Diagnosis and treatment of primary CNS lymphoma in immunocompetent patients: guidelines from the European Association for Neuro-Oncology

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The management of primary CNS lymphoma is one of the most controversial topics in neuro-oncology because of the complexity of the disease and the very few controlled studies available. In 2013, the European Association of Neuro-Oncology created a multidisciplinary task force to establish evidence-based guidelines for immunocompetent adults with primary CNS lymphoma. In this Review, we present these guidelines, which provide consensus considerations and recommendations for diagnosis, assessment, staging, and treatment of primary CNS lymphoma. Specifically, we address aspects of care related to surgery, systemic and intrathecal chemotherapy, intensive chemotherapy with autologous stem-cell transplantation, radiotherapy, intraocular manifestations, and management of elderly patients. The guidelines should aid clinicians in their daily practice and decision making, and serve as a basis for future investigations in neuro-oncology.

Introduction

Primary CNS lymphomas are extranodal, malignant non-Hodgkin lymphomas of the diffuse large B-cell type that are confined to the brain, eyes, leptomeninges, or spinal cord, in the absence of systemic lymphoma. Primary CNS lymphomas are estimated to account for up to 1% of all lymphomas, 4–6% of all extranodal lymphomas, and about 3% of all CNS tumours.[1] After a continuous rise in the incidence of primary CNS lymphoma during the 1980s and 1990s, epidemiological data in high-income countries show a decrease in incidence, particularly among young patients with AIDS.[2] By contrast, the incidence of primary CNS lymphoma continues to rise in elderly patients, who represent most patients in immunocompetent populations.[3–5]

Although the prognosis of primary CNS lymphoma remains poor, it has substantially improved in the past two decades as a result of better treatment strategies with a curative aim. However, treatment of this disease remains challenging because, despite high chemosensitivity and radiosensitivity, remissions are frequently of short duration. The blood–brain barrier limits the access of many drugs to the CNS. Furthermore, elderly patients are at especially high risk for the development of severe neurotoxic effects related to treatment.

Optimum treatment recommendations result mainly from retrospective series or single-arm phase 2 studies. Only three completed randomised trials are available for primary CNS lymphoma: one phase 3 and two phase 2 trials.[6–8] The objective of this guideline is to provide clinicians with evidence-based recommendations and consensus expert opinions for the management of patients with this disease. The guidelines focus exclusively on immunocompetent populations, which represent most patients. Primary CNS lymphoma in immunodeficient patients and rare, indolent, low-grade lymphomas that occur mainly in the CNS have a distinct pathogenesis with separate diagnostic and therapeutic implications, and will be subject to specific guidelines, beyond the scope of this Review.

Search strategy and selection criteria

The task force was established in 2013 under the auspices of the European Association for Neuro-Oncology and represents European-based medical experts from eleven countries. The task force included specialists in the management of primary CNS lymphoma—including neurologists, haematologists, medical oncologists, neurosurgeons, pathologists, ophthalmologists, and radiation oncologists. Based on best available evidence from literature review, the writing group (EB, JB, AFH, KH-X, MP, RR, US, TS, CS) produced the draft guideline, which was subsequently submitted to the review committee (UA, NC, MD, CMFD, AJMF, FG, RH, UH, RS, MT, MW). The revised guideline, taking into account the comments of the reviewers, was resubmitted by the chairman (KH-X) to the whole task force for review and amendments twice. Thereafter, final agreement was obtained in September, 2014. Any disagreement between members of the panel about the proposed recommendations that was not resolved by discussion is reported explicitly in the text.

References were identified through searches of PubMed with the search terms "primary CNS lymphoma", "primary central nervous system lymphoma", "primary intraocular lymphoma", "elderly", "radiotherapy", "chemotherapy", and "rituximab" published between January, 1980, to September, 2014. Additional articles were identified individually through searches of the authors' own records. Abstracts which had been presented at the American Society of Clinical Oncology meetings in 2013 and 2014 that were relevant to the topic, were included by task force members during manuscript preparation. The final reference list was generated on the basis of originality and relevance to the broad scope of this Review.

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***Panel 1:* Consensus statements and recommendations**

Diagnosis

- Neuroimaging with cranial MRI using fluid-attenuated inversion recovery and T1-weighted sequences before and after contrast injection is the method of choice for diagnosis and follow-up. Diffusion, dynamic susceptibility contrast, proton spectroscopy MRI, and fluorodeoxyglucose-PET can be useful for differential diagnosis but have insufficient specificity (good practice point).
- Diagnosis of primary CNS lymphoma requires histopathological confirmation before treatment; biopsy should be done using stereotactic or navigation-guided needle biopsy (panel 2) (good practice point).
- If clinically possible, steroids should be avoided before biopsy because they might prevent a histopathological diagnosis. For patients who have been pretreated with steroids, in the case of remission or unspecific inflammation in the biopsied tissue, rebiopsy is recommended when close and careful follow-up with serial MRI indicates further tumour growth (good practice point).
- Primary CNS lymphoma is diagnosed according to the WHO classification. Immunohistochemistry is required (good practice point).
- Required immunohistochemical markers include: pan-B-cell markers (CD19, CD20, PAX5), BCL6, MUM1/IRF4, and CD10 (good practice point).
- PCR analysis of immunoglobulin gene families might assist diagnosis in difficult cases, for instance in patients with corticosteroid pretreated primary CNS lymphoma (good practice point).
- If primary CNS lymphoma is suspected, the work-up should include at least one HIV blood test, a lumbar puncture (if not contraindicated), and an ophthalmological assessment (with a fundoscopy and a slit lamp examination) in all patients, including those without ocular symptoms (good practice point).
- Identification of lymphoma cells in the cerebrospinal fluid or in the vitreous fluid together with a high clinical and radiological suspicion of primary CNS lymphoma might obviate the need for a stereotactic brain biopsy to confirm the diagnosis. Since cytological diagnosis might be difficult, a review by a specialist pathologist is recommended. If any doubt remains, a brain biopsy is required (good practice point).
- Immunophenotyping by multiparameter flow cytometry of cells collected from the cerebrospinal fluid or vitreous, and immediately analysed, might add to diagnostic sensitivity (good practice point).
- The presence of B-cell monoclonality in a sample with atypical or suspicious cells and subsequent, PCR-based analysis of immunoglobulin gene rearrangements in the cerebrospinal fluid might result in false-positive results. Therefore, except in patients for whom a high clinically documented suspicion of primary CNS lymphoma exists, evidence for the clonality of the lymphocytic cell population is insufficient for the diagnosis of primary CNS lymphoma (good practice point).

Staging

- Systemic staging should include the following assessments: physical examination, bone marrow biopsy, testicular sonography, and CT scan of the chest, abdomen, and pelvis. Whole-body fluorodeoxyglucose-PET might be a better alternative to whole-body CT scan and testicular sonography (good practice point).

Prognosis

- Age and performance status, as measured by various scales, have been consistently identified as treatment-independent prognostic factors. Before treatment, patients should be assessed according to one of the existing prognostic scores to evaluate the individual risk (good practice point).
- Elderly patients should be defined as older than 60–65 years (good practice point).

Evaluation of response and follow-up

- The International Primary CNS Lymphoma Collaborative Group criteria (2005), which combines MRI, eye examination, cerebrospinal fluid analysis, and steroid dose, should be used to assess the response to treatment (good practice point).
- No evidence shows that brain fluorodeoxyglucose-PET can be used to assess responses in patients with primary CNS lymphoma in the way that it is used for other lymphomas (good practice point).
- Formal prospective neuropsychometric tests are recommended during follow-up of patients with primary CNS lymphoma who are treated within clinical trials (good practice point).

Scientific evidence was assessed and graded according to the following categories: class I evidence was derived from randomised phase 3 clinical trials; class IIa evidence derived from randomised phase 2 trials; class IIb evidence derived from phase 2 trials; class IIIa evidence derived from prospective studies, including observational studies, cohort studies, and case-control studies; class IIIb evidence derived from retrospective studies; and class IV evidence derived from uncontrolled case series, case reports, and expert opinions. To establish recommendation levels, the following criteria were used: level A required at least one class I study or two consistent class IIa studies; level B required at least one class IIa study or several class IIb and III studies; level C required at least two consistent class III studies. Pathology, genetics, clinical features, and neuroimaging were reviewed but not graded. When there was insufficient evidence to categorise recommendations in levels A–C, we classified the recommendation as a good practice point, if agreed by all members of the task force.

General recommendations

Consensus statements and recommendations were given for the following aspects of primary CNS lymphoma: pathology, genetics, clinical presentation, diagnostic confirmation, neuropathological changes of corticosteroid-treated primary CNS lymphoma, neuroimaging, cerebrospinal fluid analyses, vitreous analyses, staging, prognostic factors, response criteria to treatment, and treatment-related neurotoxic effects. Consensus statements and recommendations for the general approach to patients with primary CNS lymphoma are presented in panel 1. The evidence used to establish these recommendations and with regards to intraocular lymphoma is detailed in the appendix. Key recommendations for treatment are summarised in panel 2. Our guideline addresses treatment of histologically or cytologically verified primary CNS lymphoma. We do not specifically discuss the treatment of patients with deep-seated tumours that are not readily amenable to biopsy as no evidence-based recommendations have been made for these patients. We believe that biopsy samples can almost always be collected in specialised centres and that chemotherapy and radiotherapy interventions without histological confirmation of primary CNS lymphoma should be discouraged.

Surgery

Although few data are available in the scientific literature, surgery has traditionally been deemed to have no role in the treatment of primary CNS lymphoma. This widely adopted opinion is based on small retrospective series, the results of which suggest no clear benefits in the outcome of surgical resection when used as a sole treatment, compared with supportive care (class IIIb)[9] and compared with evidence from biopsy samples from patients who received postoperative chemotherapy or radiotherapy (class IIIb).[10,11] The absence of surgical effectiveness might be attributable to the microscopic, multifocal, and infiltrative nature of primary CNS lymphoma that can extend beyond the visible border of the lesion.[12] The high radiosensitivity and chemosensitivity of primary CNS lymphoma, and the risk of postoperative morbidity in this patient population, have likewise helped discourage surgery. However, the recommendation to restrict surgical interventions to biopsies is not based on randomised data and, more importantly, not on contemporary data based on modern neurosurgical techniques. The German Primary CNS Lymphoma Study Group-1 (G-PCNSL-SG-1) phase 3 trial[7] included an unusually high proportion of operated patients, which allowed a large retrospective analysis of the association of surgery and expected outcome. Patients with subtotal or total resections had significantly longer progression-free survival and overall survival than did patients who received biopsies. This difference in outcome was independent of the postoperative Karnofsky performance status and age. Since patients who had a biopsy more often had many deeply-seated CNS lesions than patients who received surgery, this difference might have contributed to the unfavourable outcomes in the patients who had biopsies. When adjusted for the number of lesions (depth of lesions was not analysed in the study), the difference in outcome remained statistically significant for progression-free survival, but not for overall survival (class IIIa).[13]

Systemic chemotherapy

The CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) regimen routinely used for widespread non-Hodgkin lymphomas induces responses of brief duration in patients with primary CNS lymphoma. CHOP added to radiotherapy has likewise not improved patient survival in prospective trials (class IIb).[14–16] This inefficacy is probably because the metabolite of cyclophosphamide, phosphoramide mustard, and doxorubicin are not able to cross the blood–brain barrier and therefore eradicate microscopic disease.

See Online for appendix

On the basis of convergent results from many prospective and retrospective studies, methotrexate, an antifolate and antimetabolite, given intravenously as a high dose, is currently regarded as the most important and beneficial single drug. Penetration of methotrexate into the CNS depends on the total dose and the rate of infusion. The optimum dose of methotrexate has not been established. The dose range of intravenous methotrexate that can cross the blood–brain barrier has been estimated to be 1–8 g/m², with no clear evidence for a dose–response association. Since rapid infusion of methotrexate for 3 h, at a dose of 3 g/m² or more, achieves cytotoxic levels in the cerebrospinal fluid, we recommend that methotrexate should be given according to this protocol (class IV).[17] Since efficacy of methotrexate can likewise depend on duration of exposure, the methotrexate administration interval should range between 10 days and 3 weeks (class IV).[18] The best possible number of methotrexate injections needed is unknown. A minimum of four to six injections are delivered in most chemotherapy regimens, especially if no consolidation treatment (radiotherapy or intensive chemotherapy) is scheduled in the protocol. For patients who achieve only a partial response after four or five rounds of high-dose methotrexate, additional rounds of treatment might improve the complete remission rate (class IIIa).[19] Infusions of high-dose methotrexate require pretreatment and post-treatment hyperhydration, urine alkalinisation, leucovorin rescue, and the monitoring of methotrexate concentration. Most treatment protocols combine high-dose methotrexate with various other chemotherapeutic drugs to improve response rates and outcomes. The best evidence for this combination treatment approach comes from an International Extranodal Lymphoma Study Group randomised phase 2 study[6] that compared high-dose methotrexate alone, administered at 3 g/m² per day every 21 days, to high-dose methotrexate (3 g/m² per day every 21 days [day 1])

Panel 2: **Consensus statements and recommendations for treatment of patients with primary CNS lymphoma**

Surgery

- To rapidly reduce intracranial pressure, surgical resection can be undertaken in patients with large lesions and acute symptoms of brain herniation (good practice point).
- In patients suspected of primary CNS lymphoma with a unifocal and resectable lesion, the panel did not establish consensus about whether to recommend surgical resection or the need for tissue biopsy.

Chemotherapy

- CHOP regimens and derivatives are not recommended for treatment of primary CNS lymphoma (level B).
- Chemotherapy should include high-dose methotrexate at doses of at least 3 g/m^2 so as to cross the blood–brain barrier and yield cytotoxic levels in the cerebrospinal fluid. Methotrexate should be given by intravenous infusion for 2–3 h for a minimum of four to six injections and at intervals that should not exceed 2–3 weeks (good practice point).
- Combination of high-dose methotrexate with other chemotherapeutic agents improves responses compared with high-dose methotrexate alone (level B).
- Chemotherapeutic agents to be used in combination with high-dose methotrexate should be selected from active drugs known to cross the blood–brain barrier, such as high-dose cytarabine (level B).
- High-dose methotrexate chemotherapy is feasible in elderly patients with an adequate performance status and renal function (level B).
- Blood–brain barrier disruption followed by intra-arterial methotrexate is an alternative experimental approach that is appropriate for a selected group of patients but should be undertaken only by teams with a high level of expertise (level B).
- The value of intrathecal chemotherapy as prophylaxis is unclear. Intrathecal chemotherapy (intralumbar or preferably intraventricular through an Ommaya reservoir) can be proposed whenever meningeal involvement is documented, together with an insufficient response to intravenous high-dose (at least 3 g/m^2) methotrexate-based chemotherapy (good practice point).
- Rituximab combined with a chemotherapy regimen is recommended only as an experimental regimen within clinical trials (level C).

Radiotherapy

- Whole-brain radiotherapy (WBRT), high-dose methotrexate, and combined treatments expose patients to greater risks of neurotoxic effects (level A).
- Consolidation WBRT after high-dose methotrexate based chemotherapy remains controversial. The optimum dose is not yet defined but should be chosen on the basis of the response to primary chemotherapy (good practice point).
- In patients with progressive or residual disease after primary chemotherapy, a total dose of 40–45 Gy with a 1·8–2·0 Gy dose per fraction is advisable. When these doses are used, there is no evidence for the use of a focal boost on the enhancing lesions (good practice point).
- In patients less than 60 years of age, who have achieved a complete response to induction chemotherapy, the decision for immediate WBRT (40–45 Gy in 1·8–2·0 Gy fractions) or omission of WBRT should be discussed with the patient. Reduced dose WBRT consolidation (23·4–30·0 Gy in 1·8–2·0 Gy fractions) is a therapeutic option that should be investigated in a clinical trial (good practice point).
- In patients older than 60 years, the risk of delayed neurotoxic effects with WBRT (doses greater than 30 Gy in 1·8–2·0 Gy fractions), especially after high-dose methotrexate, is too high. WBRT at these doses should be deferred or avoided (level B).

High-dose chemotherapy with autologous stem-cell transplantation (HDC-ASCT)

- HDC-ASCT is an efficient treatment in relapsed or refractory primary CNS lymphoma (level B).
- HDC-ASCT should be reserved for patients less than 60–65 years of age (good practice point).
- High-dose thiotepa-based conditioning chemotherapy should be preferred over the BEAM (carmustine, etoposide, cytarabine, and melphalan) regimen (level C).
- HDC-ASCT as consolidation for first-line treatment is experimental in primary CNS lymphoma and should be used only in clinical centres that have had sufficient training (good practice point).

Salvage treatment

- Patients with relapsed or refractory primary CNS lymphoma should be enrolled into phase 1 and 2 trials (good practice point).
- The most appropriate salvage treatment should be chosen on the basis of patient's age, performance status, comorbidities, site of relapse, previous therapy, and duration of previous responses. The expected side-effects of the chosen drug should also be assessed carefully (good practice point).
- Salvage WBRT may be preceded by induction chemotherapy, and can be given to patients who have not received radiotherapy (good practice point).
- HDC-ASCT is a valid therapeutic option in patients younger than 60–65 years with chemosensitive relapsing primary CNS lymphoma (level B).
- Salvage chemotherapy can be delivered as induction therapy before WBRT or HDC-ASCT, or as exclusive treatment in patients not eligible for WBRT or HDC-ASCT (level B).

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- Methotrexate rechallenges should be considered in patients with recurrent primary CNS lymphoma who have previously responded to high-dose methotrexate (level C).
- Patients with isolated extra-CNS relapses should be managed with anthracycline-based chemotherapy with or without HDC-ASCT(good practice point).

Primary intraocular lymphoma

- Primary intraocular lymphoma can be treated by either high-dose methotrexate-based chemotherapy (with or without WBRT) or by locally applied therapy (intravitreal chemotherapy or ocular radiotherapy) (good practice point).
- Local treatment (intravitreal chemotherapy or ocular radiotherapy) is a valid approach for patients with systemic chemotherapy contraindications or for elderly patients with relapsing intraocular disease (good practice point).
- Concurrent intraocular and CNS lymphoma should be treated no differently from primary CNS lymphoma (good practice point).
- If consolidation WBRT is proposed, it should include both eyes (good practice point).
- Refractory and relapsed intraocular lymphoma should be treated according to the characteristics of patients and previous treatments. Treatments include intravitreal injections of methotrexate, focal radiotherapy, WBRT, systemic chemotherapy, and HDC-ASCT (good practice point).

with cytarabine (2 g/m² twice per day on days 2–3) (class IIa). Patients in both treatment groups were subsequently given whole-brain radiotherapy (WBRT). A significantly higher proportion of patients in the high-dose methotrexate plus cytarabine group achieved a complete response (the study's primary endpoint) than did those assigned to methotrexate alone. The overall response rate and progression-free survival were significantly improved, although no significant increase in overall survival was noted. Two previous prospective trials[20,21] that assessed methotrexate at a dose of 8 g/m² as monotherapy without immediate consolidation treatment with WBRT showed this treatment to result in shorter progression-free survival than with polychemotherapy regimens (class IIb). Similarly, the addition of ifosfamide to high-dose methotrexate improved the response rate, but not survival, in the G-PCNSL-SG-1 trial.[7] Altogether, these data have shown only high-dose methotrexate to be defined as a chemotherapy standard of care.[22]

Chemotherapeutic treatments to be combined with high-dose methotrexate should be selected from active drugs known to cross the blood–brain barrier, such as high-dose cytarabine. The CALGB50202 multicentre phase 2 trial[23] reported promising results for high-dose cytarabine combined with etoposide as consolidation therapy without WBRT, after an induction regimen of high-dose methotrexate-based polychemotherapy (class IIb). By contrast, disappointing results were reported in a pilot study[24] that combined high-dose methotrexate (3·5 g/m²), thiotepa, and cytarabine at a reduced dose of 1 g/m². This study suggests that this reduced dose of cytarabine was too low to reach cytotoxic concentrations in the CNS (class IIIa), in accord with results from pharmacokinetic studies.[25]

Blood–brain barrier disruption by intra-arterial infusion of hypertonic mannitol has been shown to increase the drug concentrations in the CNS.[26] This procedure followed by intra-arterial methotrexate showed a good safety profile and neurocognitive tolerance in newly diagnosed patients with primary CNS lymphoma. Furthermore, these patients achieved similar outcomes to patients treated with high-dose intravenous methotrexate-based chemotherapy regimens (class IIIb).[26–28] However, by contrast with results reported in prospective studies on chemoradiotherapy, even after a follow-up longer than 10 years (class IIb),[29] blood–brain barrier disruption is not associated with a plateau in survival curves, suggesting that relapses and deaths continue, and only a small number of patients are cured. This procedure is only available to patients without contraindications to general anaesthesia and requires careful patient selection because safety depends on the extent of intracranial mass effect due to tumour. Only teams trained in blood–brain barrier disruption should provide this complex procedure, which requires cannulation of the intracranial vessels.

In summary, we recommend high-dose methotrexate-based chemotherapy for first-line treatment of primary CNS lymphoma. In patients who are ineligible for first-line high-dose methotrexate, treatment should be chosen from active salvage treatments for refractory or recurrent primary CNS lymphoma.

Intrathecal chemotherapy

Chemotherapeutic drugs given intrathecally have not been prospectively studied. Therefore, their clinical effectiveness in primary CNS lymphoma is controversial. Results of three retrospective studies[30–32] showed that patients given high-dose methotrexate did not benefit from the additional treatment with methotrexate and cytarabine given intrathecally (class IIIb). By contrast, results from two consecutive single-arm trials[33,34] using the same systemic polychemotherapy regimen suggested additional benefit when intraventricular chemotherapy was added (class IIIa). However, in view of the low level of evidence, we currently do not advocate intrathecal chemotherapy as a prophylaxis (ie, to prevent recurrence).

Rituximab

The anti-CD20 antibody rituximab has poor CNS penetration because of its large size. Therefore, the highest concentration and resultant efficacy of rituximab probably occurs during the early treatment phase when the integrity of the blood–brain barrier is reduced at the location of the contrast-enhancing tumours. The effect of rituximab when used as monotherapy in patients with primary CNS lymphoma was assessed in a study in which 12 patients with refractory or relapsed primary CNS lymphoma were given weekly intravenous infusions of 375 mg/m² rituximab for up to eight injections (class IV).[35] Tumour responses measured by MRI were reported in 36% of these patients. Other studies used intravenous rituximab in combination with a high-dose methotrexate-based chemotherapy regimen as an initial treatment for newly diagnosed primary CNS lymphoma (class IIIa, class IIIb, class IV) or as salvage treatment for recurrent disease.[19,23,36–42] On the basis of retrospective comparisons with historical controls, results of three studies suggested that the addition of rituximab to high-dose methotrexate-based chemotherapy improves the chance of complete response and overall survival in patients with newly diagnosed primary CNS lymphoma (class IIIb).[40–42] Overall, the addition of rituximab to systemic polychemotherapy was well tolerated. Injection of rituximab into the cerebrospinal fluid by either lumbar puncture or by intraventricular administration was further assessed in a phase 1 trial in patients with refractory or recurrent CNS lymphoma (class IIIa).[43] In this trial, objective responses and good tolerability were documented. In conclusion, although preliminary data suggests that it may provide some benefit, the level of evidence supporting either systemic or local use of rituximab as part of a treatment protocol for primary CNS lymphoma remains low. Two randomised trials in progress (NCT01011920; NTR2427) should be able to clarify the role of systemic rituximab in primary CNS lymphoma.

Radiotherapy

Because of the microscopically diffuse and multifocal nature of primary CNS lymphoma, radiotherapy is used to target the whole brain and the eyes. Despite a high response rate of around 50%, radiotherapy, when used alone, does not provide a substantial survival benefit in patients with primary CNS lymphoma, with a median overall survival of 10–18 months and 5-year overall survival of 5%. A phase 2 trial[44] that used radiotherapy as first-line treatment was done by the Radiation Therapy Oncology Group (RTOG) and delivered a total dose of 40 Gy with an additional 20 Gy boost delivered to contrast-enhancing lesions; median overall survival was disappointing, at 11·6 months (class IIb). Additionally, most recurrences occurred in areas that had received the highest radiotherapy dose.

Consolidation radiotherapy

Although not formally compared in a randomised trial, results of several studies[18,45–53] suggest that the combination of high-dose methotrexate with radiotherapy is better than radiotherapy alone, in terms of increasing the proportion of long-term survivors (5-year survival 20–50%) (class IIb, class IIIa, class IIIb) and overall survival by two to four times (median 30–72 months). By contrast with extracerebral non-Hodgkin lymphoma, the optimum dose of post-chemotherapy irradiation has never been prospectively investigated in primary CNS lymphoma.[54] Doses of 23–50 Gy delivered to the whole brain, with or without a tumour bed boost, are used; most protocols use a total dose of 40–45 Gy without a boost (1·8–2 Gy per fraction).

Results of the RTOG-9310 trial[55] did not show a clear benefit with hyperfractionated WBRT (class IIb). For patients who achieve a complete response after high-dose methotrexate-based chemotherapy, whether consolidation with WBRT provides better disease control or survival is unclear. Only one randomised trial[7] of radiotherapy after chemotherapy versus watch-and-wait after chemotherapy has been undertaken in patients with primary CNS lymphoma. This study (G-PCNSL-SG 1) was a non-inferiority phase 3 trial, in which patients received 4 g/m² high-dose methotrexate intravenously every 14 days for six cycles with or without ifosfamide. Patients who achieved a complete response had been randomly assigned to receive either consolidation WBRT (45 Gy in 30 fractions for 6 weeks) or no further treatment. Patients without a complete response received high-dose cytarabine or WBRT. 551 patients entered the study, but only 318 patients were treated per protocol. Overall survival was similar in patients who received consolidation WBRT and those who did not. In the per-protocol population, there was a suggestion of a progression-free survival advantage, albeit non-significant, for the group treated with WBRT, but there was no significant difference in overall survival. This trial (class I), which is, so far, the largest and only phase 3 trial in primary CNS lymphoma comparing consolidation WBRT to observation alone has caused vigorous debate within the scientific community.[56–59] Several experts believe that the unmet primary endpoint for non-inferiority and the high rate of protocol violations prevent any conclusions being made from the trial. These experts advocate that consolidation WBRT after high-dose methotrexate-based chemotherapy needs to remain the standard of care, pending further data from ongoing randomised trials. Other experts acknowledge the methodological limitations of the study, but nevertheless deem that the results contribute strongly to the accumulating retrospective scientific literature,[30,60,61] which suggests that omission of WBRT from first-line treatment results in shorter progression-free survival but does not compromise overall survival (class IIIb). Furthermore,

results of several single-arm trials[21,26,27,33,62–64] have suggested that chemotherapy alone plus a deferred radiotherapy strategy might result in similar overall survival (class IIb, class IIIa, class IIIb) with better neurocognitive preservation, as shown in those trials that combine chemotherapy and radiotherapy.

Reduced-dose consolidation radiotherapy

Since not giving consolidation WBRT for patients with complete response to chemotherapy is controversial, reduced-dose WBRT is an alternative approach, particularly for patients younger than 60 years who are at a lower risk of developing neurotoxic effects. In a subset analysis[65] from a phase 2 trial that included 25 patients younger than 60 years who achieved a complete response after initial chemotherapy and received either 45 Gy or 30·6 Gy as consolidation treatment, patients who received reduced-dose radiotherapy showed a significantly higher proportion of recurrences and a lower overall survival than did those who received high-dose radiotherapy (class IIIb). Conversely, in a retrospective study[66] of 33 patients with primary CNS lymphoma who achieved a complete response after methotrexate-based chemotherapy and were referred to consolidation WBRT, total WBRT doses of greater than 40 Gy of WBRT were not associated with improved disease control when compared with a WBRT dose of 30–36 Gy (class IIIb). More recently, in a phase 2 trial that assessed an immunochemoradiation regimen that consisted of rituximab and high-dose methotrexate-based polychemotherapy, the 31 patients who achieved a complete response and were offered reduced-dose WBRT (23 Gy) showed encouraging results both in terms of survival and neurotoxic effects (class IIb).[19] On the basis of these results, a randomised phase 2 study (RTOG-1114) comparing a regimen of rituximab, methotrexate, procarbazine, vincristine, and cytarabine with or without reduced-dose WBRT is ongoing (NCT01399372).

In summary, the role of consolidation WBRT, and optimum dose of radiotherapy, after high-dose methotrexate-based chemotherapy remains debated, especially in patients who have achieved a complete response.

High-dose chemotherapy, myeloablative conditioning, and autologous stem-cell transplantation

High-dose chemotherapy with autologous stem-cell transplantation (HDC-ASCT) is the standard treatment for chemosensitive systemic relapsing diffuse large B-cell lymphomas. However, there is only one multicentre phase 2 trial[67] investigating this treatment in patients with relapsed or refractory primary CNS lymphoma, in which a thiotepa, busulfan, cyclophosphamide conditioning regimen was used, followed by ASCT. 27 (63%) of 43 patients completed the full HDC-ASCT procedure, of whom 60% achieved a complete response. Median progression-free survival was 41 months and median overall survival was 58 months for the 27 patients who completed the full HDC-ASCT procedure. In the whole intention-to-treat population, median progression-free survival was 11 months and median overall survival was 18 months. Mortality due to toxic effects was 7% (class IIb). Updated results from this study, in addition to an independent retrospective single-centre series, confirmed the benefit of the thiotepa, busulfan, cyclophosphamide regimen followed by ASCT (class IIIb).[68,69] Data on alternative high-dose chemotherapy regimens for relapsed or refractory disease is scarce, preventing any conclusions on their use. Because of the risk of toxicity associated with HDC-ASCT, this regimen is more often given to younger patients (<60–65 years) with a good performance status which makes comparison with other salvage treatments such as second-line conventional chemotherapy regimens and WBRT in older patients, difficult.

The specific role of HDC-ASCT as a consolidation treatment in first-line treatment plan is difficult to assess due to subsequent treatment with WBRT after HDC-ASCT in initial studies that used this treatment (class IIb).[70,71] The first study that used HDC-ASCT without WBRT used the BEAM regimen (carmustine, etoposide, cytarabine, and melphalan) as a conditioning treatment and reported a disappointing median event-free survival of 9·3 months (class IIIa).[72] Subsequently, results from studies[73–76] that omitted WBRT, at least in patients that had a complete response HDC-ASCT with high-dose thiotepa-based conditioning regimens, have been encouraging (class IIIb and class IV). Therefore, although direct comparison between conditioning regimens is difficult, high-dose thiotepa-based conditioning regimens seem to be more efficient than BEAM-based regimens. In summary, HDC-ASCT is an effective treatment option for selected patients with refractory and relapsed primary CNS lymphoma. However, this option should be reserved for centres with a high level of experience with these treatments. The HDC-ASCT approach as a first-line treatment has not been proven to be superior to standard combined chemoradiotherapy and is currently under investigation in two trials (NCT00863460, NCT01011920).

Elderly patients

Although the definition of elderly is non-uniform within the literature, studies that have assessed prognostic factors have consistently correlated older age (over 50 or 60 years) with poorer outcome (appendix). Furthermore, older age (greater than 60 years) was associated with a higher risk of neurotoxic effects of chemoradiation (appendix). Therefore, 60 years of age was used as a cutoff to define the elderly population in most of the studies that we examined.

Four prospective studies[37,64,77,78] have been published on the treatment of elderly patients with primary CNS lymphoma (class IIb). Seven prospective studies[14,15,33,44,53,55,79]

of patients of all ages reported specifically on elderly patients (class IIIa) and seven retrospective studies[80–86] included 15 or more patients who were elderly (class IIIb). As reported in younger patients, treatment with steroids or cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP), in addition to radiotherapy, does not provide additional benefit compared to radiotherapy alone for elderly patients (class IIb).[14,15,44,78] In the Radiation Oncology Therapy Group (RTOG) phase 2 trial[44] that investigated high-dose radiotherapy alone, the median survival for patients over 60 years of age (27 of 41 patients) was only 7·8 months. After methotrexate-based therapy of at least 1 g/m² methotrexate, median progression-free survival in patients aged 60 or 65 years and older was between 6 and 16 months and median overall survival was between 14 and 37 months (class IIb and class III). Overall survival in most prospective studies[33,37,53,55,64,74,79–86] was less than 2 years. Except within retrospective studies, no direct comparisons have been made between high-dose methotrexate-based chemotherapy and radiotherapy in this age group.[82] However, results from the single-arm studies suggest that survival after chemotherapy is at least as good and probably better after high-dose methotrexate-based chemotherapy than after radiotherapy (class IV). Formal comparisons of different high-dose methotrexate-based regimens have not been published, but in a recently completed randomised phase 2 study[8] of elderly patients treated with either MPV-A (methotrexate, procarbazine, vincristine, cytarabine) or methotrexate plus temozolomide, toxic effects were identical in both treatment groups. There was a suggestion of benefit with MPV-A compared with methotrexate plus temozolomide in terms of the proportion of patients with a complete response, median progression-free survival, or overall survival, although these differences were not significant (class IIa).

Five prospective studies[37,53,64,77,87] measured toxic effects of chemotherapy in elderly patients (older than 60 years). With the exception of one study[53] in which an intensive multidrug regimen was used and toxic effects were extremely high in elderly patients, high-dose methotrexate-based chemotherapy up to 3·5 g/m² was well tolerated.[37,64,77,87] Treatment-related mortality was 2–7% and less than 10% of patients had grade 3–4 nephrotoxic effects. 7–10% of patients discontinued treatment because of chemotherapy-associated toxic effects and the dose was reduced in patients with decreased renal function (26–44% of patients). In general, if renal function is adequately monitored and measures are taken to reduce toxic effects, elderly patients are able to tolerate treatment with high-dose methotrexate.[3]

As shown in the appendix, the risk of delayed leukoencephalopathy is particularly high in patients older than 60 years who receive chemoradiotherapy. For patients treated with high-dose methotrexate-based chemotherapy without radiotherapy, reports[8,62,88] that include neuropsychological assessments show little or no cognitive decline due to treatment (class IIa, class IIIb).

In view of the available data on acute and long-term toxic effects of radiotherapy and chemotherapy in elderly patients with a Karnofsky performance status of 70 or greater, the treatment of choice in elderly patients is high-dose methotrexate-based chemotherapy with deferral or elimination of WBRT. In those elderly patients with poor performance status and in those older than 80 years, a worse prognosis is expected.[86] Therefore, the acute morbidities and frequent hospital admissions associated with high-dose methotrexate chemotherapy need to be individually weighed against the poorer probability of any survival benefit in this population.

Salvage treatment

About a third of patients with primary CNS lymphoma will present with disease that is refractory to first-line treatment and half of responders will relapse despite the high proportion of patients who respond to initial treatment. The prognosis of progressive or relapsed primary CNS lymphoma is poor, with few treatment options. Salvage treatments for patients with relapsed or refractory primary CNS lymphoma depend on age, performance status, site of relapse within the CNS, previous treatments, and time since the last response. If the patient did not receive any consolidation treatment after high-dose methotrexate-based induction chemotherapy, therapy with WBRT or HDC-ASCT should be considered. Two retrospective studies[89,90] have assessed WBRT delivered to patients with relapsed primary CNS lymphoma and reported a high proportion of patients with objective reponses and a short median overall survival duration of 11–16 months. These results are similar to what is expected with WBRT alone as initial treatment (class IIIb). Delayed neurotoxic effects occurred in 15–22% of patients. However, when lymphomas recur, WBRT does not extend survival compared with non-WBRT-based therapies, as shown in the G-PCNSL-SG-1 trial[7] (class IIIa).

As previously discussed in this Review, HDC-ASCT is an efficient alternative option and should preferentially be given to patients younger than 60–65 years of age and who have a tumour that is sensitive to second-line chemotherapy (class IIb).[67–69]

If the patient is not suitable for WBRT or HDC-ASCT, conventional chemotherapy can be proposed as a second-line treatment. Only a few prospective studies are available, all of which have been single-arm phase 2 trials. Therefore, comparison across trials is difficult (class IIb, class III, and class IV). Several drugs such as temozolomide,[39,91] topotecan,[92] pemetrexed,[93] bendamustine,[94] PCV regimens,[95] ifosfamide–etoposide-based regimens,[38,96] or cisplatin–cytarabine-based regimens,[97] used alone or in combination, with or without rituximab, have been shown to have slight activity. Rechallenge with methotrexate given alone or in combination with the aforementioned drugs might

likewise yield a high proportion of new objective responses and durable remission in patients who had previously achieved long-lasting responses with high-dose methotrexate-based chemotherapy, suggesting retained chemosensitivity to methotrexate (class III).[98,99] Extra-CNS relapses account for 7% of treatment failures and results of some studies[100] suggest that extra-CNS relapses are associated with a better prognosis than those in the CNS. The best salvage treatment for extra-CNS relapses remains to be defined, although excellent results have been reported with anthracycline-based chemotherapy, whether consolidated with HDC-ASCT or not.[29]

Conclusion

Our guidelines represent the state of knowledge at the time of writing. The European Association for Neuro-Oncology website will provide future updates on these guidelines.

For more on the **guidelines** see https://www.eano.eu

Contributors

KH-X chaired the task force. EB, JB, AFH, KH-X, MP, RR, US, TS, and CS wrote the draft guideline, which was subsequently submitted to the review committee UA, NC, MD, CMFD, AJMF, FG, RH, UH, RS, MT, and MW. The revised guideline, which takes into account the comments of the reviewers, was resubmitted by the chairman twice to the whole task force for review and amendments.

Declaration of interests

KH-X was the principal investigator of a trial that investigated temozolomide (Schering-Plough) in primary CNS lymphoma. UA reports personal fees from Varian and BrainLAB AG. MP reports grants from GlaxoSmithKline, Roche, Boehringer Ingelheim, personal fees from GlaxoSmithKline, Roche, Bristol-Myers Squibb. US reports personal fees from Roche, Medac, GlaxoSmithKline. MT reports honoraria ad-hoc consultancy for Hoffmann-La Roche. MW reports grants and personal fees from Roche, Merck Serono, Isarna, and Novocure, grants from Bayer and Piqur, and personal fees from Celldex and Magforce. All other authors declare no competing interests.

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