score, median survivals being 55, 41, 32 and 1 month for scores of 0, 1, 2, and 3 respectively.

Ferreri et al. (2003) proposed an alternative prognostic scoring system using the following:-

- *age >60 years*
- *ECOG performance status >1*
- *raised lactate dehydrogenase (LDH)*
- *raised CSF protein*
- *tumour involvement of deep brain matter.*

This was applied retrospectively to 378 immunocompetent PCNSL patients treated at 23 centres. Risk of death was categorized as high (score 4-5), medium (score 2-3) or low risk (score 0-1). Two-year overall survival rates were 15%, 48% and 80% respectively. Although potentially useful, this prognostic index requires confirmation using a separate cohort of patients.

Recommendation (grade C, level IV): A prognostic score should be calculated based upon age >60 years, performance status >1, raised LDH, raised CSF protein and involvement of deep brain matter.

6. Treatment of PCNSL

The optimal treatment for patients with PCNSL is poorly defined, because of a lack of randomised phase III trials. Most PCNSL trials have been small single-arm phase II studies. Comparing such studies is fundamentally flawed as differences in outcome could be biased by patient selection criteria.

Therapeutic options for PCNSL include steroid therapy, radiotherapy and chemotherapy. A proposed treatment algorithm is shown in Figure 1. Standardized response assessment criteria have recently published by the IPCG (Abrey et al, 2005) (Table 2). One of the most important adverse effects of CNS-directed radiotherapy and combined modality therapy is neurocognitive impairment. A key objective in treating PCNSL is to achieve the right balance between long-term disease control and neurotoxicity. This is a particular issue with older patients.

Recommendation (grade C, level IV). Patients and relatives should be warned of the risk of neurocognitive deterioration when consent for treatment is obtained.

Glucocorticoids. PCNSL tends to be highly sensitive to steroid therapy (Weller et al, 1999). Radiographically, resolution of disease is detectable within 48 hours of treatment. This response is usually short lived, however, with disease recurrence occurring soon after steroid withdrawal (DeAngelis et al, 1990). A response to steroid is not diagnostic of PCNSL, as similar improvement can be seen in patients with conditions such as neurosarcoidosis and multiple sclerosis. Steroid treatment should, if possible, be avoided before tissue biopsy, because the treatment can interfere with histopathological assessment. To prevent a false-negative result, biopsy should be performed only after a steroid-free interval. This approach risks a recurrence of tumour, which may progress before formal chemotherapy can be started.

Recommendation (grade C, level IV): Dexamethasone is the treatment of choice for short-term palliation but should be avoided before biopsy.

Radiotherapy. Because PCNSL is almost always multifocal, radiotherapy is usually given to the entire brain. A multi-centre prospective trial of whole brain radiotherapy (36-40 Gy) as primary therapy in 41 patients with PCNSL showed an overall response rate of 90%, with nearly 50% of patients achieving complete remission (CR) or near CR. However, 61% of patients relapsed within the radiation field, and the median survival was only 11.6 months (Nelson et al, 1992). In a recent Japanese review of 132 patients with PCNSL treated with WBRT, the median overall survival was 18 months with 39% of patients surviving at least two years. It is difficult to draw firm conclusions from this study, however, as it was retrospective and the radiotherapy was not standardised (Shibamoto et al, 2005).

The main disadvantage of WBRT is its neurotoxicity. This presents as dementia, ataxia and urinary incontinence, and is associated with MRI evidence of leucoencephalopathy, which tend to develop after a delay of several years (DeAngelis et al, 2001; Fitzsimmons et al, 2005; Batchelor & Loeffler, 2006). Neurotoxicity is more common after WBRT than after high-dose systemic MTX, and the risk is particularly high in patients who receive

combined modality therapy, especially if the radiotherapy is given after MTX (Correa et al, 2004).

Because of its limited long-term efficacy and its propensity to cause delayed neurotoxicity, WBRT alone cannot be recommended as first-line treatment of PCNSL except as palliation.

Recommendation (grade B, level III): Whole brain radiotherapy can provide effective palliation but should not be used as first-line therapy in patients who are sufficiently fit to receive chemotherapy.

CHOP-like chemotherapy. The addition of CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) to radiotherapy has improved survival in localised aggressive NHL occurring outside the brain. Several studies have examined this approach in PCNSL but have not demonstrated a survival advantage. A prospective RTOG (Radiation Therapy Oncology Group) trial treated patients with CHOD and WBRT, achieving a median survival of 16.1 months (Schultz et al, 1996). An MRC randomised trial (Mead et al, 2000) of 53 PCNSL patients showed a trend towards worse survival in the group randomised to CHOP and WBRT compared with those receiving WBRT alone (median survival 14 vs 26 months). Lahance et al, (1994) showed that although CHOP may induce an initial tumour response it was associated with a median survival of only 8.5 months. This was because of early relapse, which tended to be at sites remote from the original tumour.

CHOP chemotherapy is ineffective for PCNSL probably because it cannot cross the intact blood-brain barrier. Initially, lymphoma may disrupt the blood-brain barrier, allowing penetration of chemotherapeutic agents. However, effective treatment of the tumour may restore the blood-brain barrier, leading to incomplete resolution of disease.

Recommendation (grade A, level 1b): There is no role for CHOP-like chemotherapy in the treatment of primary CNS lymphoma.

High-dose systemic methotrexate (HD-MTX). Autopsy studies of PCNSL patients reveal widespread microscopic lymphoma deposits throughout areas of the brain that are apparently normal on MRI (Lai et al, 2002). To be effective, therefore, chemotherapy must be able to cross the normal blood-brain barrier and penetrate the brain parenchyma. This is possible with systemic MTX, in contrast to CHOP-like chemotherapy. To achieve therapeutic concentrations of MTX in the brain, high doses are required (i.e. at least $1.5\text{g}/\text{m}^2$). The steady-state blood:CSF ratio is about 30:1 (Shapiro et al, 1975), so that tumoricidal levels in the CSF are achieved with doses above $3.5\text{g}/\text{m}^2$. A three-hour infusion achieves higher CSF levels than slower infusions (Higara et al, 1999). CSF penetration is important because of the high frequency of meningeal involvement, even in the absence of a detectable CSF lymphocytosis.

Ferreri et al. (2003) examined 45 patients treated with MTX (doses between 1 and $3.5\text{g}/\text{m}^2$) and showed that outcome correlated positively with calculated area under the curve, which was in turn affected by creatinine clearance, MTX dose, rate of administration and dosing intervals (more or less than 3–4 weeks). Glass et al. (1994) showed dosing intervals of 10 days and 3 weeks to be equivalent. These findings support the use of MTX $> 3\text{g}/\text{m}^2$ delivered over not more than 3 hours at 2-3 week intervals. Although HD-MTX as a single agent without radiotherapy is effective at inducing remissions, two recent studies have shown a high rate of early relapse with median times of 12.8 months (Batchelor et al, 2003) and 13.7 months (Herrlinger et al, 2002). Glass et al. (1994) treated 25 patients with 1 – 6 courses of MTX $3.5\text{g}/\text{m}^2$ prior to radiotherapy and achieved a median survival of 33 months. O'Brien et al. (2000) treated 46 patients (median age 58 years) with two courses of MTX prior to WBRT and reported a median survival of 36 months.

HD-MTX can be safely given to elderly patients provided that due attention is given to the creatinine clearance. In a report by Jahnke et al. (2005), 154 patients received 619 cycles

of HD-MTX followed by leukovorin rescue. MTX was given at $4\text{g}/\text{m}^2$ but with attenuation if the creatinine clearance was reduced. Toxicity was generally mild and not significantly higher among the 89 patients aged > 60 years, although older patients received a lower dose on average. The EORTC 26952 trial examined single-agent HD-MTX in 50 patients over the age of 60 years with PCNSL. The main complication was myelosuppression, with grade III/IV neutropenia occurring in 19% of cases. The CR rate was 48%, one-year progression-free survival 40% and median overall survival time 14.3 months. Most patients improved or preserved their cognitive function until relapse (Hoang-Xuan et al, 2003). These results compare favourably with those achieved with WBRT.

Combination chemotherapy based on HD-MTX. The efficacy of HD-MTX might be improved by combining it with other CNS-penetrating chemotherapeutic agents. Several Phase II studies of combination regimens containing HD-MTX have shown relatively good median survival times of between 30 and 60 months; however, the results are complicated by the fact that some studies also added consolidation radiotherapy.

Bessell et al. (2002) reported a median survival of 38 months in 31 consecutive patients (median age 59 years) treated with one cycle of CHOD followed by two cycles of BVAM (carmustine, vincristine, cytarabine and $\text{MTX } 1.5\text{g}/\text{m}^2$) followed by radiotherapy. Abrey et al (2000) treated 52 patients (median age of 65 years) at a single centre with five cycles of MPV ($\text{MTX } 3.5\text{g}/\text{m}^2$, procarbazine $100\text{mg}/\text{m}^2/\text{d}$ and vincristine $1.4 \text{ mg}/\text{m}^2$) followed by WBRT and 2 courses of cytarabine ($3\text{g}/\text{m}^2$ days 1 & 2). The overall median survival was 60 months. Using a similar regimen but a lower dose of MTX ($2.5 \text{ g}/\text{m}^2$) followed by high dose cytarabine DeAngelis et al. (2002) treated 102 patients in a multicentre study and achieved a median survival of 36.9 months. Poormans et al. (2003) treated 52 patients in a multicentre trial with two cycles of MBVP ($\text{MTX } 3 \text{ g}/\text{m}^2$, teniposide, carmustine and methylprednisolone) and reported a median survival of 46 months. Moreton et al. (2004) have proposed a CNS-targeted regimen based on the pharmacokinetic properties of its individual drugs. IDARAM (idarubicin, dexamethasone, cytarabine and $\text{MTX } 2 \text{ g}/\text{m}^2$) has been piloted in a few patients, with encouraging preliminary results.

The idea that combination chemotherapy regimens based on HD-MTX might be more effective than HD-MTX alone is further supported by a large, multicentre retrospective analysis by Ferreri et al, (2002), in which the addition of high-dose cytarabine to a chemotherapeutic regimen containing MTX appeared to confer a survival advantage. Another retrospective analysis of 226 patients suggested an association between cytarabine and improved outcome, although this was not significant after adjustment for other prognostic variables (Blay et al, 1998).

In summary, although HD-MTX is widely accepted as the single most important agent in the treatment of PCNSL, it is possible that better results might be obtained when the drug is used in combination with other agents that penetrate into the CNS. The optimum combination of chemotherapeutic agents, however, remains unclear.

Recommendation (grade B, level IIa): All patients should be offered chemotherapy as first line treatment if they are sufficiently fit. Chemotherapy should consist of a regimen that includes HD-MTX (3-5 doses of $\geq 3\text{g/m}^2$ delivered over a maximum of 2-3 hours at intervals of not more than 2-3 weeks). The efficacy of HD-MTX may be improved by using it in combination with other CNS-penetrating chemotherapeutic agents such as cytarabine but such treatment should be based on established protocols and should ideally be given within the framework of a clinical trial.

Chemoradiotherapy. Many of the therapeutic regimens outlined above involve MTX-based chemotherapy followed by WBRT. Combined modality therapy can be very effective but is also associated with age-related neurotoxicity. In one retrospective study of 226 patients, many of whom received combined modality treatment, late neurotoxicity was observed in 26% of patients after a median follow-up of six years. However, since the study was retrospective, this figure may be an under-estimate. In addition to its adverse effect on quality of life, neurotoxicity was also associated with a poor prognosis. Thus, patients who developed late neurotoxicity in this series survived a median of 12 months from onset of neurotoxicity despite ongoing tumour remission.

The risk of delayed neurotoxicity is generally thought to be greatest in elderly patients. Abrey et al (1998) showed that late neurotoxicity developed in all patients older than 60 years receiving combined modality treatment, with symptoms developing after a median of 13 months. However, neurotoxicity can also occur in younger patients. Harder et al (2004) performed neuropsychological assessment on a cohort of 19 patients aged less than 60 years in remission following treatment with MBVP and consolidating radiotherapy. Cognitive impairment was found in twelve patients, and was severe in four. The patients were not assessed psychologically before treatment, so it is not possible to establish how much of the cognitive impairment was caused by the original tumour and how much was iatrogenic.

Patients who have received consolidation WBRT are more likely to develop neurotoxicity, thereby providing indirect evidence that those receiving combined modality therapy are more likely to develop this complication from the WBRT than from chemotherapy. Pels et al. (2003) treated 65 consecutive patients with MTX combination chemotherapy without elective radiotherapy. Response rates and duration were similar to those seen in studies employing chemoradiotherapy. The incidence of neurotoxicity was substantially lower, however, with only two patients developing severe cognitive dysfunction. MRI changes of leucoencephalopathy were seen in one third of patients but these were not associated with cognitive dysfunction, confirming the lack of correlation between clinical and radiological features of post-treatment neurotoxicity. Fleissbach (2003) performed a prospective neuropsychological assessment of ten patients from the above series with follow-up for a median of 36 months and demonstrated no decline in function following treatment. Correa et al. (2004) also compared the cognitive performance of patients in remission following chemotherapy alone against that of patients treated with chemoradiotherapy. Those treated with chemotherapy alone developed significantly less impairment of cognitive function than those treated with chemoradiotherapy. Indeed, chemotherapy alone can actually improve or stabilise cognitive function despite altering the MRI appearance of the white matter (Fleissbach et al, 2005; Neuwelt et al, 2005).

Omitting radiotherapy apparently reduces the risk of neurotoxicity but may increase the rate of tumour relapse. The relative importance of these two factors seems to be influenced by patient age. Abrey et al (2000) treated 22 patients aged >60 years with MTX-containing chemotherapy without cranial irradiation and compared these individuals to a similar group of 12 elderly patients who received both chemotherapy and cranial irradiation. The latter group were less likely to relapse but had a higher mortality from neurotoxicity, resulting in equivalent median survivals of 33 and 32 months, respectively. Bessell et al (2002) compared 31 patients treated with chemotherapy and WBRT (45Gy) with 26 patients who received chemotherapy and a reduced dose of consolidating WBRT (30.6Gy). In patients under 60 years of age, the reduction in radiation dose resulted in an increased rate of relapse at 3 years from 25% to 81%. There was no significant difference in relapse rate in patients aged 60 years or over. In a large retrospective analysis, Ferreri et al. (2002) was unable to detect a survival benefit from consolidating WBRT amongst patients who had achieved complete remission following MTX based chemotherapy.

Taken together, these data suggest that consolidation radiotherapy is beneficial in patients less than 60 years old; however, in patients aged 60 years or over, the balance between relapse and neurotoxicity is less clear.

Recommendation (grade B, level IIa): Consolidation WBRT should be considered in patients who achieve CR with MTX-based chemotherapy. In patients under 60 years of age, WBRT should be offered to patients unless there is a significant neurocognitive deficit following chemotherapy. In patients aged 60 years or over, neurocognitive side-effects are more likely to outweigh potential benefits.

Autologous stem-cell transplantation (ASCT). High dose therapy with stem cell rescue has been investigated in the hope of dispensing with consolidation radiotherapy in patients achieving CR after MTX-based chemotherapy. Abrey et al (2003) treated 28 patients with MTX-cytarabine induction. Fourteen patients subsequently received high-dose therapy with BEAM and stem cell rescue. The median event-free survival of these 14 patients

receiving ASCT was 9.3 months. An alternative induction regimen using TBC (thiotepa, busulfan and cyclophosphamide) followed by ASCT was used by Soussain et al. (2001) in 22 patients with relapsed or refractory disease and their results are discussed below. Cheng et al. (2003) also used TBC in seven patients, resulting in one toxicity-related death. The median event-free survival was not reached at 24 months. Taken together the current evidence does not support the use of ASCT in first line therapy.

Recommendation (grade B, level III): First line treatment with high-dose chemotherapy and autologous stem cell transplantation remains experimental and should not be conducted outside clinical trials.

Intrathecal chemotherapy. Most regimens involving intrathecal (IT) chemotherapy have reported no benefit if sufficient doses of systemic MTX were used. Glantz et al (1998) measured MTX concentrations in the CSF of patients treated with IT versus systemic high-dose MTX and found peak levels to be equivalent but more prolonged in patients receiving MTX by the intravenous route. Ferreri et al (2001) omitted intrathecal chemotherapy in a small single arm trial of 13 patients treated with MTX 3g/m², vincristine, procarbazine and consolidating WBRT. Results were in line with other MTX-containing regimens and no meningeal relapses were reported. Ferreri et al (2002) also retrospectively analysed a cohort of 370 patients and found that intrathecal chemotherapy did not improve outcome amongst those receiving systemic MTX. This lack of correlation was consistent on subgroup analysis of patients, both with and without CSF involvement.

Recommendation (grade B, level III): There is no evidence supporting a role for intrathecal chemotherapy as an adjunct to high-dose intravenous MTX in patients with PCNSL.

Rituximab. As mentioned above, almost all PCNSL express the B-cell antigen, CD20. Unfortunately, however, intravenous, rituximab does not penetrate the intact blood-brain

barrier. Shultz et al. (2004) reported the use of intraventricular or intrathecal administration of 10 – 40 mg of rituximab in six patients. A response was seen in all four patients with meningeal disease. The effectiveness and toxicity of intraventricular rituximab in relapsed CNS lymphoma has also been examined in a prospective phase I dose escalation study. Ten patients were allocated to receive 9 intraventricular injections of rituximab at doses of 10mg, 25mg or 40mg over a 5-week period. The maximum tolerated dose was found to be 25mg. Six of the 10 patients had cytological improvement of the CSF, with complete clearance of malignant cells in 4 cases. Two patients had improvement of intraocular manifestations and brain parenchymal disease regressed in one patient (Rubenstein et al. 2007). There is some evidence to suggest that the therapeutic efficacy of rituximab when given via the intrathecal route might be improved by co-administration of autologous serum (Takami et al, 2006). Taken together, these findings suggest that there may be role for intraventricular or intrathecal rituximab in the treatment of relapsed PCNSL, especially if disease is largely confined to the meninges. However, in view of the current paucity of data its use remains experimental at the present time.

Recommendation (grade B, level III): Rituximab administered via the intrathecal or intraventricular route should not be used in the routine treatment of PCNSL except in a clinical trial.

Disruption of the blood brain barrier. A few centres have evaluated chemical disruption of the blood-brain barrier, in an attempt to increase penetration of chemotherapy into cerebral tissue. Hypertonic mannitol was infused into the carotid or vertebral artery under general anaesthesia, to produce a transient osmotic disruption of the blood-brain barrier.

Doolittle et al. (2000) combined intra-arterial mannitol and chemotherapy in a multicentre trial including 53 PCNSL patients and demonstrated its safety and efficacy. CR was seen in 75% patients but survival data were not reported. Tyson et al. (2003) treated 37 relapsed PCNSL patients with intra-arterial carboplatin and blood-brain barrier disruption (BBBD). The same group is investigating the role of BBBD in combination with

immunotherapy and radioimmunotherapy. Although this approach may lead to promising developments in the future, the current survival data are not significantly better than those achieved with current intravenous HD-MTX regimens; therefore, they do not justify the technical complexity and associated risk involved in administration.

Recommendation (grade B, level IIb): Pharmacological disruption of the blood-brain barrier should not be performed as part of the treatment of PCNSL unless as part of a clinical trial.

Relapse/salvage treatment. Patients who fail MTX-based treatment and who have not previously received WBRT can receive WBRT as salvage therapy. Nguyen et al (2005) examined WBRT in 27 consecutive patients who had failed MTX-based chemotherapy. Median radiation dose was 36 Gy, and seven patients also received a boost of 19–40 Gy. Thirty-seven percent of patients achieved a CR and 37% a partial remission (PR). Median progression-free survival was 57 months for patients with CR and nine months for those achieving PR. Median overall survival was 10.9 months. This compares favourably with results achieved using WBRT as primary therapy and suggests that MTX resistance is not necessarily associated with radio-resistance.

Soussain et al. (2001) examined the use of salvage chemotherapy with cytarabine and etoposide followed by intensive chemotherapy (thiotepa, busulphan and cyclophosphamide) and stem-cell rescue in 22 patients with refractory or recurrent disease. Overall three-year survival was 64%. Other groups have attempted salvage therapy with further MTX, high-dose cytarabine or PCV (procarbazine, lomustine, vincristine) with some success. More recently, temozolomide (Reni et al, 2004), topotecan (Fischer et al, 2004) and intra-arterial carboplatin (Tyson et al, 2003) have been evaluated in a few patients with response rates of 26-37%. Arellano-Rodrigo et al. (2003) investigated the use of etoposide, ifosfamide and cytarabine in 16 patients refractory to or relapsed after treatment with CHOD/BVAM: six patients achieved a CR. The survival at 12

months was 41%. Glucocorticoids play a useful a role in short-term palliation, and there are case reports of steroids alone producing long-term disease control (Weller et al, 1999).

Recommendation (grade B, level III): Relapsed or refractory disease should be treated with salvage radiotherapy in patients who have not previously received WBRT. Dexamethasone should be considered for short-term palliation. Alternative chemotherapeutic regimens such as temozolomide or high-dose chemotherapy with autologous stem cell transplantation show promise but require further evaluation in clinical trials.

7. Treatment of Primary Intraocular Lymphoma (PIOL).

Although considered a variant of PCNSL, PIOL is associated with therapeutic considerations of its own. As with PCNSL, there is a paucity of data on which to base treatment recommendations, which therefore remain controversial.

Historically, the mainstay of treatment for PIOL was ocular radiotherapy (30–45 Gy to both eyes). High response rates were achieved but most patients relapsed in the eye and brain, the median survival being only 12-20 months (Ferreri et al., 2002; Nelson, 1999; Margolis et al, 1980). In patients who survived for longer periods, ocular complications such as radiation retinopathy, optic neuropathy, dry eye, corneal epithelial defects, loss of limbal stem cells, cataracts and glaucoma were common.

Systemic chemotherapy alone offers the possibility of simultaneous treatment of intracranial and intraocular disease without the risk of radiation-induced toxicity. Consequently, some centres have proposed this approach for combined PIOL/PCNSL (DeAngelis, 2001; Valluri et al., 1995). Most systemic chemotherapy regimens are based on HD-MTX and/or cytarabine because of their ability to penetrate the blood-brain barrier

and blood-ocular barrier (Plowman et al., 1993; Valluri et al., 1995; Batchelor, 2003a and Batchelor, 2003b).

The efficacy of systemic chemotherapy as a treatment for PIOL depends on intraocular pharmacokinetics. For example, seven of nine patients with PIOL treated with HD-MTX alone (8g/m² body surface area) showed a good ocular response, with persisting remission in four patients after 8 to 36 months (Batchelor et al., 2003b). Micromolar MTX concentrations were present in both ocular chambers four hours after the infusion in all eight patients. Following systemic treatment with high dose cytarabine, therapeutic levels in intraocular fluids as well as responses exceeding 15 months have been documented (Baumann et al., 1986). However, several studies (Soussain et al., 2001; Strauchen et al., 1989) have shown that CNS lymphoma may respond differently from intraocular disease. This suggests that penetration of chemotherapeutic agents into these two compartments may differ, and that the maintenance of sufficient levels of MTX in the vitreous humour is difficult. Systemic MTX and cytarabine can both cause ocular side-effects, which include periorbital oedema, conjunctivitis, keratitis, and photophobia (Valluri et al. 1995). To avoid these complications, some authors have suggested that MTX and/or cytarabine should be administered intrathecally instead of systemically (Mason and Fischer, 2003).

Combined modality therapy, including CNS-penetrating systemic chemotherapy, intrathecal MTX, and radiation to the brain, orbits and spinal cord is associated with a relatively long median survival of 36 months from diagnosis (Char et al. 1981). However, up to 50% of patients treated in this way relapse in the eyes, and delayed neurotoxicity is common (Abrey et al., 1998; DeAngelis et al., 2002). Once tumour relapse occurs, additional treatment with systemic chemotherapy is often required, exacerbating any pre-existing toxicity (Plowman et al., 1993). As with PCNSL without overt ocular involvement, the beneficial anti-tumour effect in PIOL of consolidation radiotherapy to the eyes and brain needs to be carefully balanced against the risk of radiation-induced toxicity.

As discussed above, high-dose chemotherapy with thiotepa, busulfan and cyclophosphamide (TBC) followed by autologous bone marrow transplantation was administered in 12 patients with refractory or recurrent PIOL or PCNSL (Soussain et al., 1996). Nine of these patients achieved CR in the brain and the eye. Median overall survival was 53 months after relapse. However, the therapy was highly toxic and proved fatal in five out of seven patients older than 60 years (Soussain et al., 1996).

Intravitreal MTX has been used to treat patients with isolated and recurrent intraocular lymphoma. Successful conservation of vision has been achieved in patients who had previously received systemic chemotherapy, with or without radiation (Helbig et al., 2003). Repeated intravitreal injections of MTX are necessary to achieve a good local tumour response. Complications include keratitis, conjunctivitis, ocular hypotony, macular oedema and cataract. The major drawback of intravitreal treatment is that it does not prevent death from CNS involvement.

A range of therapeutic agents are currently being investigated for treatment of PIOL. These include oral trofosfamide (Jahnke et al., 2004) and monoclonal antibody therapy directed against B-cell antigens (e.g. rituximab). However, owing to paucity of data, these should be regarded as experimental at the present time.

Recommendation (grade B, level III): Concurrent intraocular and CNS lymphoma should be treated with systemic HD-MTX-based chemotherapy followed by radiation to both globes and possibly also the brain if the patient is less than 60 years old. Isolated intraocular disease should be treated in the same way. Intravitreal MTX is an effective treatment option for patients with recurrent disease confined to the eyes.

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Table 1**IPCG guidelines for baseline evaluation**

Pathology	Clinical	Laboratory	Imaging
Centralised review of pathology	Complete medical and neurological examination	HIV serology	Contrast-enhanced cranial MRI scan (CT if MRI contraindicated)
Immunophenotyping	Dilated eye examination, including slit lamp examination and fundoscopy	Vitreous biopsy +/- chorioretinal biopsy, immunohistochemistry, IgH-PCR ¹ , serum LDH level	CT of chest, abdomen and pelvis
	Record prognostic factors (age, performance status)	CSF cytology, flow cytometry, IgH-PCR	Bone marrow aspirate and trephine biopsy
	Serial evaluation of cognitive function	24-hour urine collection for creatinine clearance if HD-MTX planned	Testicular ultrasound in elderly males

¹ Polymerase chain reaction for detection of immunoglobulin heavy chain rearrangements.

Table 2**IPCG response criteria**

Response	Brain imaging	Glucocorticoid dose	Eye examination	CSF cytology
CR	No enhancing disease	None	Normal	Negative
uCR	No enhancing disease Minimal enhancing disease	Any Any	Normal Minor RPE ¹ abnormality	Negative Negative
PR	50% decrease in enhancement No enhancing disease	NA NA	Minor RPE abnormality or normal Decrease in vitreous cells or retinal infiltrate	Negative Persistent or suggestive of disease
PD	25% increase in enhancement Any new site of disease	NA	Recurrent or new disease	Recurrent or positive
SD	All scenarios not covered by responses above			

¹ Retinal pigment epithelium

Figure 1. Suggested treatment algorithm for first-line therapy

