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

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Abstract: The management of primary central nervous system (PCNSL) is one of the most controversial topics in neuro-oncology because of the complexity of the disease and the very limited number of controlled studies available. In 2013, the European Association of Neuro-Oncology (EANO) created a multidisciplinary task force to establish evidence-based guidelines for immunocompetent adult patients with PCNSL. The guideline provides consensus considerations and recommendations for diagnosis, staging and treatment of PCNSL, including surgery, systemic and intrathecal chemotherapy, intensive chemotherapy with autologous stem cell transplantation, radiotherapy, intraocular manifestations, and specific management of elderly patients. The guideline should aid the clinicians in everyday practice and decision making and serve as a basis for future research in the field.

***Reply to Reviewers Comments**

Dear Editor,

Thank you for your suggestions to improve further our paper. Please, find in attached file our revised manuscript which have take into account all your editorial recommendations. You will find below our point by point replies to your editorial comments. We hope that you will find now the manuscript suitable for publication in Lancet Oncology.

Kind regards

Khe Hoang-Xuan, MD,PhD

Responses to the Editor comments

1) In response to Reviewer 1, comment 2, please revert and move the intraocular lymphoma section back to the appendix as in the original version.

RESPONSE: The intraocular lymphoma section is now back to the appendix with the corresponding references

2) In response to your reply to Reviewer 2, comment 1, please leave the tables as they are.

RESPONSE: OK

3) In response to your reply to comment 3 from Reviewer 3 (regarding guidelines for treatment of patients for which there are no evidence based recommendations), please summarize your reply and add it to the text to clarify that it is not possible to provide evidence-based recommendations for patients with tumours that cannot be or are too risky to biopsy.

RESPONSE: Two sentences have been added in the general recommendation section (p.4)

"Our guideline covers treatment of histologically or cytologically proven PCNSL. We have not covered specifically the treatment of patients with deep seated tumours not readily amenable to biopsy for which there are no evidence-based recommendations. We believe that biopsies are almost always possible in specialized centers and that chemotherapy and/or radiotherapy interventions without histological confirmation of PCNSL should be discouraged."

EANO Guideline for the diagnosis and treatment of primary CNS lymphoma in immunocompetent patients.

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Abstract

The management of primary central nervous system (PCNSL) is one of the most controversial topics in neuro-oncology because of the complexity of the disease and the very limited number of controlled studies available. In 2013, the European Association of Neuro-Oncology (EANO) created a multidisciplinary task force to establish evidence-based guidelines for immunocompetent adult patients with PCNSL. The guideline provides consensus considerations and recommendations for diagnosis, staging and treatment of PCNSL, including surgery, systemic and intrathecal chemotherapy, intensive chemotherapy with autologous stem cell transplantation, radiotherapy, intraocular manifestations, and specific management of elderly patients. The guideline should aid the clinicians in everyday practice and decision making and serve as a basis for future research in the field.

Introduction

Primary central nervous system lymphomas (PCNSL) are extranodal malignant non-Hodgkin lymphomas (NHL) of the diffuse large B cell (DLBCL) type confined to the brain, eyes, leptomeninges, or spinal cord in the absence of systemic lymphoma. Currently PCNSL are estimated to account for up to 1% of lymphomas, 4-6% of all extranodal lymphomas, and about 3% of all CNS tumors.[1] After a continuous increase in the 1980's and 1990's, epidemiologic data in Western countries show a decrease in the incidence of PCNSL, particularly among young patients suffering from AIDS.[2] In contrast, the incidence continues intriguingly to rise in the elderly who represent consequently the large majority of patients in the immunocompetent population in some recent studies.[3-5] Although the prognosis of PCNSL remains poor, it has significantly improved over the past two decades as a result of better treatment strategies with a curative aim. Treatment of PCNSL is challenging. Despite a high chemosensitivity and radiosensitivity, remissions are frequently short-lasting; the blood brain-barrier (BBB) limits the access of many drugs to the CNS; and patients, especially the elderly, are at high risk of developing severe treatment related-neurotoxicity. To date, therapeutic knowledge to define the optimal treatment mainly results from retrospective series or single arm phase II studies, with only three completed randomized trials available: one phase III and two phase II. The objective of this guideline is to provide clinicians with evidence-based recommendations and consensus expert opinions on the management of patients with PCNSL. The present guideline focuses on the immunocompetent population which represents the vast majority of the patients today. PCNSL of immunodeficient patients and the rare indolent low grade lymphomas occurring primarily in the CNS, which have a distinct pathogenesis with separate diagnostic and therapeutic implications, will be subject to specific guidelines.

Search strategy and selection criteria

The guideline task force was set up in 2013 under the auspices of the EANO (European Assocation for Neuro-Oncology) and selected to be representative of European-based medical experts (10 countries). The panel covered all fields of expertise in the management of PCNSL, i.e. neurologists, haematologists, medical oncologists, neurosurgeons, pathologists, ophthalmologists and radiation oncologists. Based on best available evidence from literature review, the writing group (EB, JB, AH, KHX, MP, RR, US, TS, CS) produced the draft guideline, which was subsequently submitted to the review committee (UA, NC, MD, CD, AF, FG, RH, UH, RS, MT, MW). The revised guideline, taking into account the comments of the reviewers, was resubmitted by the chairman to the whole task force for review and amendments twice. Therafter, final agreement was obtained in September 2014. When

analyzing results and drawing recommendations, at any stage, differences were resolved by discussiondiscussion and, if persisting, were reported in the text. References for this review 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” from January 1980 to September 2014. Articles were also identified through searches of the authors` own files. The final reference list was generated on the basis of originality and relevance to the broad scope of this review. Abstracts presented at the annual ASCO meeting in 2013 and 2014 relevant to the topic were included by task force members during manuscript preparation. The scientific evidence of papers collected from the literature was evaluated and graded as follows and recommendations were given accordingly. Class I evidence was derived from prospective, randomized, phase III clinical trials; class IIa evidence was derived from prospective randomized phase II trials, class IIb evidence was derived from phase II trials; class IIIa was derived from prospective studies, including observational studies, cohort studies and case–control studies; class IIIb evidence was derived from retrospective studies; class IV evidence was derived from uncontrolled case series, case reports and expert opinion. As for recommendations, level A required at least one class I study or two consistent class IIa studies, level B at least one class IIa study or overwhelming class IIb and III evidence and level C at least two consistent class III studies. Pathology, genetics, clinical features and neuroimaging were simply reviewed but not graded. When sufficient evidence for recommendations A–C was not available, we gave a recommendation as a “Good Practice Point”, if agreed by all members of the Task Force.

General recommendations

Consensus statements and recommendations for the general approach to patients with PCNSL, including: 1/ pathology and genetics, 2/ clinical presentation, 3/ diagnostic confirmation, 4/ neuropathology of corticosteroid-treated PCNSL, 5/ neuroimaging, 6/ cerebrospinal fluid (CSF) analyses, 7/ vitreous analyses, 8/ staging, 9/ prognostic factors, 10/ response criteria to treatment, and 11/ treatment-related neurotoxicity are presented in table 1. The evidences used to establish these recommendations are detailed in the supplementary webappendix. Key recommendations for treatment are summarized in table 2. The evidences concerning intraocular lymphoma are presented in the webappendix. Our guideline covers treatment of histologically or cytologically proven PCNSL. We have not covered specifically the treatment of patients with deep seated tumours not readily amenable to biopsy for which there are no evidence-based recommendations. We believe that biopsies are almost always possible in specialized centers and that chemotherapy and/or radiotherapy interventions without histological confirmation of PCNSL should be discouraged.

Surgery

Although very few data are available in the literature, surgery has traditionally been considered to have no role in the treatment of PCNSL. This widely adopted opinion is based on small retrospective series suggesting no clear benefit in outcome of surgical resection used as sole treatment compared with supportive care (Class IIIb),[6] and compared with biopsy in patients having received post-operative chemotherapy and/or radiotherapy (Class IIIb).[7,8] This may be explained by the microscopically multifocal and infiltrative nature of PCNSL that may extend beyond the visible border of the lesion.[9] The relative radiosensitivity and high chemosensitivity of PCNSL, and the increased risks of postoperative morbidity of this patient population have also contributed to discourage surgery. However, the recommendation to restrict surgical interventions to biopsies is not based on randomized data and, more importantly, not on contemporary data reflecting modern neurosurgery. The German PCNSL Study Group–1 phase III trial included an unusually high rate of operated patients, which allowed the largest and most recent retrospective analysis of an association of surgery and outcome. A significantly longer progression free survival (PFS) and overall survival (OS) in patients with subtotal or gross total resections compared with biopsied patients was reported. This difference in outcome was independent of post-operative Karnofsky performance status (KPS) and age. Since biopsied patients more often had multiple and/or deeply seated CNS lesions than resected patients, these features may have contributed to the unfavourable outcome. When adjusted for the number of lesions (site of the lesions was not analyzed in the study), the difference in outcome remained significant in term of PFS but did not reach the significance threshold for OS (Class IIIa).[10]

Systemic chemotherapy

The CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) regimen commonly used for systemic NHL induces short-lasting responses in PCNSL and its addition to radiotherapy has not shown a survival benefit in prospective trials (Class IIb).[11-13] This inefficacy is probably due to the fact that phosphoramide mustard and doxorubicin are not able to cross the blood-brain barrier (BBB) to eradicate microscopic disease. Based on convergent results from numerous prospective and retrospective studies, high-dose (HD) intravenous (iv) methotrexate (MTX), an antifolate and antimetabolite, is now considered the most important and beneficial single agent. Penetration of MTX into the CNS depends both on the total dose and rate of infusion. The optimal dose of MTX has not been determined. It has been estimated that the iv MTX should range between 1 g/m^2 and 8 g/m^2 to cross the BBB. In the absence of clear evidence for dose-response relationship, and since rapid infusion of MTX $\geq$ 3g/m^2 over 3 hours achieves cytotoxic levels in the CSF, there is a growing consensus to deliver MTX according to this protocol (Class IV).[14] Since efficacy of MTX may also depend on duration of exposure, MTX administration interval should range between 10 days and 3

weeks (Class IV).[15] The optimal number of MTX injections to deliver is unknown. A minimum of 4-6 injections is delivered in most chemotherapy regimens, especially if no consolidation treatment (radiotherapy and/or intensive chemotherapy) is scheduled in the protocol. For patients who achieved only partial response (PR) after 4-5 courses of HD MTX, additional courses may improve the complete remission rate (Class IIIa).[16] Infusions of HD MTX require pre- and post-hyperhydration, urine alkalinization, leucovorin rescue and MTX concentration monitoring. Currently most treatment protocols combine HD MTX with a variety of other chemotherapeutic agents to improve response rate and outcome. The best evidence to support this approach comes from an IELSG randomized phase II study comparing HD MTX alone, administered at 3 g/m^2/d every 21 days, to HD MTX with cytarabine (2 g/m^2 twice per day on days 2–3)(Class IIa).[17] Both chemotherapy arms were followed by WBRT. This study showed a significantly higher complete response (CR) rate in the HD MTX-cytarabine arm. Regarding secondary endpoints, a significantly improved overall response rate (ORR), PFS and a trend towards better OS in the HD MTX-cytarabine arm were noticed. Two previous prospective trials evaluating HD MTX at a dose of $8g/m^2$ as single agent and without immediate consolidation WBRT resulted in a shorter PFS when compared to polychemotherapy regimens (Class IIb).[18,19] Similarly, the addition of ifosfamide to HD-MTX improved response rate, but not survival, in the G-PCNSL-SG-1 trial.[20] Altogether, these data resulted in the recognition that only HD MTX can be defined as a chemotherapy standard of care.[21] Chemotherapeutic agents to be combined with HD MTX should be selected among active drugs known to cross the BBB, such as HD cytarabine. Recently, the CALGB50202 multicenter phase II trial reported promising results using HD cytarabine combined with etoposide as consolidation without WBRT following a HD MTX-based polychemotherapy as induction regimen (Class IIb).[22] In contrast, very disappointing results have been reported in a pilot study combining HD MTX ($3.5g/m^2$), thiotepa and cytarabine at a reduced dose of $1g/m^2$ suggesting that the cytarabine dose probably was suboptimal to reach cytototoxic levels in the CNS (Class IIIa),[23] as supported by pharmacokinetic studies.[24] Another approach is BBB disruption (BBBD) by intra-arterial (IA) infusion of hypertonic mannitol followed by intra-arterial (IA) chemotherapy to increase the drug concentration in the CNS. BBBD with IA MTX administrated in newly diagnosed PCNSL demonstrated a good safety profile and neurocognitive tolerance and achieved comparable outcomes to those observed with HD-intravenous MTX based chemotherapy regimens (Class IIIb).[25-27] However, conversely to those reported in prospective studies on chemoradiotherapy, even after a follow-up longer than 10 years (Class IIb),[28] BBBD is not associated with a plateau in survival curves, suggesting a continuum of relapses and deaths. This procedure requires patient selection as safety depends on the extent of intracranial mass effect and the procedure is limited to patients with no contraindications for general anesthesia. It should be managed by teams trained in BBBD as it is complex, requiring cannulation of the intracranial vessels. In summary, HD MTX is the drug of choice for PCNSL. In patients who are not eligible for HD MTX, treatment should be chosen from treatments

active as salvage in refractory or recurrent PCNSL after initial HD MTX based chemotherapy (see salvage treatment section).

Intrathecal chemotherapy

Intrathecal (IT) chemotherapy administration has not been prospectively studied and its efficacy in PCNSL remains debated. Three retrospective studies did not demonstrate benefit from the addition of intrathecal drugs (MTX, cytarabine) in patients treated with HD MTX dosed at 3g/m^2 (Class IIIb).[29-31] In contrast, two consecutive single arm trials using the same systemic polychemotherapy regimen suggested additional benefit when intraventricular chemotherapy was added (Class IIIa).[32,33] However, given the low level of evidence, we currently do not advocate IT chemotherapy as prophylaxis.

Rituximab

Based on its poor penetration into the CNS related to its large size, the maximal concentration and efficacy of the anti-CD20 antibody rituximab in the CNS might be assumed to occur in the early treatment phase, during BBB breakdown within the tumors. The effect of rituximab when used as monotherapy in PCNSL was evaluated in a single study in which 12 patients with refractory or relapsed PCNSL were treated with a weekly iv dose of 375 mg/m^2 rituximab infusion for up to eight doses (Class IV).[34] MRI responses were observed in 36% of patients. Other studies used iv rituximab in combination with a HD MTX-based chemotherapy regimen as initial treatment for newly-diagnosed PCNSL or as salvage treatment for recurrent PCNSL (Class IIIa, Class IIIb and IV).[16,22,35-41] Three studies suggested that the addition of rituximab to HD MTX-based chemotherapy improves the CR and OS ratein patients with newly-diagnosed PCNSL based on retrospective comparison with historical controls (Class IIIb).[39-41] Overall, the addition of rituximab to systemic polychemotherapy is well tolerated. Injection of rituximab into the CSF via either lumbar puncture or by intraventricular administration was evaluated in phase I for refractory or recurrent CNS lymphoma patients (Class IIIa).[42] In these studies objective responses and good tolerability were documented confirming small case series. In conclusion, the existing level of evidence supporting either systemic or local use of rituximab as part of treatment protocol for PCNSL remains low. Yet, the preliminarily available information suggests that it may add some benefit. Two ongoing randomized trials (NCT01011920; NTR2427) should clarify the role of systemic rituximab in PCNSL.

Radiotherapy

Because of the microscopically diffuse and multifocal nature of PCNSL, radiotherapy (RT) has so far involved the whole brain, including the eyes. Despite a high response rate in the range of 50%, RT used as sole treatment modality, provides limited survival benefit in PCNSL patients, with a median OS duration of 10–18 months and a 5-year survival rate of 5%. The only phase II trial, conducted by the RTOG, which delivered a total dose of 40 Gy with an additional 20-Gy boost to contrast-enhancing lesions, reported a disappointing 11.6 month OS (Class IIb).[43] In addition, the majority of relapses occurred in fields that had received the highest RT dose. Although not formally compared in a randomized trial, a wide consensus is shared which considers that HD MTX-chemoradiation is superior to RT-alone, allowing for a 2 to 4-fold increase in OS (median: 30-72 months) and long-term survivors (5-year survival of 20-50%) for many protocols (Class IIb, IIIa IIIb).[15,44-52] In contrast to extracerebral NHL, the optimal dose of post-chemotherapy irradiation has never been prospectively investigated in PCNSL.[53] Doses of 23–50 Gy to the whole brain, with or without a tumor bed boost, are currently used, with most of the protocols delivering a total dose of 40–45 Gy without boost, and standard fractionation (1.8-2Gy/fraction). The RTOG-9310 trial did not show a clear benefit with hyperfractionated WBRT (Class IIb).[54] For patients who achieve a CR after HD MTX-based chemotherapy, it remains unclear whether consolidation with WBRT provides better disease control or survival. There has only been one randomized trial of radiotherapy versus watch-and-wait after chemotherapy for PCNSL. This study (G-PCNSL-SG 1) conducted in Germany was a non-inferiority phase III trial, in which patients received HD MTX 4g/m^2 iv every 14 days for 6 cycles with or without ifosfamide. Those patients who achieved a CR had been randomized initially between consolidating WBRT, 45 Gy in 30 fractions over 6 weeks or no further immediate treatment. Patients without a CR received HD cytarabine or WBRT. A total of 551 patients entered the study, but 318 patients were treated per-protocol. OS was similar in both arms. In the whole per-protocol population, the WBRT arm was associated with a trend (not significant) for better PFS, as compared with the no WBRT arm but with no significant difference in OS.[20] This trial (Class I), which is, to date, the largest one and only phase III trial in PCNSL has raised vigourous debate within the community.[55-58] Several experts consider that the unmet primary endpoint for non-inferiority and the high rate of protocol violations prevent any conclusions being drawn from the trial and advocate keeping consolidation WBRT after HD MTX-based chemotherapy as the standard of care, whilst awaiting results from further, ongoing randomized trials; while others, acknowledging the methodological limitations of the study, consider nevertheless that the results contribute strongly to the accumulating retrospective literature suggesting that omission of WBRT from first-line treatment results in shorter PFS but does not compromise OS (Class IIIb).[29,59,60] In addition, several single arm trials have suggested that chemotherapy alone, plus a deferred RT strategy may result in comparable OS with those reported for combined chemo-RT but with better neurocognitive preservation (Class IIb, IIIa, IIIb).[19,25,26,32,61-63] Since withdrawing consolidation WBRT for patients with CR to chemotherapy remains controversial, especially in patients less than 60 years old who are at lower risk of developing neurotoxicity, reduced

dose WBRT is another alternative approach. Conflicting results have been reported. A subset analysis from a phase II trial that included 25 patients aged <60 years who achieved a CR after initial chemotherapy and received either 45 Gy or 30.6 Gy as consolidation treatment showed a significantly higher recurrence rate and lower OS rate in the reduced-dose RT group (Class IIIb).[64] On the other hand, in a restrospective study of 33 patients with PCNSL who achieved CR after MTX-containing chemotherapy and were referred to consolidation WBRT, total doses ≥ 40 Gy were not associated with improved disease control in comparison with a WBRT dose of 30-36 Gy (Class IIIb).[65] More recently, a phase II trial evaluating an immunochemoradiation regimen (R-MPVA) including rituximab and HD MTX-based polychemotherapy, the 31 CR patients were offered reduced dose WBRT (23 Gy in complete responders) with encouraging results both in term of survival and neurotoxicity (Class IIb).[16] Based on these results, a randomized phase II study (RTOG-1114) comparing the R-MPV regimen with or without reduced-dose WBRT is currently ongoing (NCT01399372). In summary, the role of consolidation WBRT following HD-MTX based chemotherapy remains debated especially in patients in CR. In addition, the optimal dose has not been defined yet.

High-dose chemotherapy, myeloablative conditioning and autologous stem cell transplantation (HDC /ASCT)

HDC/ASCT is the standard treatment for chemosensitive relapsing systemic DLBCL. For patients with relapsed or refractory PCNSL, there is only one multicenter phase II trial evaluating HDC/ASCT, with TBC conditioning regimen (thiotepa, busulfan, cyclophosphamide). The CR rate was 60%, median PFS and OS were 41 and 58 months respectively for the 27 patients out of 43 who completed the full HDC/ASCT procedure. For the whole population of this trial, the intent-to-treat median PFS and OS times were 11 and 18 months respectively. The toxicity-related mortality was 7% (Class IIb).[66] An update of this study to which additional cases have been included, and an independent retrospective single center series confirmed the benefit of the TBC regimen followed by ASCT (Class IIIb).[67,68] Experiences with other HDC regimens in this setting of patients are limited to a few cases, which prevent any conclusions being drawn. Because of its toxicity risks, the HDC/ASCT is likely to be proposed for younger patients (<60-65 years) with a good performance status, which makes it difficult to compare with other salvage treatments, including second-line conventional chemotherapy regimens and WBRT. The specific role of HDC/ASCT as consolidation in first-line treatment is difficult to evaluate since WBRT was administered after HDC/ASCT in early studies (Class IIb).[69,70] The first study with HDC/ASCT without WBRT used the BEAM regimen (BCNU, etoposide, cytarabine, and melphalan) as conditioning and reported a disappointing median event-free survival of 9.3 months (Class IIIa).[71] Subsequently, encouraging studies for which WBRT had been omitted at least in patients in CR after HDC/ASCT using HD thiotepa-based conditioning regimens have been reported (Class IIIb and IV).[72-75] Taken together, although direct comparison between conditioning

regimens applied is difficult, HD thiotepa-based conditioning regimens seem more efficient than BEAM-based regimens. In summary, HDC/ASCT represents an effective treatment option for selected refractory and relapsed PCNSL patients, but should be reserved to experienced centers. Superiority of the HDC/ASCT approach compared to standard combined chemo-radiotherapy as first line treatment has not been proven and is currently under investigation in two ongoing trials (NCT00863460, NCT01011920).

Elderly patients

Definition of 'elderly' is not uniform. However, in the studies available which have evaluated prognostic factors, older ages (over 50 and over 60) were consistently correlated with worse outcome (see the section on prognostic factors in appendix). Furthermore, for chemoradiation-induced neurotoxicity age>60 was found to be highly prognostic (see the section on neurotoxicity in appendix). Therefore, age of 60 has been used as cut-off to define the elderly population in most of the studies. Four prospective studies have been published on treatment of elderly patients with PCNSL (Class IIb),[36,63,76,77] seven prospective studies on patients of all ages but reporting specifically on older patients (Class IIIa),[11,12,32,43,52,54,78] and seven retrospective studies reporting on ≥ 15 patients (Class IIIb).[79-85] As in younger patients, results in patients treated with steroids or CHOP/CHOD in addition to radiotherapy do not differ from results after radiotherapy only (Class IIb).[11,12,43,77] In the RTOG phase II trial, the median survival was only 7.8 months.[43] After HD-MTX-based therapy, defined as dose of MTX ≥ 1 g/m^2 PFS in patients aged 60 or 65 and older is reported between 6 and 16 months and OS between 14 and 37 months (Class IIb and Clas III) with OS in the majority of prospective studies under 2 years.[32,36,52,54,63,73,78-85] Other than within retrospective studies no direct comparisons have been made between treatment with HD-MTX-based chemotherapy and radiotherapy in this age group.[81] However, the impression from the single arm studies is that survival after chemotherapy is at least as good and probably better after HD MTX-based chemotherapy than after radiotherapy (Class IV). Formal comparisons of different HD MTX-based regimens have not been published but in a recently completed randomized phase II study, toxicity was identical, CR rate, median PFS and survival appeared better after MPV-A (MTX, procarbazine, vincristine, cytarabine) than after MTX and temozolomide though the difference was not significant (Class IIa).[86] Five prospective studies report on chemotherapy toxicity in patients aged over 60. With the exception of one study, in which an intensive multi-drug regimen was used and toxicity was exceedingly high in older patients,[52] HD MTX-based chemotherapy up to 3.5 g/m^2 was well tolerated with 2-7% treatment-related mortality, less than 10% grade 3-4 nephrotoxicity and 7-10% of patients discontinuing treatment due to chemotherapy-associated toxicity, though MTX dose was reduced because of decreased renal function in 26-44% of patients.[36,63,76,87] Retrospective studies substantiate this view. Thus, in general, older patients tolerate treatment with HD-MTX well when adequate supportive measures are used and renal

function is accurately monitored.[3] As discussed in the neurotoxicity section (appendix), risk of delayed leukoencephalopathy is particularly high in patients older than 60 years managed with chemoradiotherapy. For patients treated with HD-MTX-based chemotherapy without radiotherapy no studies reporting specifically on older patients are available, but reports including neuropsychological assessment of patients of all ages show little or no cognitive decline compared with post-treatment evaluations (Class IIIb).[61,88] Given the available data on acute and long-term toxicity of radiotherapy and chemotherapy in older patients with performance status KPS ≥ 70, treatment with HD MTX-based chemotherapy with deferral or elimination of WBRT is the treatment of choice. In older patients in poor condition and in the very old (over 80) who both have a worse prognosis,[85] the acute morbidities and frequent admissions to hospital associated with HD-MTX chemotherapy need to be individually weighed against the more limited survival benefits in this population.

Salvage treatment

About one third of patients with PCNSL will present with disease that is refractory to first-line treatment and half of responders will relapse despite high response rates seen with initial treatment. The prognosis of progressive or relapsed PCNSL remains poor with limited treatment options. Salvage treatments for relapsed or refractory PCNSL patients depend on age, performance status, site of relapse within the CNS, prior treatments and time duration from last response. If the patient did not receive any consolidating treatment after the HD MTX-based induction chemotherapy, WBRT or HDC/ASCT should be considered. Two retrospective studies have evaluated WBRT delivered in relapsed PCNSL and reported a high rate of objective reponses and a short median survival of 11-16 months - quite similar to what is expected with WBRT alone as initial treatment (Class IIIb).[89,90] Delayed neurotoxicity occurred in 15%–22% of patients. However, in the setting of recurrence, WBRT did not prolong survival compared with non-WBRT-based therapies in the G-PCNSL-SG-1 trial (Class IIIa).[20] HDC/ASCT is an efficient alternative option, as has been previously discussed, and which should be preferentially proposed for patients aged < 60-65 years and with a tumour sensitive to second-line chemotherapy (Class llb) (see section above).[66-68] Otherwise, if the patient is not suitable for WBRT or HDC/ASCT , conventional chemotherapy can be proposed as second-line treatment. There is however, only a limited number of prospective studies available for guidance and these have been single-arm phase ll trials complicating any comparison across trials (Class llb, lll and lV for all studies in this section). Several drugs used as single agent or in combination, with or without rituximab, have been evaluated and demonstrated modest activity such as temozolomide,[38,91] topotecan,[92] pemetrexed,[93] bendamustine,[94] PCV regimen,[95] ifosfamide-etoposide based regimen,[37,96], or cisplatin-cytarabine based regimen.[97] MTX rechallenge given as single agent or in combination may also yield a high rate of new objective response and durable remission in patients who previously achieved prolonged response with HD MTX-based chemotherapy, suggesting retained

chemosensitivity to MTX (Class III).[98,99] Extra-CNS relapses account for 7% of failures, and some studies suggest that extra-CNS relapses are associated with a better prognosis than CNS-involving relapses;[100] the best salvage treatment for this condition remains to be defined, but excellent results have been reported with anthracycline-based chemotherapy consolidated or not with HDC/ASCT.[28]

Conclusions

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

Contributors

KHX chaired the task force. Based on best available evidence from literature review, the writing group (EB, JB, AH, KHX, MP, RR, US, TS, CS) produced the draft guideline, which was subsequently submitted to the review committee (UA, NC, MD, CD, AF, FG, RH, UH, RS, MT, MW). The revised guideline, taking into account the comments of the reviewers, was resubmitted by the chairman to the whole task force for review and amendments twice.

Declaration of interest

KHX was the principal investigator of a trial investigating temozolomide (Scherring-Plough) in PCNSL and declare no competing interest. UA reports personal fees from Varian and BrainLAB AG outside the submitted work. MP reports grants from GSK, Roche, Böhringer-Ingelheim, personal fees from GSK, Roche, BMS, outside the submitted work.US reports personal fees from Roche, Medac, GSK, outside the submitted work. MT reports honoraria ad hoc consultancy for Hoffmann La Roche, outside the submitted work. MW reports grants and personal fees from Roche, Merck Serono, Isarna, Novocure, grants from Bayer, Piqur, personal fees from Celldex, Magforce, outside the submitted work. EB, JB, FG, AH, NC, RR, AJMF, MD, CD, TS, RS, CS, declare no competing interest.

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REFERENCES

1. Kluin PM, Deckert M, Ferry JA. Primary diffuse large B-cell lymphoma of the CNS. In: Swerdlow SH, Campo E, Harris NL, editors. World Health Organisation Classification of Tumours Pathology and Genetics of Tumours of the Haematopoietic and Lymphoid Tissues. Lyon: IARC Press, 2008; 240–41.
2. Kadan-Lottick NS, Skluzacek MC, Gurney JG. Decreasing incidence rates of primary central nervous system lymphoma. *Cancer* 2002; **95**:193–202.
3. Bessell EM, Dickinson P, Dickinson S, et al. Increasing age at diagnosis and worsening renal function in patients with primary central nervous system lymphoma. *J Neurooncol* 2011; **104**:191-93.
4. Villano JL, Koshy M, Shaikh H, et al. Age, gender, and racial differences in incidence and survival in primary CNS lymphoma. *Br J Cancer* 2011; **105**:1414-18.
5. O'Neill BP, Decker PA, Tieu C, et al. The changing incidence of primary central nervous system lymphoma is driven primarily by the changing incidence in young and middle-aged men and differs from time trends in systemic diffuse large B-cell non-Hodgkin's lymphoma. *Am J Hematol* 2013;**88**:997-1000.
6. Henry JM, Heffner RR, Dillard SH, et al. Primary malignant lymphomas of the central nervous system. *Cancer* 1974;**34**:1293–302.
7. Bataille B, Delwail V, Menet E, et al. Primary intracerebral malignant lymphoma: A report of 248 cases. *J Neurosurg* 2000;**92**:261-66.
8. Bellinzona M, Roser F, Ostertag H, et al. Surgical removal of primary central nervous system lymphomas (PCNSL) presenting as space occupying lesions: a series of 33 cases. *Eur J Surg Oncol* 2005;**31**:100–05.
9. Lai R, Rosenblum MK, DeAngelis LM. Primary CNS lymphoma: a whole-brain disease? *Neurology* 2002;**59**:1557-62.
10. Weller M, Martus P, Roth P, et al. Surgery for primary CNS lymphoma? Challenging a paradigm. *Neuro Oncol* 2012; **14**:1481-84.
11. O'Neill BP, O'Fallon JR, Earle JD et al. Primary central nervous system non-Hodgkin's lymphoma: survival advantages with combined initial therapy ? *Int J Radiat Oncol Biol Phys* 1995;**33**:663–73.
12. Schultz C, Scott C, Sherman W et al. Pre-irradiation chemotherapy with Cyclophosphamide, doxorubicin, vincristine, and Dexamethasone (CHOD) for PCNSL: Initial report of Radiation Therapy Oncology Group (RTOG) protocol 88-06. *J Clin Oncol* 1996;**14**:556–64.
13. Mead GM, Bleehen NM, Gregor A, et al. A Medical Research Council randomized trial in patients with primary cerebral non-Hodgkin lymphoma: cerebral radiotherapy with and without cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy. *Cancer* 2000; **89**:1359-70.
14. Hiraga S, Arita N, Ohnishi T, et al. Rapid infusion of high-dose methotrexate resulting in enhanced penetration into CSF and intensified tumour response in PCNSL. *J Neurosurgery* 1999; **91**:221-30.
15. Glass J, Gruber ML, Cher L, et al. Preirradiation methotrexate chemotherapy of primary central nervous system lymphoma: long-term outcome. *J Neurosurg* 1994;**81**:188-95.
16. Morris PG, Correa DD, Yahalom J, et al. Rituximab, methotrexate, procarbazine, and vincristine followed by consolidation reduced-dose whole-brain radiotherapy and cytarabine in newly diagnosed primary CNS lymphoma: final results and long-term outcome. *J Clin Oncol* 2013;**31**:3971-79.
17. Ferreri AJ, Reni M, Foppoli M, et al. High-dose cytarabine plus high-dose methotrexate versus high-dose methotrexate alone in patients with primary CNS lymphoma: A randomised phase 2 trial. *Lancet* 2009;**374**:1512-20.
18. Herrlinger U, Schabet M, Brugger W, et al. German Cancer Society Neuro-Oncology Working Group NOA-03 multicentre trial of single agent high dose methotrexate for primary CNS lymphoma. *Ann Neurol 2002 ;* **51:**247–52.

19. Batchelor T, Carson K, O'Neill A, et al. Treatment of primary cerebral lymphoma with methotrexate and deferred radiotherapy: Report of NABTT 96-07. *J Clin Oncol* 2003;**21**:1044-49.
20. Thiel E, Korfel A, Martus P, et al. High-dose methotrexate with or without whole brain radiotherapy for primary CNS lymphoma (G-PCNSL-SG-1): A phase 3, randomised, non-inferiority trial. *Lancet Oncol* 2010;**11**:1036-47.
21. Bergner N, Monsef I, Illerhaus G et al Role of chemotherapy additional to high-dose methotrexate for primary central nervous system lymphoma (PCNSL). *Cochrane Database Syst Rev* 2012;**11**: CD009355.
22. Rubenstein JL, Hsi ED, Johnson JL, et al. Intensive chemotherapy and immunotherapy in patients with newly diagnosed primary CNS lymphoma: CALGB 50202 (Alliance 50202). *J Clin Oncol* 2013;**31**:3061-68.
23. Ferreri AJ, Licata G, Foppoli M et al. Clinical relevance of the dose of cytarabine in the upfront treatment of primary CNS lymphomas with methotrexate-cytarabine combination. *Oncologist* 2011;**16**:336-41.
24. Slevin ML, Piall EM, Aherne GW et al. Effect of dose and schedule on pharmacokinetics of high-dose cytosine arabinoside in plasma and cerebrospinal fluid. *J Clin Oncol* 1983;**1**:546 – 51.
25. Neuwelt EA, Goldman DL, Dahlborg SA et al. Primary CNS lymphoma treated with osmotic blood-brain barrier disruption: prolonged survival and preservation of cognitive function. *J Clin Oncol* 1991;**9**:1580-90.
26. McAllister LD, Doolittle ND, Guastadisegni PE et al. Cognitive outcomes and long-term follow-up results after enhanced chemotherapy delivery for primary central nervous system lymphoma. *Neurosurgery* 2000;**46**:51-60.
27. Angelov L, Doolittle ND, Kraemer DF, et al. Blood-brain barrier disruption and intra-arterial methotrexate-based therapy for newly diagnosed primary CNS lymphoma: A multi-institutional experience. *J Clin Oncol* 2009;**27**:3503-09.
28. Ferreri AJ, Ciceri F, Brandes AA et al. MATILDE chemotherapy regimen for primary CNS lymphoma: results at a median follow-up of 12 years. *Neurology* 2014, **82**:1370-73.
29. Ferreri AJ, Reni M, Pasini F et al. Multicenter study of treatment of primary CNS lymphoma. *Neurology* 2002;**58**:1513-20.
30. Khan RB, Shi W, Thaler HT. Is intrathecal methotrexate necessary in the treatment of primary CNS lymphoma? *J Neurooncol* 2002;**58**:175-78.
31. Sierra Del Rio M, Ricard D, Houillier C, et al. Prophylactic intrathecal chemotherapy in primary CNS lymphoma. *J Neurooncol* 2012;**106**:143-46.
32. Pels H, Schmidt-Wolf IG, Glasmacher A et al. Primary central nervous system lymphoma: results of a pilot and phase II study of systemic and intraventricular chemotherapy with deferred radiotherapy. *J Clin Oncol* 2003;**21**:4489-95.
33. Pels H, Juergens A, Glasmacher A, et al. Early relapses in primary CNS lymphoma after response to polychemotherapy without intraventricular treatment: Results of a phase II study. *J Neurooncol* 2009;**91**:299-305.
34. Batchelor TT, Grossman SA, Mikkelsen T, et al. Rituximab monotherapy for patients with recurrent primary CNS lymphoma. *Neurology* 2011;**76**:929-30.
35. Chamberlain MC, Johnston SK. High-dose methotrexate and rituximab with deferred radiotherapy for newly diagnosed primary B-cell CNS lymphoma. *Neuro Oncol* 2010;**12**:736-44.
36. Fritsch K, Kasenda B, Hader C, et al. Immunochemotherapy with rituximab, methotrexate, procarbazine, and lomustine for primary CNS lymphoma (PCNSL) in the elderly. *Ann Oncol* 2011; **22**:2080-85
37. Mappa S, Marturano E, Licata G, et al. Salvage chemoimmunotherapy with rituximab, ifosfamide and etoposide (R-IE regimen) in patients with primary CNS lymphoma relapsed or refractory to high-dose methotrexate-based chemotherapy. *Hematol Oncol* 2013:**31**:143-50.
38. Nayak L, Abrey LE, Drappatz J, et al. Multicenter phase II study of rituximab and temozolomide in recurrent primary central nervous system lymphoma. *Leuk Lymphoma* 2013;**54**:58-61.

39. Birnbaum T, Stadler EA, von Baumgarten L, et al. Rituximab significantly improves complete response rate in patients with primary CNS lymphoma. *J Neurooncol* 2012;**109**:285-91.
40. Gregory G, Arumugaswamy A, Leung T, et al. Rituximab is associated with improved survival for aggressive B cell CNS lymphoma. *Neuro Oncology* 2013; **15**:1068-73.
41. Holdhoff M, Ambady P, Abdelaziz A, et al. High-dose methotrexate with or without rituximab in newly diagnosed primary CNS lymphoma *Neurology* 2014;**83**;235-39.
42. Rubenstein JL, Li J, Chen L, et al. Multicenter phase 1 trial of intraventricular immunochemotherapy in recurrent CNS lymphoma. *Blood* 2013;**121**:745-51.
43. Nelson DF, Martz KL, Bonner H et al. Non-Hodgkin's lymphoma of the brain: can high dose, large volume radiation therapy improve survival? Report on a prospective trial by the Radiation Therapy Oncology Group (RTOG. *Int J Radiat Oncol Biol Phys* 1992;**23**: 9-17.
44. DeAngelis LM, Yahalom J, Thaler HT, et al. Combined modality treatment for primary central nervous system lymphoma. *J Clin Oncol* 1992; **10**: 635-43.
45. Blay JY, Bouhour D, Carrie C et al. The C5R protocol: a regimen of high-dose chemotherapy and radiotherapy in primary cerebral non-Hodgkin's lymphoma of patients with no known cause of immunosuppression. *Blood*. 1995;**86**:2922-29.
46. O'Brien P, Roos D, Pratt G et al. Phase II multicenter study of brief single-agent methotrexate followed by irradiation in primary CNS lymphoma. *J Clin Oncol* 2000;**18**:519-26.
47. Omuro AM, DeAngelis LM, Yahalom J et al. Chemoradiotherapy for primary CNS lymphoma: an intent-to-treat analysis with complete follow-up. *Neurology* 2005;**64**:69-74.
48. Abrey LE, Yahalom J, De Angelis L. Treatment of primary CNS lymphoma: the next step. *J Clin Oncol* 2000;**18**:3144–50.
49. Bessell EM, Graus F, Lopez-Guillermo A, et al. CHOD/BVAM regimen plus radiotherapy in patients with primary CNS non-Hodgkins lymphoma. *Int J Radiation Oncology Biol Phys* 2003; **50**: 457-64.
50. Poortmans PM, Kluin-Nelemans HC, Haaxma-Reiche H et al. High-dose methotrexate-based chemotherapy followed by consolidating radiotherapy in non-AIDS-related primary central nervous system lymphoma: European Organization for Research and Treatment of Cancer Lymphoma Group Phase II Trial 20962. *J Clin Oncol* 2003;**21**:4483-88.
51. Gavrilovic IT, Hormigo A, Yahalom J et al. Long-term follow-up of high-dose methotrexate-based therapy with and without whole brain irradiation for newly diagnosed primary CNS lymphoma. *J Clin Oncol* 2006;**24**:4570-74.
52. Ghesquieres H, Ferlay C, Sebban C, et al. Long-term follow-up of an age-adapted C5R protocol followed by radiotherapy in 99 newly diagnosed primary CNS lymphomas: a prospective multicentric phase II study of the Groupe d'Etude des Lymphomes de l'Adulte (GELA). *Ann Oncol* 2010; **21**:842-50.
53. Lowry L, Smith P, Qian W et al. Reduced dose radiotherapy for local control in non-Hodgkin lymphoma: a randomised phase III trial. *Radiother. Oncol* 2011; **100**: 86-92.
54. DeAngelis LM, Seiferheld W, Schold SC et al. Combination chemotherapy and radiotherapy for primary central nervous system lymphoma: Radiation Therapy Oncology Group Study 93-10. *J Clin Oncol* 2002;**20**:4643-48.
55. Ferreri, A. J. DeAngelis L, Illerhaus G *et al.* Whole-brain radiotherapy in primary CNS lymphoma. *Lancet Oncol* 2011;**12**, 118–119.
56. Weller M. The vanishing role of whole brain radiotherapy in primary central nervous system lymphoma. *Neuro Oncol* 2014;**16**: 1035-36.
57. DeAngelis LM. Whither whole brain radiotherapy for primary CNS lymphoma? *Neuro Oncol* 2014 **;16**:1032-34
58. Zacher J, Kasenda B, Enger A et al. The role of additional radiotherapy for primary central nervous system lymphoma. *Cochrane Database Syst Rev*. 2014;6:CD009211.
59. Omuro AM, Taillandier L, Chinot O et al. Methotrexate (MTX), procarbazine and CCNU for primary central nervous system lymphoma (PCNSL) in patients younger than 60: Can radiotherapy (RT) be deferred? *J Neurooncol* 2006: **104**:323-30.
60. Ekenel M, Iwamoto FM, Ben-Porat LS et al. Primary central nervous system lymphoma: the role of consolidation treatment after a complete response to high-dose methotrexate-based chemotherapy. *Cancer* 2008;**113**:1025-31.

61. Jürgens A, Pels H, Rogowski S, et al. Long-term survival with favorable cognitive outcome after chemotherapy in primary central nervous system lymphoma. *Ann Neurol* 2010;**67**:182-89.
62. Sandor V, Stark-Vancs V, Pearson D et al. Phase II trial of chemotherapy alone for primary CNS and intraocular lymphoma. *J Clin Oncol* 1998;**16**:3000–06.
63. Hoang-Xuan K, Taillandier L, Chinot O et al. Chemotherapy alone as initial treatment for primary CNS lymphoma in patients older than 60 years: a multicenter phase II study (26952) of the European Organization for Research and Treatment of Cancer Brain Tumor Group. *J Clin Oncol 2003*;**21**:2726-31.
64. Bessell EM, Lopez-Guillermo A, Villa S, et al. Importance of radiotherapy in the outcome of,patients with primary CNS lymphoma: An analysis of the CHOD/BVAM regimen followed by two different radiotherapy treatments. *J Clin Oncol* 2002; **20**: 231-236.
65. Ferreri AJ, Verona C, Politi L, et al. Consolidation radiotherapy in primary CNS lymphomas: Impact on outcome of different fields and doses in patients in complete remission after upfront chemotherapy..*Int J Radiat Oncol Biol Phys* 2011;**80**:169-75.
66. Soussain C, Hoang-Xuan K, Taillandier L et al. Intensive chemotherapy followed by hematopoietic stem-cell rescue for refractory and recurrent primary CNS and intraocular lymphoma: Société Française de Greffe de Moëlle Osseuse-Thérapie Cellulaire. *J Clin Oncol* 2008;**26**:2512-18.
67. Soussain C,Choquet S, Fourme E,et al Intensive chemotherapy with thiotepa, busulfan and cyclophosphamide and hematopoietic stem cell rescue in relapsed or refractory primary CNS and intraocular lymphoma: a retrospective study of 79 cases. Haematologica 2012; **97**:1751-56
68. Welch MR, Sauter CS, Matasar MJ et al. Autologous Stem Cell Transplant in Recurrent or Refractory Primary or Secondary CNS Lymphoma Using Thiotepa, Busulfan and Cyclophosphamide (TBC). *LeuK Lymphoma* 2014 (in press)
69. Colombat P, Lemevel A, Bertrand P et al. High-dose chemotherapy with autologous stem cell transplantation as first-line therapy for primary CNS lymphoma in patients younger than 60 years: a multicenter phase II study of the GOELAMS group. *Bone Marrow Transplant* 2006;**38**:417–20.
70. Illerhaus G, Marks R, Ihorst G et al. High-dose chemotherapy with autologous stem-cell transplantation and hyperfractionated radiotherapy as first-line treatment of primary CNS lymphoma. *J Clin Oncol* 2006;**24**:3865-70.
71. Abrey LE, Moskowitz CH, Mason WP, et al. Intensive methotrexate and cytarabine followed by high dose chemotherapy with autologous stem cell rescue in patients with,newly diagnosed primary CNS lymphoma: An intent to treat analysis. *J Clin Oncol* 2003; **21**: 4151-56.
72. Alimohamed N, Daly A, Owen C, et al. Upfront thiotepa, busulfan, cyclophosphamide, and autologous stem cell transplantation for primary CNS lymphoma: a single centre experience. *Leuk Lymphoma*. 2012;**53**:862-67.
73. Illerhaus G, Müller F, Feuerhake F et al. High-dose chemotherapy and autologous stem-cell transplantation without consolidating radiotherapy as first-line treatment for primary lymphoma of the central nervous system. *Haematologica*. 2008;**93**:147-48.
74. Kiefer T, Hirt C, Späth C, Schüler F, et al. Ostdeutsche Studiengruppe Hämatologie und Onkologie. Long-term follow-up of high-dose chemotherapy with autologous stem-cell transplantation and response-adapted whole-brain radiotherapy for newly diagnosed primary CNS lymphoma: results of the multicenter Ostdeutsche Studiengruppe Hamatologie und Onkologie OSHO-53 phase II study. *Ann Oncol.* 2012;**23**:1809-12.
75. Schorb E, Kasenda B, Atta J, et al. Prognosis of patients with primary central nervous system lymphoma after high-dose chemotherapy followed by autologous stem cell transplantation. *Haematologica*. 2013;**98**:765-70.
76. Illerhaus G, Marks R, Muller F,et al. High-dose methotrexate combined with procarbazine and CCNU for primary CNS lymphoma in the elderly: results of a prospective pilot and phase II study. *Ann Oncol* 2009; **20**:319-25.
77. Laack NN, Ballman KV, Brown PB, et al. Whole-brain radiotherapy and high-dose methylprednisolone for elderly patients with primary central nervous system lymphoma: Results of North Central Cancer Treatment Group (NCCTG) 96-73-51. *Int J Radiat Oncol Biol Phys* 2006; **65**:1429-39.

78. Roth P, Martus P, Kiewe P, et al. Outcome of elderly patients with primary CNS lymphoma in the G-PCNSL-SG-1 trial. *Neurology*. 2012;**79**:890-96.
79. Omuro AM, Taillandier L, Chinot O et al. Temozolomide and methotrexate for primary central nervous system lymphoma in the elderly. *J Neurooncol* 2007;**85**:207-11.
80. Ney DE, Reiner AS, Panageas KS, et al. Characteristics and outcomes of elderly patients with primary central nervous system lymphoma: the Memorial Sloan-Kettering Cancer Center experience. *Cancer* 2010; **116**:4605-12.
81. Schuurmans M, Bromberg JE, Doorduijn J, et al. Primary central nervous system lymphoma in the elderly: a multicentre retrospective analysis. *Br J Haematol* 2010; 151:179-84.
82. Taoka K, Okoshi Y, Sakamoto N, Takano S, et al. A non radiation-containing, intermediate-dose methotrexate regimen for elderly patients with primary central nervous system lymphoma. *Int J Hematol* 2010; **92**:617-23.
83. Zhu JJ, Gerstner ER, Engler DA, et al. High-dose methotrexate for elderly patients with primary CNS lymphoma. *Neuro Oncol* 2009; **11**:211-15.
84. Kurzwelly D, Glas M, Roth P, et al. Primary CNS lymphoma in the elderly: temozolomide therapy and MGMT status. *J Neurooncol* 2010; **97**:389-92
85. Welch MR, Omuro A, DeAngelis LM. Outcomes of the oldest patients with primary CNS lymphoma treated at Memorial Sloan-Kettering Cancer Center. *Neuro Oncol* 2012; **14**:1304-11.
86. Omuro AM, Chinot O, Taillandier L, et al. Multicenter randomized phase II trial of methotrexate (MTX) and temozolomide (TMZ) versus MTX, procarbazine, vincristine, and cytarabine for primary CNS lymphoma (PCNSL) in the elderly: An Anocef and Goelams Intergroup study. *J Clin Oncol* **31**, 2013 (suppl; abstr 2032).
87. Jahnke K, Korfel A, Martus P, et al, German Primary Central Nervous System Lymphoma Study Group (G-PCNSL-SG). High-dose methotrexate toxicity in elderly patients with primary central nervous system lymphoma. *Ann Oncol*. 2005;**16**:445-49.
88. Correa DD, Shi W, Abrey LE, DeAngelis LM, et al. Cognitive functions in primary CNS lymphoma after single or combined modality regimens. *Neuro Oncol* 2012; 14:101-08
89. Hottinger AF, DeAngelis LM, Yahalom J et al. Salvage whole brain radiotherapy for recurrent or refractory primary CNS lymphoma. *Neurology* 2007;**69**: 1178-82.
90. Nguyen PL, Chakravarti A, Finkelstein DM et al. Results of whole-brain radiation as salvage of methotrexate failure for immunocompetent patients with primary CNS lymphoma. *J Clin Oncol* 2005;**23**:1507-13.
91. Reni M, Zaja F, Mason W et al. Temozolomide as salvage treatment in primary brain lymphomas. Br J Cancer. 2007;**96**:864-67
92. Fischer L, Thiel E, Klasen HA *et al.* Prospective trial on topotecan salvage therapy in primary CNS lymphoma. *Ann. Oncol* 2006*;* **17**:1141–45.
93. Raizer J J, Rademaker A, Evens A M et al.: Pemetrexed in the treatment of relapsed/refractory primary central nervous system lymphoma. *Cancer* 2012;**118**: 3743-48.
94. Chamberlain MC. Salvage therapy with bendamustine for methotrexate refractory recurrent primary CNS lymphoma: a retrospective case series. *J Neurooncol*. 2014 ; **118**:155-62
95. Herrlinger U, Brugger W, Bamberg M et al.: PCV salvage chemotherapy for recurrent primary CNS lymphoma. *Neurology* 2000; **54**: 1707-08.
96. Arellano-Rodrigo E, Lopez-Guillermo A, Bessell EM, et al. Salvage treatment with etoposide (VP-16), ifosfamide and cytarabine (Ara-C) for patients with recurrent primary central nervous system lymphoma. *Eur J Haematol*. 2003;**70**:219-24
97. Sierra del Rio M, Choquet S, Hoang-Xuan K et al. Platine and cytarabine-based salvage treatment for primary central nervous system lymphoma. *J Neurooncol.* 2011;**10**:409-14.
98. Plotkin SR, Betensky RA, Hochberg FH et al. Treatment of relapsed central nervous system lymphoma with high-dose methotrexate. *Clin Cancer Res* 2004;**10**:5643–46
99. Pentsova E, Deangelis LM, Omuro A. Methotrexate re-challenge for recurrent primary central nervous system lymphoma. *J Neurooncol*. 2014;**117**:161-65
100. Provencher S, Ferlay C, Alaoui-Slimani K et al. Clinical characteristics and outcome of isolated extracerebral relapses of primary central nervous system lymphoma: a case series. *Hematol Oncol.* 2011;**29**:10-16

Table 1: Consensus statements and recommendations for the general approach to patients with PCNSL including establishment of diagnosis, baseline work-up and response to treatment

Diagnosis

- Cranial MRI with FLAIR and T1 weighted sequences before and after contrast injection is the neuroimaging method of choice for the diagnosis and follow-up of PCNSL. Diffusion, dynamic susceptibility contrast, proton spectroscopy MRI, and FDG-PET can be useful in the differential diagnosis but are not specific (Good Practice Point).
- The diagnosis of PCNSL requires pathological confirmation before treatment (Good Practice Point).
- When PCNSL is suspected, the standard surgical procedure for diagnosis is a stereotactic or navigation guided needle biopsy (Good Practice Point, see section on surgery for discussion).
- Because it may prevent the histopathological diagnosis, it is recommended, if clinically possible, to avoid steroids before biopsy. In case of remission and/or unspecific inflammation in the tissue biopsied in steroid-pretreated patients, rebiopsy is recommended when close and careful follow-up with serial MRI indicates further tumor growth (Good Practice Point).
- PCNSL are diagnosed according to the WHO classification. Immunohistochemistry is required (Good Practice Point, see pathology section in the webappendix).
- Required immunohistochemical markers for the lymphoma cell characterization should include: pan-B cell markers (CD19,CD20,PAX5), BCL6, MUM1/IRF4, CD10 (Good Practice Point).
- PCR analysis of immunoglobuline gene families may contribute to diagnosis in difficult cases, in particular when inflammatory disorders such as multiple sclerosis or corticosteroid-mitigated PCNSL are considered. (Good Practice Point).
- In case of a suspicion of PCNSL, the work-up should include at least an HIV blood test, a lumbar puncture (if not contraindicated) and an ophthalmologic evaluation (with a fundoscopy and a slit lamp examination) in all patients, including those without ocular symptoms (Good Practice Point).
- The identification of lymphoma cells in the CSF or the vitreous may obviate the need for a stereotactic brain biopsy to confirm the diagnosis only in the setting of high clinical and radiological suspicion of PCNSL. As cytologic diagnosis may be difficult, a review by a specialist pathologist is recommended, and in any doubt a brain biopsy is required (Good Practice Point).
- Immunophenotyping by multiparameter flow cytometry of cells collected in the CSF or vitreous and immediately analyzed may add to diagnostic sensitivity.
- if B-cell monoclonality is shown in a sample with atypical/suspicious cells. PCR based analysis of immunoglobulin gene rearrangement in the CSF reportedly may show false positives. Therefore, evidence for the clonality of the lymphocytic cell population considered separately remains insufficient for the diagnosis for PCNSL except in case of high clinically documented suspicion of PCNSL (Good Practice Point).

Staging

- Systemic staging should include: physical examination, CT-scan of the chest, abdomen and pelvis, testicular sonography and bone marrow biopsy. FDG body PET may represent an improved alternative to total body CT-scan and testicular sonography (Good Practice Point).

Prognosis

- Age and performance status have been consistently identified as treatment-independent prognostic factors in PCNSL. Evaluating the individual risk of a PCNSL patient before treatment according to one of the existing prognostic scores is recommended (Good Practice Point).
- Age over 60-65 is used to define the elderly population in PCNSL (Good Practice Point).

Evaluation of response and follow-up

- The International Primary CNS Lymphoma Collaborative Group (IPCG) criteria (2005) combining MRI, eye examination, CSF analysis and steroid dose should be used to evaluate response to treatment (Good Practice Point).
- There is no evidence as yet that brain FDG PET can be used to assess response in PCNSL in the way that it is used for other lymphomas (Good Practice Point).
- Formal prospective neuropsychometric testing is recommended in the follow-up of patients treated in clinical trials on PCNSL (Good Practice Point).

Table 2: Consensus statements and recommendations for treatment of patients with PCNSL

Surgery

- Surgical resection may be considered in patients suffering from a large space occupying lesion with acute symptoms of brain herniation to reduce rapidly intracranial pressure (Good practice point).
- In patients with an unifocal and resectable lesion suspected of PCNSL, no consensus was met in the panel to recommend either surgical resection or biopsy

Chemotherapy

- CHOP-regimens and derivatives are not indicated in PCNSL (Level B).
- Chemotherapy should include MTX at HD ($\geq 3g/m^2$) both to cross the BBB and yield cytotoxic levels in the CSF. It should be delivered in 2-3 hour iv infusions for a minimum of 4-6 injections and at intervals that should not exceed 2-3 weeks (Good Practice Point).
- Combination of HD-MTX with other chemotherapeutic agents improves the response rates with respect to HD-MTX alone (Level B).
- Chemotherapeutic agents to combine with HD MTX should be selected among active drugs known to cross BBB, such as HD cytarabine (Level B).
- HD-MTX-chemotherapy is feasible in elderly patients with adequate performance status and renal function (Level B).
- BBBD followed by IA MTX is an alternative experimental approach appropriated for a selected group of patients that should be undertaken by trained teams only (Level B).
- The value of IT chemotherapy as prophylaxis is unclear. IT chemotherapy (intralumbar or preferably intraventricular through an Ommaya reservoir) can be proposed in case of documented meningeal involvement with insufficient response to iv HD MTX (>3g/ m2) based chemotherapy (Good Practice Point).
- Rituximab combined with a chemotherapy regimen is still an experimental regimen that has its main place in clinical trials (Level C).

Radiotherapy

- WBRT, HD MTX, and *a fortiori* combined treatment expose patients to an increased risk of neurotoxicity (Level A).
- The role of consolidation WBRT following HD-MTX based chemotherapy remains debated. In addition, the optimal dose is not yet defined, but it should be chosen on the base of 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 Gy dose /fraction appears advisable. With such doses, there is no evidence to add a focal boost on the enhancing lesions (Good Practice Point).
- In patients < 60 years who have achieved a CR to induction chemotherapy, the option of immediate WBRT (40 - 45 Gy in 1.8 - 2.0 Gy fractions) or WBRT omission should be discussed with the patient. Reduced dose WBRT consolidation (23.4 - 30 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 > 60 years, the risk of delayed neurotoxicity, after WBRT (doses >30 Gy in 1.8-2.0 Gy fractions) especially if following HDMTX , is unacceptably high and WBRT at this dose 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 PCNSL (Level B).
- HDC/ASCT should be reserved for patients < 60-65 years (Good Practice Point).
- High-dose thiotepa-based conditioning chemotherapy should be preferred over the BEAM regimen (Level C).
- HDC/ASCT as consolidation in first-line treatment remains experimental in PCNSL and should be restricted by selected trained centers (Good Practice Point).

Primary intraocular lymphoma (PIOL)

- PIOL may be treated by either HD-MTX-based chemotherapy (with or without WBRT) or by local therapy (intravitreal chemotherapy or ocular RT) (Good Practice Point).
- Local treatment (intravitreal chemotherapy or ocular RT) is a valid approach for patients with systemic chemotherapy contraindications or for elderly patients with relapsing intraocular disease (Good Practice Point).
- Concurrent intraocular and CNS lymphoma should be treated no differently from PCNSL (Good Practice Point).
- If consolidation WBRT is proposed, it should include both eyes (Good Practice Point).

- Refractory and relapsed IOL should be treated according to the patients' characteristics and prior treatments. Treatments include intravitreal injections of MTX, focal radiotherapy, WBRT, systemic chemotherapy and HDC/ASCT (Good Practice Point).

Salvage treatment

- Patients with relapsed / refractory PCNSL should be enrolled into phase I-II trials (Good Practice Point).
- The choice of the most appropriate salvage treatment should depend upon the patient's age, performance status, comorbidity, site of relapse, prior therapy, and duration of previous response. The expected side effects of the chosen drug must also be considered carefully (Good Practice Point).
- Salvage WBRT may be proposed in radiotherapy-naïve patients; it may be preceded by induction chemotherapy (Good Practice Point)
- HDC/ASCT is a valid therapeutic option in patients aged <60-65 years with chemosensitive relapsing PCNSL (Level B).
- Salvage chemotherapy can be delivered as induction therapy before WBRT or HDC/ASCT, or as exclusive treatment in patients not eligible for these therapies.
- MTX re-challenge should be considered in recurrent PCNSL patients who previously responded to HD MTX (Level C).
- Isolated extra-CNS relapses should be managed with anthracycline-based chemotherapy followed or not by HDC/ASCT (Good Practice Point)

WEBAPPENDIX

This webappendix summarizes evidences used for EANO`s recommendations for the general approach to PCNSL patients with coverage of diagnostic aspects – pathology and genetics, clinical presentation, pathological confirmation, neuropathology of corticosteroid-treated PCNSL, cerebrospinal fluid (CSF) analyses, vitreous analyses, staging,– as well as prognostic factors, response criteria to treatment, treatment related neurotoxicity and treatment of intraocular lymphoma.

Pathology and genetics

PCNSL is a mature B cell lymphoma corresponding to DLBCL of the CNS. Morphologically, haematopoietic tumor cells, mostly resembling centroblasts, are scattered throughout the brain tissue and also exhibit a marked angiotropism with sheets of tumor cells clustering within and around blood vessel wall. Immunohistochemistry is required for the diagnosis. In addition to the expression of pan-B cell markers (CD19, CD20, PAX5), the tumor cells of PCNSL are characterized by a $BCL6^{+}IRF/MUM1+CD10^{-}$ immunophenotype with high proliferative activity (Ki-67 indexes of 70-90%), together with high expression of the MYC and BCL2 proteins.[1-3] With rare exception, Epstein-Barr Virus (EBV) is absent from PCNSL of immunocompetent patients. Ongoing activity of the germinal center program and blocked terminal B cell differentiation together with pathways deregulated by genetic alterations (B cell receptor, toll like receptor, NF-kB pathways) may foster B cell activation and brisk proliferation and be of pathogenetic relevance.[4-9] Analysis of the molecular landscape of PCNSL indicates that aberrant somatic hypermutation which targets several genes (*PIM1, TTF, MYC, KLH14, OSPL10, SUSD2*) may play an important role in the pathogenesis of PCNSL, [9,10] and that alterations in genes of role in CNS development may facilitate DLBCL manifestation in the CNS.[10] Epigenetic studies revealed frequent gene silencing due to CpG island hypermethylation in individual genes including *MGMT, CDKN2A*, and *DAPK*.[11,12] Recurring chromosomal losses affected the 6q, 6p21.32 (*HLA* locus) and 9p21 (*CDKN2A* locus) regions.[5,13] However, to date, no specific molecular genetic signature distinguishes clearly PCNSL from non-CNS DLBCL, suggesting an important role of the microenvironement in explaining the peculiar behaviour of PCNSL. For research, collecting frozen samples and developing a network for PCNSL tumor banks should be encouraged.

Diagnosis

Clinical presentation
Presenting symptoms may include cognitive decline and/or personality changes, focal neurological deficits and increased intracranial pressure. Seizures are less frequent (10%). Ocular symptoms, due to an involvement of retina, choroid or vitreous, are represented by floaters and/or blurred vision; they can be either isolated (10%) or coexist with cerebral symptoms (10-20%). However, up to one-half of patients with PCNSL and ocular involvement have no visual symptoms. Insidious onset and delayed diagnosis of intraocular lymphoma are common.[14] In immunocompetent patients, cranial MRI with contrast enhancement typically shows intense and homogeneously enhancing single lesions (70%) or multiple lesions (30%) with modest surrounding edema, usually located in periventricular areas and/or deep gray matter.[15,16] Although suggestive, all these MRI findings are not specific. Advanced imaging techniques, especially FDG-PET, diffusion tensor imaging, dynamic susceptibility contrast MRI (DSC-MRI) and proton MR spectroscopy can increase the diagnostic accuracy and help in differentiating PCNSL from other brain tumors or non-tumor lesions.[17-26] However, although some signatures are highly suggestive of PCNSL, especially when present together (low regional cerebral blood volume ratios, high percentage of signal-intensity recovery at the end of the first pass of contrast agent relative to baseline, very high lipid resonances), they are not sufficiently specific in practice to replace pathological confirmation.

Pathological confirmation
Diagnosis always needs to be confirmed pathologically, according to the WHO classification in most cases by stereotactic needle biopsy.[1] In classical cases, combined histology and immunohistochemistry yields the diagnosis of PCNSL, i.e. DLBCL of the CNS. In such cases, molecular studies are not required. In equivocal cases PCR testing for clonality may aid the diagnosis.[27,28]

Neuropathology of corticosteroid-treated PCNSL
As the tumor cells of PCNSL are potentially highly sensitive to corticosteroids, they may undergo rapid apoptosis. Transient tumor shrinkage or disappearance of contrast enhancement may occur even after short

exposure to steroids in approximately 40% of PCNSL, coupled with significant neurological improvement.[29] Stereotactic or navigation guided needle biopsy in this setting may be non-diagnostic in up to 50% of cases.[30] In the absence of tumor blasts, resorptive changes with prominent infiltration of macrophages, T cells, reactive astrocytes , and prominent microglial activation may prevail. In some cases, a few enlarged B cells may persist, being suspicious of blast. In such cases, PCR analysis of immunoglobuline genes may demonstrate monoclonality. However, a small number of B cells may pretend monoclonality ("pseudoclonality"). Therefore, unless patients are rapidly deteriorating with suggestive radiological features of PCNSL, it is usually recommended to defer corticosteroids until histologic confirmation has been obtained. Clinicians referring from peripheral hospitals should discuss with the specialist neurosurgical centre before starting corticosteroids. If, nevertheless, corticosteroids have been given with a subsequent objective response, tapering corticosteroids within one or two weeks and delaying biopsy until tumor regrowth would be a reasonable option. Since regrowth occur in most cases within a few weeks after discontinuation corticosteroids, a serial MRI follow-up with one month interval may be recommended at least the first three months. If no significant changes in contrast enhancement or progression are observed, biopsy seems associated with a relatively good probability of yielding a diagnosis despite steroid pre-treatment.[31]

CSF analysis

The identification of lymphoma cells in the CSF or in a vitreous biopsy, when possible, may obviate the need for a brain biopsy for the diagnostic confirmation, only in the setting of high clinical and radiological suspicion of PCNSL. Frequently, CSF is characterized by elevated protein levels in 75% and mild pleiocytosis in 50% of patients. However, lymphoma cells are detected in only 10-30% in the CSF.[32,33] Cellular immunophenotyping by flow cytometry in the CSF and PCR analysis of immunoglobulin heavy and light chain genes may help to distinguish malignant cells from reactive lymphocytes by identifying clonal B-cell populations even when cytological examination is negative[34,35] However, low cell numbers in the CSF sample are frequently found and may make flow cytometric analysis difficult. A relatively high ratio of PCR false negatives has been reported in PCNSL.[33,36] Different CSF molecular genetic markers and proteins including microRNA (miR-21, miR-19b, and miR-92),[37] soluble CD19,[38] antithrombin III,[39] free immunoglobulin light chains,[40] and interleukin-10 and CXCL13,[41] are potentially useful diagnostic biomarkers for PCNSL but require further validation before being used in routine practice. As cytologic diagnosis may be difficult, in any doubt or inconsistencies with the patient clinical setting, a pathological confirmation by a brain biopsy is recommended.

Vitreous analysis

Ophthalmologic evaluation includes fundoscopy and slit lamp examination. Fluorescein angiography may be useful for lymphomatous involvement of the retina.[14] Ophthalmologic involvement has to be confirmed by vitreous biopsy when eyes are the unique site of disease. Positive cytology is obtained in 70% of cases in trained pathology department. As for CSF, immunophenotyping and detection of IgH or T-cell receptor rearrangements by PCR analysis indicating monoclonality are helpful tools for diagnosis.[42,43] High levels of interleukin 10 (IL10) and/or high IL10 / IL6 ratio in ocular fluids are strongly suggestive of B-cell lymphomatous uveitis,[44] but are not diagnostic.

Staging

The aims of staging are both to specify the extent of the lymphoma within the CNS and to exclude the presence of the disease elsewhere. If not contraindicated and already performed at the diagnostic work-up, all patients should have a lumbar puncture for CSF cytology. Systemic involvement is present in up to 12% of the cases.[45,46] Since identification of a systemic site of the lymphoma has important implications for the treatment strategy, an international workshop to standardize baseline evaluation recommended performing at least a CT-scan of the chest, abdomen and pelvis, a bone marrow biopsy, a testicular ultrasound in elderly males.[47] FDG body PET, which is more sensitive than the body CT-scan,[48]is not yet an established routine diagnostic investigation, but is used in some European countries as an integral part of diagnostic work-up.

Prognostic factors

Age and performance status have been consistently recognized as the most important therapy-independent prognostic factors.[49-53] Based on retrospective cohorts of PCNSL, other variables including serum lactate dehydrogenase (LDH) levels, involvement of deep brain structures,[53-55] CSF protein levels,[50,53] and extent of lesions within the CNS (multifocal versus unifocal),[52] have been correlated with outcome, and some of them are integrated with age and performance status in different prognostic scoring systems. Hence, three clinically meaningful prognostic scores are available for PCNSL: the IELSG score,[53] the MSKCC score,[51] and the Nottingham-Barcelona score.[52] All of them distinguished 3 different risk groups. Using such scoring systems is useful to compare studies in order to avoid as much as possible selection biases. Since then, other prognostic

factors have been correlated with unfavorable outcome and need to be validated in independent series: elevated FDG uptake on PET,[56] chromosome 6q deletion or *CDKN2A* homozygous deletion in the tumor DNA,[5,57] and delayed response to initial chemotherapy, as compared to early response.[58] Several variables have yielded opposite results in retrospective studies, such as apparent diffusion coefficient (ADC) value derived from diffusion-weighted imaging,[59-61]BCL-6 expression analysis,[62-66] and MTX exposure reflected by MTX area under the curve (AUC).[67-70]

Response criteria

In 2005 the International Primary CNS Lymphoma Collaborative Group (IPCG) published a consensus opinion to standardize response criteria and outcome measures in immunocompetent patients with PCNSL.[47] These response criteria define CR as complete disappearance of contrast enhancement on MRI, no evidence of ocular lymphoma, negative CSF cytology and discontinuation of corticosteroid use for at least 2 weeks prior to the evaluation of response. Since corticosteroids may mask presence of residual disease its discontinuation is included as an essential requirement. The IPCG also delineated which findings are compatible with unconfirmed CR (CRu). It is important to sort out CRu from PR because the latter means failure of primary treatment. According to the IPCG outline CRu includes those cases who fulfill the criteria for CR with the following limitations: at time of evaluation the patient is still on any dose of corticosteroids, MRI continues to show small but persistent enhancing abnormalities related to biopsy/surgical site or to focal hemorrhage, and the follow-up ophthalmologic examination shows persistent minor abnormality which is unlikely to represent ocular lymphoma. PR is defined as 50% decrease in enhancing tumor or residual disease on eye examinations, or persistent or suspicious CSF cytology. Progressive disease (PD) is recognized as 25% increase in the enhancing lesion or appearance of any new site of disease in the CNS or as systemic disease, recurrent or new ocular disease, or recurrent or positive CSF cytology. Of note, these definitions do not take into account the non-enhancing lesion best visualized on T2-Flair MRI, whose differential diagnosis may be challenging since it could be treatment-related white matter changes (including leukoencephalopathy) but also correspond to infiltrative PD.[71] There no evidence as yet that brain FDG PET can be used to assess response in PCNSL in the way that it is used for other lymphomas.

Delayed neurotoxicity

Delayed treatment-related neurotoxicity has been systematically evaluated in few studies (Class II and III). However, there is a general perception and agreement, that the combination of HD MTX and WBRT is associated with disabling neurotoxicity with an incidence of 25% to 35% and related mortality of 30%.[50,72] This deleterious treatment complication typically occurs several months to years after successful treatment. Neuropsychological examination may confirm impaired psychomotor speed, executive function, attention and memory.[73] Affected patients show cortical/subcortical atrophy and leukoencephalopathy,[73-75] which may leave them demented, ataxic and incontinent. Median survival after onset of clinically-evident neurotoxicity is less than 1-2 years.[50,72,75] Autopsy findings include myelin and axonal loss, gliosis, spongiosis, thinning of white matter, small and large vessel disease, and necrosis.[75,76] Of note, imaging abnormalities may not always correlate with the neurologic impairment severity over time. In a retrospective mono-institutional series analysis of 183 patients, only the administration of WBRT was identified as an independent risk factor for the development of late neurotoxicity: in this series, 2% treated with chemotherapy alone developed clinically-evident neurotoxicity, while 33% treated with combination chemo-/radiotherapy were affected. The cumulative incidence of neurotoxicity for the whole group was 5% at 2 years and 24% at 5 years, with a substantially higher risk in patients ≥ 60 years (Class IIIb).[75] They are related to clinically and radiologically overt neurotoxicity. The prevalence of treatment-related "subtle" cognitive dysfunction amongst patients treated for PCNSL is probably largely underestimated as formal psychometric evaluationshave not been routinely performed in most prospective studies. Small case series identified WBRT, and not chemotherapy, as the primary cause of neurotoxicity in PCNSL.[76,77] These results have been confirmed by 3 long-term evaluations (Class IIIb). [78-80] In the most recent analysis of 80 long-term survivors of PCNSL, free of tumor and having completed treatment with different regimens at least two years prior to evaluation, those who had received WBRT showed significantly lower mean scores in attention and executive function, motor skills, and neuropsychological composite score, associated with poorer quality of life measures (Class IIIb).[80] Moreover, on brain imaging, mean areas of total T2 abnormalities in the WBRT group were more than twice the mean of any other non-WBRT group. These results caution against the routine administration of WBRT as part of upfront treatment and call for the implementation of formal neuropsychometric testing in clinical trials on PCNSL.[73]

Intraocular lymphoma

Intraocular infiltration can be the exclusive site of disease at presentation, the so-called primary intra-ocular lymphoma (PIOL), or as a part of PCNSL with concomitant brain or meningeal disease. The optimal treatment for intraocular lymphoma is not known. Data on therapy and outcome are scarce and limited to retrospective case reports or mostly small series with heterogeneous patient populations and treatments. As many as 90 % of patients with PIOL patients consequently develop brain involvement over the course of the disease and dissemination to the brain is the main cause of death.[14,81] The median survival of isolated PIOL is approximately 60 months.[81,82] Treatment may be focal, including ocular RT (historically, total dose of 35-40 Gy, 2 Gy per fraction using opposed lateral beams to include both globes) (Class IV) and intravitreal chemotherapy. [83-86] Uncontrolled series have reported clinical remission with repeated intravitreal MTX and more recently after rituximab injections (Class IV).[85,86] Treatment may be also extensive, including systemic chemotherapy and WBRT. Intraocular responses have been reported with HD MTX,[87] HD cytarabine,[88,89] ifosfamide, trofosfamide used as single agent,[90] with MTX-based polychemotherapy and after HDC/ASCT (Class IV).[91] A large retrospective multicenter study did not show any difference in PIOL between focal and extensive therapy in terms of disease control and survival (Class IIIb).[81] Unfortunately, this and other studies failed to provide reliable predictors of brain dissemination in PIOL patients; thus, some experts recommend local therapy for disease confined to the eyes, but others consider that initial treatment of PIOL should not differ from that of PCNSL i.e. high-dose MTX-based polychemotherapy followed, or not, by WBRT in order to eradicate possible concomitant microscopic disease in the brain and in the CSF responsible for relapse. In this case, local treatments would remain options for refractory or recurrent disease confined to the eyes. The management decision should take into account the individual risk of treatment toxicities (including those related to ocular treatment) and local expertise.[14,92] When intraocular lymphoma is concurrent with brain lesions, it has not been identified as an independent prognostic factor and the prognosis is similar to that of the PCNSL without intraocular disease (Class IIIb).[93] Accordingly, patients with concomitant intraocular and cerebral disease should be treated no differently from PCNSL. The value of additional local ocular treatment (i.e. intravitreal chemotherapy or ocular radiotherapy if WBRT has not been delivered) to systemic chemotherapy remains matter of debate, with conflicting results in two retrospective studies (Class IIIb). [93,94]

References

1. Kluin PM, Deckert M, Ferry JA. Primary diffuse large B-cell lymphoma of the CNS. In: Swerdlow SH, Campo E, Harris NL, editors. World Health Organisation Classification of Tumours Pathology and Genetics of Tumours of the Haematopoietic and Lymphoid Tissues. Lyon: IARC Press, 2008; 240–41.
2. Camilleri-Broet S, Criniere E, Broet P, et al. A uniform activated Bcell- like immunophenotype might explain the poor prognosis of primary central nervous system lymphomas: analysis of 83 cases. *Blood* 2006; **107**: 190–96.
3. Brunn A, Nagel I, Montesinos-Rongen M et al. Frequent triple-hit expression of *MYC, BCL2*, and *BCL6* in primary lymphoma of the central nervous system and absence of a favorable MYC(low)BCL2 (low) subgroup may underlie the inferior prognosis as compared to systemic diffuse large B cell lymphomas. *Acta Neuropathol* 2013; **126**:603-05
4. Deckert M, Montesinos-Rongen M, Brunn A, et al. Systems biology of primary CNS lymphoma: from genetic aberrations to modeling in mice. *Acta Neuropathol*. 2014 ;**127**:175-88
5. Gonzalez-Aguilar A, Idbaih A, Boisselier B, et al. Recurrent mutations of *MYD88* and *TBL1XR1* in primary central nervous system lymphomas. *Clin. Cancer Res*. 2012;**18**:5203–5211
6. Montesinos-Rongen M, Godlewska E, Brunn A, et al. Activating L265P mutations of the *MYD88* gene are common in primary central nervous system lymphoma. *Acta Neuropathol* 2011;**122**:791–92
7. Montesinos-Rongen M, Schäfer E, Siebert R, et al.. Genes regulating the B cell receptor pathway are recurrently mutated in primary central nervous system lymphoma. *Acta Neuropathol* 2012;**124**:905–06.
8. Montesinos-Rongen M, Schmitz R, Brunn A, et al. Mutations of *CARD11* but not *TNFAIP3* may activate the NF-kappaB pathway in primary CNS lymphoma. *Acta Neuropathol*. 2010;**120**:529–35.
9. Bruno A, Boisselier B, Labreche K, et al. Mutational analysis of primary central nervous system lymphoma. *Oncotarget* 2014;**5**:5065-75
10. Vater I, Montesinos-Rongen M, Schlesner M et al. The mutational pattern of primary lymphoma of the central nervous system determined by whole-exome sequencing. *Leukemia* 2014.doi: 10.1038/leu.2014.264
11. Chu LC, Eberhart CG, Grossman SA, et al. Epigenetic silencing of multiple genes in primary CNS lymphoma. *Int J Cancer* 2006; **119**: 2487–91.

12. Ferreri AJ, Dell'Oro S, Capello D, et al. Aberrant methylation in the promoter region of the reduced folate carrier gene is a potential mechanism of resistance to methotrexate in primary central nervous system lymphomas. *Br J Haematol* 2004; **126**: 657–64.

13. Braggio E, McPhail ER, Macon W, et al. Primary central nervous system lymphomas: a validation study of array-based comparative genomic hybridization in formalin-fixed paraffin-embedded tumor specimens. *Cancer Res*. 2011;**17**:4245–53

14. Chan CC, Rubenstein JL, Coupland SE, et al. Primary vitreoretinal lymphoma: a report from an International Primary Central Nervous System Lymphoma Collaborative Group symposium. *Oncologist*. 2011;**16**:1589-99

15. Bühring U, Herrlinger U, Krings T et al. MRI features of primary central nervous system lymphomas at presentation. *Neurology* 2001;**57**:393–96

16. Kuker W, Nagele T, Korfel A, et al: Primary central nervous system lymphomas (PCNSL): MRI features at presentation in 100 patients. *J Neurooncol* 2005; **72**:169-77

17. Kawai N, Okubo S, Miyake K, et al. Use of PET in the diagnosis of primary CNS lymphoma in patients with atypical MR findings. *Ann Nucl Med*. 2010; **24**:335-43

18. Yamashita K, Yoshiura T, Hiwatashi A, et al. Differentiating primary CNS lymphoma from glioblastoma multiforme: assessment using arterial spin labeling,diffusion-weighted imaging, and ^{1}□F-fluorodeoxyglucose positron emission tomography. *Neuroradiology*. 2013; **55**:135-43

19. Toh CH, Castillo M, Wong AM,et al.. Primary cerebral lymphoma and glioblastoma multiforme: differences in diffusion characteristics evaluated with diffusion tensor imaging. *AJNR*. 2008;**29**:471-75

20. Mangla R, Kolar B, Zhu T, et al. Percentage signal recovery derived from MR dynamic susceptibility contrast imaging is useful to differentiate common enhancing malignant lesions of the brain. *AJNR* 2011;**32**:1004-10

21. Radbruch A, Wiestler B, Kramp L,et al. Differentiation of glioblastoma and primary CNS lymphomas using susceptibility weighted imaging. *Eur J Radiol*. 2013;**82**:552-56.

22. Blasel S, Jurcoane A, Bähr O, Weise L, et al. MR perfusion in and around the contrast-enhancement of primary CNS lymphomas. *J Neurooncol*. 2013;**114**:127-34.

23. Toh CH, Wei KC, Chang CN, et al. Differentiation of primary central nervous system lymphomas and glioblastomas: comparisons of diagnostic performance of dynamic susceptibility contrast-enhanced perfusion MR imaging without and with contrast-leakage correction. *AJNR* 2013 ;**34**:1145-49

24. Kickingereder P, Sahm F, Wiestler B, et al. Evaluation of Microvascular Permeability with Dynamic Contrast-Enhanced MRI for the Differentiation of Primary CNS Lymphoma and Glioblastoma: Radiologic-Pathologic Correlation. *AJNR* 2014;**35**:1503-08

25. Chawla S, Zhang Y, Wang S, et al. Proton magnetic resonance spectroscopy in differentiating glioblastomas from primary cerebral lymphomas and brain metastases. *J Comput Assist Tomogr* 2010;**34**:836-41

26. Lu SS, Kim SJ, Kim HS, et al. Utility of proton MR spectroscopy for differentiating typical and atypical primary central nervous system lymphomas from tumefactive demyelinating lesions. *AJNR* 2014; **35**:270-77

27. Shaw A, Iyer V, Rooney N, et al. Diagnosis of primary cerebral lymphomas: possible value of PCR testing in equivocal cases requiring rebiopsy. *Br J Neurosurg* 2014: **28**:214-19

28. Deckert M, Brunn A, Montesinos-Rongen M et al. Primary lymphoma of the central nervous system--a diagnostic challenge. *Hematol Oncol* 2014;**32**:57-67

29. Pirotte B, Levivier M, Goldman et al. Glucocorticoid-induced long-term remission in primary cerebral lymphoma: case report and review of the literature. *J Neurooncol*. 1997;**32**:63-69

30. Brück W, Brunn A, Klapper W et al. Differential diagnosis of lymphoid infiltrates in the central nervous system: experience of the Network Lymphomas and Lymphomatoid Lesions in the nervous system. *Pathologe* 2013;**34**:186-97

31. Porter AB, Giannini C, Kaufmann T, et al. Primary central nervous system lymphoma can be histologically diagnosed after previous corticosteroid use: a pilot study to determine whether corticosteroids prevent the diagnosis of primary central nervous system lymphoma. *Ann Neurol* 2008;**63**:662-67

32. Balmaceda C, Gaynor JJ, Sun M, et al. Leptomeningeal tumour in primary central nervous system lymphoma: Recognition, significance, and implications. *Ann Neurol* 1995;**38**:202-09.

33. Korfel A, Weller M, Martus P, et al. Prognostic impact of meningeal dissemination in primary CNS lymphoma (PCNSL): experience from the G-PCNSL-SG1 trial. *Ann Oncol* 2013;**23**:2374-80

34. Hegde U, Filie A, Little RF, et al. High incidence of occult leptomeningeal disease detected by flow cytometry in newly diagnosed aggressive B-cell lymphomas at risk for central nervous system involvement: the role of flow cytometry versus cytology. *Blood* 2005; **105**:496-502

35. Schroers R, Baraniskin A, Heute C, et al.. Diagnosis of leptomeningeal disease in diffuse large B-cell lymphomas of the central nervous system by flow cytometry and cytopathology. *Eur J Haematol.* 2010;**85**:520-28

36. Fischer, L., Martus, P., Weller, M., et al. Meningeal dissemination in primary CNS lymphoma: prospective evaluation of 282 patients. *Neurology* 2008, **71**,1102–08.

37. Baraniskin A, Kuhnhenn J, Schlegel U, et al. Identification of microRNAs in the cerebrospinal fluid as marker for primary diffuse large B-cell lymphoma of the central nervous system. *Blood* 2011;**117**:3140-46.

38. Muñiz C, Martín-Martín L, López A, et al. Spanish Group for the Study of Central Nervous System Disease in Non-Hodgkin Lymphoma. Contribution of cerebrospinal fluid sCD19 levels to the detection of CNS lymphoma and its impact on disease outcome. *Blood* 2014; **123**:1864-69

39. Roy S, Josephson SA, Fridlyand, J, et al. Protein biomarker identification in the CSF of patients with CNS lymphoma. *J Clin Oncol* 2008, **26**,:96–105.

40. Schroers, R., Baraniskin, A., Heute, C, et al. Detection of free immunoglobulin light chains in cerebrospinal fluids of patients with central nervous system lymphomas. *Eur J Haematol* 2010; **85**: 236–42.

41. Rubenstein JL, Wong VS, Kadoch C, et al. CXCL13 plus interleukin 10 is highly specific for the diagnosis of CNS lymphoma. *Blood.* 2013 6;**121**:4740-48.

42. Shen DF, Zhuang Z, LeHoang P et al. Utility of microdissection and polymerase chain reaction for the detection of immunoglobulin gene rearrangement and translocation in primary intraocular lymphoma. *Ophthalmology* 1998;**105**:1664 –69.

43. Misotten T, Tielemans D, Bromberg JE et al. Multicolor flowcytometric immunophenotyping is a valuable tool for detection of intraocular lymphoma. *Ophtalmology* 2013;**120**:991-96

44. Cassoux N, Giron A, Bodaghi B et al. IL-10 measurement in aqueous humor for screening patients with suspicion of primary intraocular lymphoma. *Invest Ophthalmol Vis Sci* 2007;**48**:3253–59

45. O'Neill BP, Dinapoli RP, Kurtin PJ, et al. Occult systemic non-Hodgkin's lymphoma in patients initially diagnosed as primary central nervous system lymphoma: How much staging is enough? *J Neurooncol* 1995;**25**:67-71.

46. Ferreri AJ, Reni M, Zoldan MC, et al. Importance of complete staging in non-Hodgkin's lymphoma presenting as a cerebral mass lesion. *Cancer* 1996;**77**:827-33.

47. Abrey LE, Batchelor TT, Ferreri AJ, et al. Report of an international workshop to standardize baseline evaluation and response criteria for primary CNS lymphoma. *J Clin Oncol*. 2005;**23**:5034-43.

48. Mohile NA, Deangelis LM, Abrey LE. Utility of brain FDG-PET in primary CNS lymphoma. *Clin Adv Hematol Oncol.* 2008; **6** :818-20

49. Corry J, et al. Primary central nervous system lymphoma: age and performance status are more important than treatment modality. *Int J Radiat Oncol Biol Phys*. 1998;**41**:615-20.

50. Blay JY, Conroy T, Chevreau C, et al et al. High-dose methotrexate for the treatment of primary cerebral lymphomas: analysis of survival and late neurologic toxicity in a retrospective series. *J Clin Oncol* 1998; **16**:864-71.

51. Abrey LE, Ben-Porat L, Panageas KS, et al. Primary central nervous system lymphoma: the Memorial Sloan-Kettering Cancer Center prognostic model. *J Clin Oncol* 2006 ;**24**:5711-15.

52. Bessell EM, Graus F, Lopez-Guillermo A et al. Primary non-Hodgkin's lymphoma of the CNS treated with CHOD/BVAM or BVAM chemotherapy before radiotherapy: Long-term survival and prognostic factors. *Int J Radiat Oncol Biol Phys 2004*;**59**:501–08.

53. Ferreri AJ, Blay JY, Reni M, et al. Prognostic scoring system for primary CNS lymphomas: the International Extranodal Lymphoma Study Group experience. *J Clin Oncol*.2003 ;**21**:266-72

54. Ghesquières H, Drouet Y, Sunyach MP, et al. Evidence of time-dependent prognostic factors predicting early death but not long-term outcome in primary CNS lymphoma: a study of 91 patients. *Hematol Oncol* 2013;**31**:317-24

55. Iwadate Y, Suganami A, Ikegami S, et al. Non-deep-seated primary CNS lymphoma: therapeutic responses and a molecular signature. *J Neurooncol.*2014 ; **117**:261-68

56. Kasenda B, Haug V, Schorb E, et al. 18F-FDG PET is an independent outcome predictor in primary central nervous system lymphoma. *J Nucl Med* 2013;**54**:184-91.

57. Cady FM, O'Neill BP, Law ME, et al. Del(6)(q22) and BCL6 rearrangements in primary CNS lymphoma are indicators of an aggressive clinical course. *J Clin Oncol* 2008;**26**:4814-19.

58. Pels H, Juergens A, Schirgens I, et al. Early complete response during chemotherapy predicts favorable outcome in patients with primary CNS lymphoma. *Neuro Oncol* 2010;**12**:720-24.

59. Barajas RF Jr., Rubenstein JL, Chang JS, et al. Diffusion weighted MR imaging derived apparent diffusion coefficient is predictive of clinical outcome in primary central nervous system lymphoma. *AJNR* 2010;**31**:60–66.

60. Wieduwilt M, Valles F, Issa S et al. Immunochemotherapy with intensive consolidation for primary CNS lymphoma: a pilot study and prognostic assessment by diffusion-weighted MRI. *Clin Cancer Res* 2012; **18**: 1146-55

61. Morris PG, Correa DD, Yahalom J, et al. Rituximab, methotrexate, procarbazine, and vincristine followed by consolidation reduced-dose whole-brain radiotherapy and cytarabine in newly diagnosed primary CNS lymphoma: final results and long-term outcome. *J Clin Oncol*. 2013;**31**:3971-79

62. Braaten KM, Betensky RA, de Leval L, et al. BCL-6 expression predicts improved survival in patients with primary central nervous system lymphoma. *Clin Cancer Res* 2003; **9**: 1063–69.

63. Levy O, Deangelis LM, Filippa DA, et al. Bcl-6 predicts improved prognosis in primary central nervous system lymphoma. *Cancer* 2008; **112**: 151–56.

64. Lossos IS, Jones CD, Warnke R, et al. Expression of a single gene, BCL-6, strongly predicts survival in patients with diffuse large B-cell lymphoma. *Blood* 2001; **98**: 945–51.

65. Preusser M, Woehrer A, Koperek O, et al. Primary central nervous system lymphoma: a clinicopathological study of 75 cases. Pathology 2010;**42**:547-52.

66. Rubenstein JL, Hsi ED, Johnson JL, Jung SH, Nakashima MO, Grant B, et al. Intensive chemotherapy and immunotherapy in patients with newly diagnosed primary CNS lymphoma: CALGB 50202 (Alliance 50202). *J Clin Oncol* 2013 ;**31**:3061-68

67. Ferreri AJ, Guerra E, Regazzi M, et al. Area under the curve ofmethotrexate and creatinine clearance are outcome-determining factors in primary CNS lymphomas. *Br J Cancer* 2004;**90**: 353–58.

68. Joerger M, Huitema AD, Krahenbuhl S, et al. Methotrexate area under the curve is an important outcome predictor in patients with primary CNS lymphoma: pharmacokinetic pharmacodynamic analysis from the IELSG no. 20 trial. *Br J Cancer* 2010;**102**:673–77.

69. Blasco H, Senecal D, Le Gouge A, et al. Influence of methotrexate exposure on outcome in patients treated with MBVP chemotherapy for primary central nervous system lymphoma. *Br J Clin Pharmacol* 2010;**70**:367–75.

70. Morris PG, Abrey LE, Reiner AS, et al. Methotrexate area under the curve as a prognostic factor in primary CNS lymphoma treated with immunochemoradiotherapy. *Leuk Lymphoma*, 2011;**52**:1891-97

71. Fischer L, Koch A, Schlegel U, et al. Non-enhancing relapse of a primary CNS lymphoma with multiple diffusion-restricted lesions. *J Neurooncol* 2011;**102**:163-66.

72. Abrey LE, DeAngelis LM, Yahalom J. Long-term survival in primary CNS lymphoma. *J Clin Oncol* 1998; **16**:859-63

73. Correa DD, Maron L, Harder H, et al. Cognitive functions in primary central nervous system lymphoma: literature review and assessment guidelines. *Ann Oncol* 2007; **18**:1145-51

74. Wassenberg MW, Bromberg JE, Witkamp TD et al. White matter lesions and encephalopathy in patients treated for primary central nervous system lymphoma. *J Neurooncol* 2001; **52**:73-80

75. Omuro AM, Ben-Porat LS, Panageas KS *et al.* Delayed neurotoxicity in primary central nervous system lymphoma. *Arch Neurol* 2005; **62**:1595–600

76. Harder H, Holtel H, Bromberg JEC et al. Cognitive status and quality of life after treatment for primary CNS lymphoma. *Neurology* 2004;**62**:544-47

77. Correa DD, DeAngelis LM, Shi W. et al. Cognitive functions in survivors of primary central nervous system lymphoma. *Neurology* 2004;**62**:548-55

78. Jürgens A, Pels H, Rogowski S, et al. Long-term survival with favorable cognitive outcome after chemotherapy in primary central nervous system lymphoma. *Ann Neurol* 2010;**67**:182-89.

79. Correa DD, Shi W, Abrey LE, DeAngelis LM, et al. Cognitive functions in primary CNS lymphoma after single or combined modality regimens. *Neuro Oncol* 2012; **14**:101-08.

80. Doolittle ND, Korfel A, Lubow MA, et al. Long-term cognitive function, neuroimaging, and quality of life in primary CNS lymphoma. *Neurology* 2013; **81**:84-92

81. Grimm SA, Pulido JS, Jahnke K, Schiff D, et al. Primary intraocular lymphoma: an International Primary Central Nervous System Lymphoma Collaborative Group Report. *Ann Oncol* 2007 ;**18**:1851-55.

82. Hormigo A, Abrey L, Heinemann MH, DeAngelis LM. Ocular presentation of primarycentral nervous system lymphoma: diagnosis and treatment. *Br J Haematol* 2004;**126**:202-08

83. Margolis L, Fraser R, Lichter A, et al.. The role of radiation therapy in the management of ocular reticulum cell sarcoma. *Cancer.* 1980;**45**:688-92

84. Berenbom A, Davila RM, Lin HS, et al. Treatment outcomes for primary intraocular lymphoma: implications for external beam radiotherapy. *Eye* 2007;**21**:1198-201

85. Frenkel S, Hendler K, Siegal T, et al. Intravitreal methotrexate for treating vitreoretinal lymphoma: 10 years of experience. *Br J Ophthalmol* 2008;**92**:383-88

86. Hashida N, Ohguro N, Nishida K. Efficacy and Complications of Intravitreal Rituximab Injection for Treating Primary Vitreoretinal Lymphoma.*Transl Vis Sci Technol* 2012; **1**:1-11

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87. Batchelor TT, Kolak G, Ciordia R, et al. High-dose methotrexate for intraocular lymphoma. *Clin Cancer Res* 2003;**9**:711-15.
88. Siegel MJ, Dalton J, Friedman AH, et al. Ten-year experience with primary ocular 'reticulum cell sarcoma' (large cell non-Hodgkin's lymphoma*). Br J Ophthalmol* 1989;**73**:342-46.
89. Strauchen JA, Dalton J, Friedman AH. Chemotherapy in the management of intraocular lymphoma. *Cancer* 1989;**63**:1918-21
90. Jahnke K, Thiel E, Bechrakis NE, Willerding G, et al. Ifosfamide or trofosfamide in patients with intraocular lymphoma. *J Neurooncol* 2009 ;**93**:213-17
91. Soussain C, Suzan F, Hoang-Xuan K, et al. Results of intensive chemotherapy followed by haematopoietic stem cell rescue in 22 patients with refractory or recurrent primary CNS lymphoma or intraocular lymphoma. *J Clin Oncol* 2001; **19**:742-49.
92. Rajagopal R, Harbour JW. Diagnostic testing and treatment choices in primary vitreoretinal lymphoma. *Retina* 2011;**31**:435–40
93. Grimm SA, McCannel CA, Omuro AM, et al. Primary CNS lymphoma with intraocular involvement: International PCNSL Collaborative Group Report. *Neurology* 2008 ;**71**:1355-60
94. Ferreri AJ, Blay JY, Reni M, et al. International Extranodal Lymphoma Study Group (IELSG). Relevance of intraocular involvement in the management of primary central nervous system lymphomas. *Ann Oncol* 2002;**13**:531-38

EANO Guideline for the diagnosis and treatment of primary CNS lymphoma in immunocompetent patients.

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Abstract

The management of primary central nervous system (PCNSL) is one of the most controversial topics in neuro-oncology because of the complexity of the disease and the very limited number of controlled studies available. In 2013, the European Association of Neuro-Oncology (EANO) created a multidisciplinary task force to establish evidence-based guidelines for immunocompetent adult patients with PCNSL. The guideline provides consensus considerations and recommendations for diagnosis, staging and treatment of PCNSL, including surgery, systemic and intrathecal chemotherapy, intensive chemotherapy with autologous stem cell transplantation, radiotherapy, intraocular manifestations, and specific management of elderly patients. The guideline should aid the clinicians in everyday practice and decision making and serve as a basis for future research in the field.

Introduction

Primary central nervous system lymphomas (PCNSL) are extranodal malignant non-Hodgkin lymphomas (NHL) of the diffuse large B cell (DLBCL) type confined to the brain, eyes, leptomeninges, or spinal cord in the absence of systemic lymphoma. Currently PCNSL are estimated to account for up to 1% of lymphomas, 4-6% of all extranodal lymphomas, and about 3% of all CNS tumors.[1] After a continuous increase in the 1980's and 1990's, epidemiologic data in Western countries show a decrease in the incidence of PCNSL, particularly among young patients suffering from AIDS.[2] In contrast, the incidence continues intriguingly to rise in the elderly who represent consequently the large majority of patients in the immunocompetent population in some recent studies.[3-5] Although the prognosis of PCNSL remains poor, it has significantly improved over the past two decades as a result of better treatment strategies with a curative aim. Treatment of PCNSL is challenging. Despite a high chemosensitivity and radiosensitivity, remissions are frequently short-lasting; the blood brain-barrier (BBB) limits the access of many drugs to the CNS; and patients, especially the elderly, are at high risk of developing severe treatment related-neurotoxicity. To date, therapeutic knowledge to define the optimal treatment mainly results from retrospective series or single arm phase II studies, with only three completed randomized trials available: one phase III and two phase II. The objective of this guideline is to provide clinicians with evidence-based recommendations and consensus expert opinions on the management of patients with PCNSL. The present guideline focuses on the immunocompetent population which represents the vast majority of the patients today. PCNSL of immunodeficient patients and the rare indolent low grade lymphomas occurring primarily in the CNS, which have a distinct pathogenesis with separate diagnostic and therapeutic implications, will be subject to specific guidelines.

Search strategy and selection criteria

The guideline task force was set up in 2013 under the auspices of the EANO (European Assocation for Neuro-Oncology) and selected to be representative of European-based medical experts (10 countries). The panel covered all fields of expertise in the management of PCNSL, i.e. neurologists, haematologists, medical oncologists, neurosurgeons, pathologists, ophthalmologists and radiation oncologists. Based on best available evidence from literature review, the writing group (EB, JB, AH, KHX, MP, RR, US, TS, CS) produced the draft guideline, which was subsequently submitted to the review committee (UA, NC, MD, CD, AF, FG, RH, UH, RS, MT, MW). The revised guideline, taking into account the comments of the reviewers, was resubmitted by the chairman to the whole task force for review and amendments twice. Therafter, final agreement was obtained in September 2014. When

analyzing results and drawing recommendations, at any stage, differences were resolved by discussiondiscussion and, if persisting, were reported in the text. References for this review 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” from January 1980 to September 2014. Articles were also identified through searches of the authors` own files. The final reference list was generated on the basis of originality and relevance to the broad scope of this review. Abstracts presented at the annual ASCO meeting in 2013 and 2014 relevant to the topic were included by task force members during manuscript preparation. The scientific evidence of papers collected from the literature was evaluated and graded as follows and recommendations were given accordingly. Class I evidence was derived from prospective, randomized, phase III clinical trials; class IIa evidence was derived from prospective randomized phase II trials, class IIb evidence was derived from phase II trials; class IIIa was derived from prospective studies, including observational studies, cohort studies and case–control studies; class IIIb evidence was derived from retrospective studies; class IV evidence was derived from uncontrolled case series, case reports and expert opinion. As for recommendations, level A required at least one class I study or two consistent class IIa studies, level B at least one class IIa study or overwhelming class IIb and III evidence and level C at least two consistent class III studies. Pathology, genetics, clinical features and neuroimaging were simply reviewed but not graded. When sufficient evidence for recommendations A–C was not available, we gave a recommendation as a “Good Practice Point”, if agreed by all members of the Task Force.

General recommendations

Consensus statements and recommendations for the general approach to patients with PCNSL, including: 1/ pathology and genetics, 2/ clinical presentation, 3/ diagnostic confirmation, 4/ neuropathology of corticosteroid-treated PCNSL, 5/ neuroimaging, 6/ cerebrospinal fluid (CSF) analyses, 7/ vitreous analyses, 8/ staging, 9/ prognostic factors, 10/ response criteria to treatment, and 11/ treatment-related neurotoxicity are presented in table 1. The evidences used to establish these recommendations are detailed in the supplementary webappendix. Key recommendations for treatment are summarized in table 2. The evidences concerning intraocular lymphoma are presented in the webappendix. Our guideline covers treatment of histologically or cytologically proven PCNSL. We have not covered specifically the treatment of patients with deep seated tumours not readily amenable to biopsy for which there are no evidence-based recommendations. We believe that biopsies are almost always possible in specialized centers and that chemotherapy and/or radiotherapy interventions without histological confirmation of PCNSL should be discouraged.

Surgery

Although very few data are available in the literature, surgery has traditionally been considered to have no role in the treatment of PCNSL. This widely adopted opinion is based on small retrospective series suggesting no clear benefit in outcome of surgical resection used as sole treatment compared with supportive care (Class IIIb),[6] and compared with biopsy in patients having received post-operative chemotherapy and/or radiotherapy (Class IIIb).[7,8] This may be explained by the microscopically multifocal and infiltrative nature of PCNSL that may extend beyond the visible border of the lesion.[9] The relative radiosensitivity and high chemosensitivity of PCNSL, and the increased risks of postoperative morbidity of this patient population have also contributed to discourage surgery. However, the recommendation to restrict surgical interventions to biopsies is not based on randomized data and, more importantly, not on contemporary data reflecting modern neurosurgery. The German PCNSL Study Group–1 phase III trial included an unusually high rate of operated patients, which allowed the largest and most recent retrospective analysis of an association of surgery and outcome. A significantly longer progression free survival (PFS) and overall survival (OS) in patients with subtotal or gross total resections compared with biopsied patients was reported. This difference in outcome was independent of post-operative Karnofsky performance status (KPS) and age. Since biopsied patients more often had multiple and/or deeply seated CNS lesions than resected patients, these features may have contributed to the unfavourable outcome. When adjusted for the number of lesions (site of the lesions was not analyzed in the study), the difference in outcome remained significant in term of PFS but did not reach the significance threshold for OS (Class IIIa).[10]

Systemic chemotherapy

The CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) regimen commonly used for systemic NHL induces short-lasting responses in PCNSL and its addition to radiotherapy has not shown a survival benefit in prospective trials (Class IIb).[11-13] This inefficacy is probably due to the fact that phosphoramide mustard and doxorubicin are not able to cross the blood-brain barrier (BBB) to eradicate microscopic disease. Based on convergent results from numerous prospective and retrospective studies, high-dose (HD) intravenous (iv) methotrexate (MTX), an antifolate and antimetabolite, is now considered the most important and beneficial single agent. Penetration of MTX into the CNS depends both on the total dose and rate of infusion. The optimal dose of MTX has not been determined. It has been estimated that the iv MTX should range between 1 g/m^2 and 8 g/m^2 to cross the BBB. In the absence of clear evidence for dose-response relationship, and since rapid infusion of MTX $\geq$ 3g/m^2 over 3 hours achieves cytotoxic levels in the CSF, there is a growing consensus to deliver MTX according to this protocol (Class IV).[14] Since efficacy of MTX may also depend on duration of exposure, MTX administration interval should range between 10 days and 3 weeks (Class IV).[15] The optimal number of MTX injections to deliver is unknown. A minimum of 4-6

injections is delivered in most chemotherapy regimens, especially if no consolidation treatment (radiotherapy and/or intensive chemotherapy) is scheduled in the protocol. For patients who achieved only partial response (PR) after 4-5 courses of HD MTX, additional courses may improve the complete remission rate (Class IIIa).[16] Infusions of HD MTX require pre- and post-hyperhydration, urine alkalinization, leucovorin rescue and MTX concentration monitoring. Currently most treatment protocols combine HD MTX with a variety of other chemotherapeutic agents to improve response rate and outcome. The best evidence to support this approach comes from an IELSG randomized phase II study comparing HD MTX alone, administered at 3 g/m^2/d every 21 days, to HD MTX with cytarabine (2 g/m^2 twice per day on days 2–3)(Class IIa).[17] Both chemotherapy arms were followed by WBRT. This study showed a significantly higher complete response (CR) rate in the HD MTX-cytarabine arm. Regarding secondary endpoints, a significantly improved overall response rate (ORR), PFS and a trend towards better OS in the HD MTX-cytarabine arm were noticed. Two previous prospective trials evaluating HD MTX at a dose of $8g/m^2$ as single agent and without immediate consolidation WBRT resulted in a shorter PFS when compared to polychemotherapy regimens (Class IIb).[18,19] Similarly, the addition of ifosfamide to HD-MTX improved response rate, but not survival, in the G-PCNSL-SG-1 trial.[20] Altogether, these data resulted in the recognition that only HD MTX can be defined as a chemotherapy standard of care.[21] Chemotherapeutic agents to be combined with HD MTX should be selected among active drugs known to cross the BBB, such as HD cytarabine. Recently, the CALGB50202 multicenter phase II trial reported promising results using HD cytarabine combined with etoposide as consolidation without WBRT following a HD MTX-based polychemotherapy as induction regimen (Class IIb).[22] In contrast, very disappointing results have been reported in a pilot study combining HD MTX ($3.5g/m^2$), thiotepa and cytarabine at a reduced dose of $1g/m^2$ suggesting that the cytarabine dose probably was suboptimal to reach cytototoxic levels in the CNS (Class IIIa),[23] as supported by pharmacokinetic studies.[24] Another approach is BBB disruption (BBBD) by intra-arterial (IA) infusion of hypertonic mannitol followed by intra-arterial (IA) chemotherapy to increase the drug concentration in the CNS. BBBD with IA MTX administrated in newly diagnosed PCNSL demonstrated a good safety profile and neurocognitive tolerance and achieved comparable outcomes to those observed with HD-intravenous MTX based chemotherapy regimens (Class IIIb).[25-27] However, conversely to those reported in prospective studies on chemoradiotherapy, even after a follow-up longer than 10 years (Class IIb),[28] BBBD is not associated with a plateau in survival curves, suggesting a continuum of relapses and deaths. This procedure requires patient selection as safety depends on the extent of intracranial mass effect and the procedure is limited to patients with no contraindications for general anesthesia. It should be managed by teams trained in BBBD as it is complex, requiring cannulation of the intracranial vessels. In summary, HD MTX is the drug of choice for PCNSL. In patients who are not eligible for HD MTX, treatment should be chosen from treatments active as salvage in refractory or recurrent PCNSL after initial HD MTX based chemotherapy (see salvage treatment section).

Intrathecal chemotherapy

Intrathecal (IT) chemotherapy administration has not been prospectively studied and its efficacy in PCNSL remains debated. Three retrospective studies did not demonstrate benefit from the addition of intrathecal drugs (MTX, cytarabine) in patients treated with HD MTX dosed at 3g/m^2 (Class IIIb).[29-31] In contrast, two consecutive single arm trials using the same systemic polychemotherapy regimen suggested additional benefit when intraventricular chemotherapy was added (Class IIIa).[32,33] However, given the low level of evidence, we currently do not advocate IT chemotherapy as prophylaxis.

Rituximab

Based on its poor penetration into the CNS related to its large size, the maximal concentration and efficacy of the anti-CD20 antibody rituximab in the CNS might be assumed to occur in the early treatment phase, during BBB breakdown within the tumors. The effect of rituximab when used as monotherapy in PCNSL was evaluated in a single study in which 12 patients with refractory or relapsed PCNSL were treated with a weekly iv dose of 375 mg/m^2 rituximab infusion for up to eight doses (Class IV).[34] MRI responses were observed in 36% of patients. Other studies used iv rituximab in combination with a HD MTX-based chemotherapy regimen as initial treatment for newly-diagnosed PCNSL or as salvage treatment for recurrent PCNSL (Class IIIa, Class IIIb and IV).[16,22,35-41] Three studies suggested that the addition of rituximab to HD MTX-based chemotherapy improves the CR and OS ratein patients with newly-diagnosed PCNSL based on retrospective comparison with historical controls (Class IIIb).[39-41] Overall, the addition of rituximab to systemic polychemotherapy is well tolerated. Injection of rituximab into the CSF via either lumbar puncture or by intraventricular administration was evaluated in phase I for refractory or recurrent CNS lymphoma patients (Class IIIa).[42] In these studies objective responses and good tolerability were documented confirming small case series. In conclusion, the existing level of evidence supporting either systemic or local use of rituximab as part of treatment protocol for PCNSL remains low. Yet, the preliminarily available information suggests that it may add some benefit. Two ongoing randomized trials (NCT01011920; NTR2427) should clarify the role of systemic rituximab in PCNSL.

Radiotherapy

Because of the microscopically diffuse and multifocal nature of PCNSL, radiotherapy (RT) has so far involved the whole brain, including the eyes. Despite a high response rate in the range of 50%, RT used as sole treatment modality, provides limited survival benefit in PCNSL patients, with a median OS duration of 10–18 months and a 5-year survival rate of 5%. The only phase II trial, conducted by

the RTOG, which delivered a total dose of 40 Gy with an additional 20-Gy boost to contrast-enhancing lesions, reported a disappointing 11.6 month OS (Class IIb).[43] In addition, the majority of relapses occurred in fields that had received the highest RT dose. Although not formally compared in a randomized trial, a wide consensus is shared which considers that HD MTX-chemoradiation is superior to RT-alone, allowing for a 2 to 4-fold increase in OS (median: 30-72 months) and long-term survivors (5-year survival of 20-50%) for many protocols (Class IIb, IIIa IIIb).[15,44-52] In contrast to extracerebral NHL, the optimal dose of post-chemotherapy irradiation has never been prospectively investigated in PCNSL.[53] Doses of 23–50 Gy to the whole brain, with or without a tumor bed boost, are currently used, with most of the protocols delivering a total dose of 40–45 Gy without boost, and standard fractionation (1.8-2Gy/fraction). The RTOG-9310 trial did not show a clear benefit with hyperfractionated WBRT (Class IIb).[54] For patients who achieve a CR after HD MTX-based chemotherapy, it remains unclear whether consolidation with WBRT provides better disease control or survival. There has only been one randomized trial of radiotherapy versus watch-and-wait after chemotherapy for PCNSL. This study (G-PCNSL-SG 1) conducted in Germany was a non-inferiority phase III trial, in which patients received HD MTX 4g/m^2 iv every 14 days for 6 cycles with or without ifosfamide. Those patients who achieved a CR had been randomized initially between consolidating WBRT, 45 Gy in 30 fractions over 6 weeks or no further immediate treatment. Patients without a CR received HD cytarabine or WBRT. A total of 551 patients entered the study, but 318 patients were treated per-protocol. OS was similar in both arms. In the whole per-protocol population, the WBRT arm was associated with a trend (not significant) for better PFS, as compared with the no WBRT arm but with no significant difference in OS.[20] This trial (Class I), which is, to date, the largest one and only phase III trial in PCNSL has raised vigourous debate within the community.[55-58] Several experts consider that the unmet primary endpoint for non-inferiority and the high rate of protocol violations prevent any conclusions being drawn from the trial and advocate keeping consolidation WBRT after HD MTX-based chemotherapy as the standard of care, whilst awaiting results from further, ongoing randomized trials; while others, acknowledging the methodological limitations of the study, consider nevertheless that the results contribute strongly to the accumulating retrospective literature suggesting that omission of WBRT from first-line treatment results in shorter PFS but does not compromise OS (Class IIIb).[29,59,60] In addition, several single arm trials have suggested that chemotherapy alone, plus a deferred RT strategy may result in comparable OS with those reported for combined chemo-RT but with better neurocognitive preservation (Class IIb, IIIa, IIIb).[19,25,26,32,61-63] Since withdrawing consolidation WBRT for patients with CR to chemotherapy remains controversial, especially in patients less than 60 years old who are at lower risk of developing neurotoxicity, reduced dose WBRT is another alternative approach. Conflicting results have been reported. A subset analysis from a phase II trial that included 25 patients aged <60 years who achieved a CR after initial chemotherapy and received either 45 Gy or 30.6 Gy as consolidation treatment showed a significantly higher recurrence rate and lower OS rate in the reduced-dose RT group (Class IIIb).[64] On the other

hand, in a restrospective study of 33 patients with PCNSL who achieved CR after MTX-containing chemotherapy and were referred to consolidation WBRT, total doses ≥ 40 Gy were not associated with improved disease control in comparison with a WBRT dose of 30-36 Gy (Class IIIb).[65] More recently, a phase II trial evaluating an immunochemoradiation regimen (R-MPVA) including rituximab and HD MTX-based polychemotherapy, the 31 CR patients were offered reduced dose WBRT (23 Gy in complete responders) with encouraging results both in term of survival and neurotoxicity (Class IIb).[16] Based on these results, a randomized phase II study (RTOG-1114) comparing the R-MPV regimen with or without reduced-dose WBRT is currently ongoing (NCT01399372). In summary, the role of consolidation WBRT following HD-MTX based chemotherapy remains debated especially in patients in CR. In addition, the optimal dose has not been defined yet.

High-dose chemotherapy, myeloablative conditioning and autologous stem cell transplantation (HDC /ASCT)

HDC/ASCT is the standard treatment for chemosensitive relapsing systemic DLBCL. For patients with relapsed or refractory PCNSL, there is only one multicenter phase II trial evaluating HDC/ASCT, with TBC conditioning regimen (thiotepa, busulfan, cyclophosphamide). The CR rate was 60%, median PFS and OS were 41 and 58 months respectively for the 27 patients out of 43 who completed the full HDC/ASCT procedure. For the whole population of this trial, the intent-to-treat median PFS and OS times were 11 and 18 months respectively. The toxicity-related mortality was 7% (Class IIb).[66] An update of this study to which additional cases have been included, and an independent retrospective single center series confirmed the benefit of the TBC regimen followed by ASCT (Class IIIb).[67,68] Experiences with other HDC regimens in this setting of patients are limited to a few cases, which prevent any conclusions being drawn. Because of its toxicity risks, the HDC/ASCT is likely to be proposed for younger patients (<60-65 years) with a good performance status, which makes it difficult to compare with other salvage treatments, including second-line conventional chemotherapy regimens and WBRT. The specific role of HDC/ASCT as consolidation in first-line treatment is difficult to evaluate since WBRT was administered after HDC/ASCT in early studies (Class IIb).[69,70] The first study with HDC/ASCT without WBRT used the BEAM regimen (BCNU, etoposide, cytarabine, and melphalan) as conditioning and reported a disappointing median event-free survival of 9.3 months (Class IIIa).[71] Subsequently, encouraging studies for which WBRT had been omitted at least in patients in CR after HDC/ASCT using HD thiotepa-based conditioning regimens have been reported (Class IIIb and IV).[72-75] Taken together, although direct comparison between conditioning regimens applied is difficult, HD thiotepa-based conditioning regimens seem more efficient than BEAM-based regimens. In summary, HDC/ASCT represents an effective treatment option for selected refractory and relapsed PCNSL patients, but should be reserved to experienced centers. Superiority of the HDC/ASCT approach compared to standard combined chemo-radiotherapy as first line treatment

has not been proven and is currently under investigation in two ongoing trials (NCT00863460, NCT01011920).

Elderly patients

Definition of 'elderly' is not uniform. However, in the studies available which have evaluated prognostic factors, older ages (over 50 and over 60) were consistently correlated with worse outcome (see the section on prognostic factors in appendix). Furthermore, for chemoradiation-induced neurotoxicity age>60 was found to be highly prognostic (see the section on neurotoxicity in appendix). Therefore, age of 60 has been used as cut-off to define the elderly population in most of the studies. Four prospective studies have been published on treatment of elderly patients with PCNSL (Class IIb),[36,63,76,77] seven prospective studies on patients of all ages but reporting specifically on older patients (Class IIIa),[11,12,32,43,52,54,78] and seven retrospective studies reporting on ≥ 15 patients (Class IIIb).[79-85] As in younger patients, results in patients treated with steroids or CHOP/CHOD in addition to radiotherapy do not differ from results after radiotherapy only (Class IIb).[11,12,43,77] In the RTOG phase II trial, the median survival was only 7.8 months.[43] After HD-MTX-based therapy, defined as dose of MTX ≥ 1 g/m^2 PFS in patients aged 60 or 65 and older is reported between 6 and 16 months and OS between 14 and 37 months (Class IIb and Clas III) with OS in the majority of prospective studies under 2 years.[32,36,52,54,63,73,78-85] Other than within retrospective studies no direct comparisons have been made between treatment with HD-MTX-based chemotherapy and radiotherapy in this age group.[81] However, the impression from the single arm studies is that survival after chemotherapy is at least as good and probably better after HD MTX-based chemotherapy than after radiotherapy (Class IV). Formal comparisons of different HD MTX-based regimens have not been published but in a recently completed randomized phase II study, toxicity was identical, CR rate, median PFS and survival appeared better after MPV-A (MTX, procarbazine, vincristine, cytarabine) than after MTX and temozolomide though the difference was not significant (Class IIa).[86] Five prospective studies report on chemotherapy toxicity in patients aged over 60. With the exception of one study, in which an intensive multi-drug regimen was used and toxicity was exceedingly high in older patients,[52] HD MTX-based chemotherapy up to 3.5 g/m^2 was well tolerated with 2-7% treatment-related mortality, less than 10% grade 3-4 nephrotoxicity and 7-10% of patients discontinuing treatment due to chemotherapy-associated toxicity, though MTX dose was reduced because of decreased renal function in 26-44% of patients.[36,63,76,87] Retrospective studies substantiate this view. Thus, in general, older patients tolerate treatment with HD-MTX well when adequate supportive measures are used and renal function is accurately monitored.[3] As discussed in the neurotoxicity section (appendix), risk of delayed leukoencephalopathy is particularly high in patients older than 60 years managed with chemoradiotherapy. For patients treated with HD-MTX-based chemotherapy without radiotherapy no studies reporting specifically on older patients are available, but reports including neuropsychological

assessment of patients of all ages show little or no cognitive decline compared with post-treatment evaluations (Class IIIb).[61,88] Given the available data on acute and long-term toxicity of radiotherapy and chemotherapy in older patients with performance status KPS ≥ 70, treatment with HD MTX-based chemotherapy with deferral or elimination of WBRT is the treatment of choice. In older patients in poor condition and in the very old (over 80) who both have a worse prognosis,[85] the acute morbidities and frequent admissions to hospital associated with HD-MTX chemotherapy need to be individually weighed against the more limited survival benefits in this population.

Salvage treatment

About one third of patients with PCNSL will present with disease that is refractory to first-line treatment and half of responders will relapse despite high response rates seen with initial treatment. The prognosis of progressive or relapsed PCNSL remains poor with limited treatment options. Salvage treatments for relapsed or refractory PCNSL patients depend on age, performance status, site of relapse within the CNS, prior treatments and time duration from last response. If the patient did not receive any consolidating treatment after the HD MTX-based induction chemotherapy, WBRT or HDC/ASCT should be considered. Two retrospective studies have evaluated WBRT delivered in relapsed PCNSL and reported a high rate of objective reponses and a short median survival of 11-16 months - quite similar to what is expected with WBRT alone as initial treatment (Class IIIb).[89,90] Delayed neurotoxicity occurred in 15%–22% of patients. However, in the setting of recurrence, WBRT did not prolong survival compared with non-WBRT-based therapies in the G-PCNSL-SG-1 trial (Class IIIa).[20] HDC/ASCT is an efficient alternative option, as has been previously discussed, and which should be preferentially proposed for patients aged < 60-65 years and with a tumour sensitive to second-line chemotherapy (Class llb) (see section above).[66-68] Otherwise, if the patient is not suitable for WBRT or HDC/ASCT , conventional chemotherapy can be proposed as second-line treatment. There is however, only a limited number of prospective studies available for guidance and these have been single-arm phase ll trials complicating any comparison across trials (Class llb, lll and lV for all studies in this section). Several drugs used as single agent or in combination, with or without rituximab, have been evaluated and demonstrated modest activity such as temozolomide,[38,91] topotecan,[92] pemetrexed,[93] bendamustine,[94] PCV regimen,[95] ifosfamide-etoposide based regimen,[37,96], or cisplatin-cytarabine based regimen.[97] MTX rechallenge given as single agent or in combination may also yield a high rate of new objective response and durable remission in patients who previously achieved prolonged response with HD MTX-based chemotherapy, suggesting retained chemosensitivity to MTX (Class III).[98,99] Extra-CNS relapses account for 7% of failures, and some studies suggest that extra-CNS relapses are associated with a better prognosis than CNS-involving relapses;[100] the best salvage treatment for this condition remains to be defined, but excellent results have been reported with anthracycline-based chemotherapy consolidated or not with HDC/ASCT.[28]

Conclusions

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

Contributors

KHX chaired the task force. Based on best available evidence from literature review, the writing group (EB, JB, AH, KHX, MP, RR, US, TS, CS) produced the draft guideline, which was subsequently submitted to the review committee (UA, NC, MD, CD, AF, FG, RH, UH, RS, MT, MW). The revised guideline, taking into account the comments of the reviewers, was resubmitted by the chairman to the whole task force for review and amendments twice.

Declaration of interest

KHX was the principal investigator of a trial investigating temozolomide (Scherring-Plough) in PCNSL and declare no competing interest. UA reports personal fees from Varian and BrainLAB AG outside the submitted work. MP reports grants from GSK, Roche, Böhringer-Ingelheim, personal fees from GSK, Roche, BMS, outside the submitted work.US reports personal fees from Roche, Medac, GSK, outside the submitted work. MT reports honoraria ad hoc consultancy for Hoffmann La Roche, outside the submitted work. MW reports grants and personal fees from Roche, Merck Serono, Isarna, Novocure, grants from Bayer, Piqur, personal fees from Celldex, Magforce, outside the submitted work. EB, JB, FG, AH, NC, RR, AJMF, MD, CD, TS, RS, CS, declare no competing interest.

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REFERENCES

1. Kluin PM, Deckert M, Ferry JA. Primary diffuse large B-cell lymphoma of the CNS. In: Swerdlow SH, Campo E, Harris NL, editors. World Health Organisation Classification of Tumours Pathology and Genetics of Tumours of the Haematopoietic and Lymphoid Tissues. Lyon: IARC Press, 2008; 240–41.
2. Kadan-Lottick NS, Skluzacek MC, Gurney JG. Decreasing incidence rates of primary central nervous system lymphoma. *Cancer* 2002; **95**:193–202.
3. Bessell EM, Dickinson P, Dickinson S, et al. Increasing age at diagnosis and worsening renal function in patients with primary central nervous system lymphoma. *J Neurooncol* 2011; **104**:191-93.
4. Villano JL, Koshy M, Shaikh H, et al. Age, gender, and racial differences in incidence and survival in primary CNS lymphoma. *Br J Cancer* 2011; **105**:1414-18.
5. O'Neill BP, Decker PA, Tieu C, et al. The changing incidence of primary central nervous system lymphoma is driven primarily by the changing incidence in young and middle-aged men and differs from time trends in systemic diffuse large B-cell non-Hodgkin's lymphoma. *Am J Hematol* 2013;**88**:997-1000.
6. Henry JM, Heffner RR, Dillard SH, et al. Primary malignant lymphomas of the central nervous system. *Cancer* 1974;**34**:1293–302.
7. Bataille B, Delwail V, Menet E, et al. Primary intracerebral malignant lymphoma: A report of 248 cases. *J Neurosurg* 2000;**92**:261-66.
8. Bellinzona M, Roser F, Ostertag H, et al. Surgical removal of primary central nervous system lymphomas (PCNSL) presenting as space occupying lesions: a series of 33 cases. *Eur J Surg Oncol* 2005;**31**:100–05.
9. Lai R, Rosenblum MK, DeAngelis LM. Primary CNS lymphoma: a whole-brain disease? *Neurology* 2002;**59**:1557-62.
10. Weller M, Martus P, Roth P, et al. Surgery for primary CNS lymphoma? Challenging a paradigm. *Neuro Oncol* 2012; **14**:1481-84.
11. O'Neill BP, O'Fallon JR, Earle JD et al. Primary central nervous system non-Hodgkin's lymphoma: survival advantages with combined initial therapy ? *Int J Radiat Oncol Biol Phys* 1995;**33**:663–73.
12. Schultz C, Scott C, Sherman W et al. Pre-irradiation chemotherapy with Cyclophosphamide, doxorubicin, vincristine, and Dexamethasone (CHOD) for PCNSL: Initial report of Radiation Therapy Oncology Group (RTOG) protocol 88-06. *J Clin Oncol* 1996;**14**:556–64.
13. Mead GM, Bleehen NM, Gregor A, et al. A Medical Research Council randomized trial in patients with primary cerebral non-Hodgkin lymphoma: cerebral radiotherapy with and without cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy. *Cancer* 2000; **89**:1359-70.
14. Hiraga S, Arita N, Ohnishi T, et al. Rapid infusion of high-dose methotrexate resulting in enhanced penetration into CSF and intensified tumour response in PCNSL. *J Neurosurgery* 1999; **91**:221-30.
15. Glass J, Gruber ML, Cher L, et al. Preirradiation methotrexate chemotherapy of primary central nervous system lymphoma: long-term outcome. *J Neurosurg* 1994;**81**:188-95.
16. Morris PG, Correa DD, Yahalom J, et al. Rituximab, methotrexate, procarbazine, and vincristine followed by consolidation reduced-dose whole-brain radiotherapy and cytarabine in newly diagnosed primary CNS lymphoma: final results and long-term outcome. *J Clin Oncol* 2013;**31**:3971-79.
17. Ferreri AJ, Reni M, Foppoli M, et al. High-dose cytarabine plus high-dose methotrexate versus high-dose methotrexate alone in patients with primary CNS lymphoma: A randomised phase 2 trial. *Lancet* 2009;**374**:1512-20.
18. Herrlinger U, Schabet M, Brugger W, et al. German Cancer Society Neuro-Oncology Working Group NOA-03 multicentre trial of single agent high dose methotrexate for primary CNS lymphoma. *Ann Neurol 2002 ;* **51:**247–52.

19. Batchelor T, Carson K, O'Neill A, et al. Treatment of primary cerebral lymphoma with methotrexate and deferred radiotherapy: Report of NABTT 96-07. *J Clin Oncol* 2003;**21**:1044-49.
20. Thiel E, Korfel A, Martus P, et al. High-dose methotrexate with or without whole brain radiotherapy for primary CNS lymphoma (G-PCNSL-SG-1): A phase 3, randomised, non-inferiority trial. *Lancet Oncol* 2010;**11**:1036-47.
21. Bergner N, Monsef I, Illerhaus G et al Role of chemotherapy additional to high-dose methotrexate for primary central nervous system lymphoma (PCNSL). *Cochrane Database Syst Rev* 2012;**11**: CD009355.
22. Rubenstein JL, Hsi ED, Johnson JL, et al. Intensive chemotherapy and immunotherapy in patients with newly diagnosed primary CNS lymphoma: CALGB 50202 (Alliance 50202). *J Clin Oncol* 2013;**31**:3061-68.
23. Ferreri AJ, Licata G, Foppoli M et al. Clinical relevance of the dose of cytarabine in the upfront treatment of primary CNS lymphomas with methotrexate-cytarabine combination. *Oncologist* 2011;**16**:336-41.
24. Slevin ML, Piall EM, Aherne GW et al. Effect of dose and schedule on pharmacokinetics of high-dose cytosine arabinoside in plasma and cerebrospinal fluid. *J Clin Oncol* 1983;**1**:546 – 51.
25. Neuwelt EA, Goldman DL, Dahlborg SA et al. Primary CNS lymphoma treated with osmotic blood-brain barrier disruption: prolonged survival and preservation of cognitive function. *J Clin Oncol* 1991;**9**:1580-90.
26. McAllister LD, Doolittle ND, Guastadisegni PE et al. Cognitive outcomes and long-term follow-up results after enhanced chemotherapy delivery for primary central nervous system lymphoma. *Neurosurgery* 2000;**46**:51-60.
27. Angelov L, Doolittle ND, Kraemer DF, et al. Blood-brain barrier disruption and intra-arterial methotrexate-based therapy for newly diagnosed primary CNS lymphoma: A multi-institutional experience. *J Clin Oncol* 2009;**27**:3503-09.
28. Ferreri AJ, Ciceri F, Brandes AA et al. MATILDE chemotherapy regimen for primary CNS lymphoma: results at a median follow-up of 12 years. *Neurology* 2014, **82**:1370-73.
29. Ferreri AJ, Reni M, Pasini F et al. Multicenter study of treatment of primary CNS lymphoma. *Neurology* 2002;**58**:1513-20.
30. Khan RB, Shi W, Thaler HT. Is intrathecal methotrexate necessary in the treatment of primary CNS lymphoma? *J Neurooncol* 2002;**58**:175-78.
31. Sierra Del Rio M, Ricard D, Houillier C, et al. Prophylactic intrathecal chemotherapy in primary CNS lymphoma. *J Neurooncol* 2012;**106**:143-46.
32. Pels H, Schmidt-Wolf IG, Glasmacher A et al. Primary central nervous system lymphoma: results of a pilot and phase II study of systemic and intraventricular chemotherapy with deferred radiotherapy. *J Clin Oncol* 2003;**21**:4489-95.
33. Pels H, Juergens A, Glasmacher A, et al. Early relapses in primary CNS lymphoma after response to polychemotherapy without intraventricular treatment: Results of a phase II study. *J Neurooncol* 2009;**91**:299-305.
34. Batchelor TT, Grossman SA, Mikkelsen T, et al. Rituximab monotherapy for patients with recurrent primary CNS lymphoma. *Neurology* 2011;**76**:929-30.
35. Chamberlain MC, Johnston SK. High-dose methotrexate and rituximab with deferred radiotherapy for newly diagnosed primary B-cell CNS lymphoma. *Neuro Oncol* 2010;**12**:736-44.
36. Fritsch K, Kasenda B, Hader C, et al. Immunochemotherapy with rituximab, methotrexate, procarbazine, and lomustine for primary CNS lymphoma (PCNSL) in the elderly. *Ann Oncol* 2011; **22**:2080-85
37. Mappa S, Marturano E, Licata G, et al. Salvage chemoimmunotherapy with rituximab, ifosfamide and etoposide (R-IE regimen) in patients with primary CNS lymphoma relapsed or refractory to high-dose methotrexate-based chemotherapy. *Hematol Oncol* 2013:**31**:143-50.
38. Nayak L, Abrey LE, Drappatz J, et al. Multicenter phase II study of rituximab and temozolomide in recurrent primary central nervous system lymphoma. *Leuk Lymphoma* 2013;**54**:58-61.

39. Birnbaum T, Stadler EA, von Baumgarten L, et al. Rituximab significantly improves complete response rate in patients with primary CNS lymphoma. *J Neurooncol* 2012;**109**:285-91.

40. Gregory G, Arumugaswamy A, Leung T, et al. Rituximab is associated with improved survival for aggressive B cell CNS lymphoma. *Neuro Oncology* 2013; **15**:1068-73.

41. Holdhoff M, Ambady P, Abdelaziz A, et al. High-dose methotrexate with or without rituximab in newly diagnosed primary CNS lymphoma *Neurology* 2014;**83**;235-39.

42. Rubenstein JL, Li J, Chen L, et al. Multicenter phase 1 trial of intraventricular immunochemotherapy in recurrent CNS lymphoma. *Blood* 2013;**121**:745-51.

43. Nelson DF, Martz KL, Bonner H et al. Non-Hodgkin's lymphoma of the brain: can high dose, large volume radiation therapy improve survival? Report on a prospective trial by the Radiation Therapy Oncology Group (RTOG. *Int J Radiat Oncol Biol Phys* 1992;**23**: 9-17.

44. DeAngelis LM, Yahalom J, Thaler HT, et al. Combined modality treatment for primary central nervous system lymphoma. *J Clin Oncol* 1992; **10**: 635-43.

45. Blay JY, Bouhour D, Carrie C et al. The C5R protocol: a regimen of high-dose chemotherapy and radiotherapy in primary cerebral non-Hodgkin's lymphoma of patients with no known cause of immunosuppression. *Blood*. 1995;**86**:2922-29.

46. O'Brien P, Roos D, Pratt G et al. Phase II multicenter study of brief single-agent methotrexate followed by irradiation in primary CNS lymphoma. *J Clin Oncol* 2000;**18**:519-26.

47. Omuro AM, DeAngelis LM, Yahalom J et al. Chemoradiotherapy for primary CNS lymphoma: an intent-to-treat analysis with complete follow-up. *Neurology* 2005;**64**:69-74.

48. Abrey LE, Yahalom J, De Angelis L. Treatment of primary CNS lymphoma: the next step. *J Clin Oncol* 2000;**18**:3144–50.

49. Bessell EM, Graus F, Lopez-Guillermo A, et al. CHOD/BVAM regimen plus radiotherapy in patients with primary CNS non-Hodgkins lymphoma. *Int J Radiation Oncology Biol Phys* 2003; **50**: 457-64.

50. Poortmans PM, Kluin-Nelemans HC, Haaxma-Reiche H et al. High-dose methotrexate-based chemotherapy followed by consolidating radiotherapy in non-AIDS-related primary central nervous system lymphoma: European Organization for Research and Treatment of Cancer Lymphoma Group Phase II Trial 20962. *J Clin Oncol* 2003;**21**:4483-88.

51. Gavrilovic IT, Hormigo A, Yahalom J et al. Long-term follow-up of high-dose methotrexate-based therapy with and without whole brain irradiation for newly diagnosed primary CNS lymphoma. *J Clin Oncol* 2006;**24**:4570-74.

52. Ghesquieres H, Ferlay C, Sebban C, et al. Long-term follow-up of an age-adapted C5R protocol followed by radiotherapy in 99 newly diagnosed primary CNS lymphomas: a prospective multicentric phase II study of the Groupe d'Etude des Lymphomes de l'Adulte (GELA). *Ann Oncol* 2010; **21**:842-50.

53. Lowry L, Smith P, Qian W et al. Reduced dose radiotherapy for local control in non-Hodgkin lymphoma: a randomised phase III trial. *Radiother. Oncol* 2011; **100**: 86-92.

54. DeAngelis LM, Seiferheld W, Schold SC et al. Combination chemotherapy and radiotherapy for primary central nervous system lymphoma: Radiation Therapy Oncology Group Study 93-10. *J Clin Oncol* 2002;**20**:4643-48.

55. Ferreri, A. J. DeAngelis L, Illerhaus G *et al.* Whole-brain radiotherapy in primary CNS lymphoma. *Lancet Oncol* 2011;**12**, 118–119.

56. Weller M. The vanishing role of whole brain radiotherapy in primary central nervous system lymphoma. *Neuro Oncol* 2014;**16**: 1035-36.

57. DeAngelis LM. Whither whole brain radiotherapy for primary CNS lymphoma? *Neuro Oncol* 2014 **;16**:1032-34

58. Zacher J, Kasenda B, Enger A et al. The role of additional radiotherapy for primary central nervous system lymphoma. *Cochrane Database Syst Rev*. 2014;6:CD009211.

59. Omuro AM, Taillandier L, Chinot O et al. Methotrexate (MTX), procarbazine and CCNU for primary central nervous system lymphoma (PCNSL) in patients younger than 60: Can radiotherapy (RT) be deferred? *J Neurooncol* 2006: **104**:323-30.

60. Ekenel M, Iwamoto FM, Ben-Porat LS et al. Primary central nervous system lymphoma: the role of consolidation treatment after a complete response to high-dose methotrexate-based chemotherapy. *Cancer* 2008;**113**:1025-31.

61. Jürgens A, Pels H, Rogowski S, et al. Long-term survival with favorable cognitive outcome after chemotherapy in primary central nervous system lymphoma. *Ann Neurol* 2010;**67**:182-89.
62. Sandor V, Stark-Vancs V, Pearson D et al. Phase II trial of chemotherapy alone for primary CNS and intraocular lymphoma. *J Clin Oncol* 1998;**16**:3000–06.
63. Hoang-Xuan K, Taillandier L, Chinot O et al. Chemotherapy alone as initial treatment for primary CNS lymphoma in patients older than 60 years: a multicenter phase II study (26952) of the European Organization for Research and Treatment of Cancer Brain Tumor Group. *J Clin Oncol 2003*;**21**:2726-31.
64. Bessell EM, Lopez-Guillermo A, Villa S, et al. Importance of radiotherapy in the outcome of,patients with primary CNS lymphoma: An analysis of the CHOD/BVAM regimen followed by two different radiotherapy treatments. *J Clin Oncol* 2002; **20**: 231-236.
65. Ferreri AJ, Verona C, Politi L, et al. Consolidation radiotherapy in primary CNS lymphomas: Impact on outcome of different fields and doses in patients in complete remission after upfront chemotherapy..*Int J Radiat Oncol Biol Phys* 2011;**80**:169-75.
66. Soussain C, Hoang-Xuan K, Taillandier L et al. Intensive chemotherapy followed by hematopoietic stem-cell rescue for refractory and recurrent primary CNS and intraocular lymphoma: Société Française de Greffe de Moëlle Osseuse-Thérapie Cellulaire. *J Clin Oncol* 2008;**26**:2512-18.
67. Soussain C,Choquet S, Fourme E,et al Intensive chemotherapy with thiotepa, busulfan and cyclophosphamide and hematopoietic stem cell rescue in relapsed or refractory primary CNS and intraocular lymphoma: a retrospective study of 79 cases. Haematologica 2012; **97**:1751-56
68. Welch MR, Sauter CS, Matasar MJ et al. Autologous Stem Cell Transplant in Recurrent or Refractory Primary or Secondary CNS Lymphoma Using Thiotepa, Busulfan and Cyclophosphamide (TBC). *LeuK Lymphoma* 2014 (in press)
69. Colombat P, Lemevel A, Bertrand P et al. High-dose chemotherapy with autologous stem cell transplantation as first-line therapy for primary CNS lymphoma in patients younger than 60 years: a multicenter phase II study of the GOELAMS group. *Bone Marrow Transplant* 2006;**38**:417–20.
70. Illerhaus G, Marks R, Ihorst G et al. High-dose chemotherapy with autologous stem-cell transplantation and hyperfractionated radiotherapy as first-line treatment of primary CNS lymphoma. *J Clin Oncol* 2006;**24**:3865-70.
71. Abrey LE, Moskowitz CH, Mason WP, et al. Intensive methotrexate and cytarabine followed by high dose chemotherapy with autologous stem cell rescue in patients with,newly diagnosed primary CNS lymphoma: An intent to treat analysis. *J Clin Oncol* 2003; **21**: 4151-56.
72. Alimohamed N, Daly A, Owen C, et al. Upfront thiotepa, busulfan, cyclophosphamide, and autologous stem cell transplantation for primary CNS lymphoma: a single centre experience. *Leuk Lymphoma*. 2012;**53**:862-67.
73. Illerhaus G, Müller F, Feuerhake F et al. High-dose chemotherapy and autologous stem-cell transplantation without consolidating radiotherapy as first-line treatment for primary lymphoma of the central nervous system. *Haematologica*. 2008;**93**:147-48.
74. Kiefer T, Hirt C, Späth C, Schüler F, et al. Ostdeutsche Studiengruppe Hämatologie und Onkologie. Long-term follow-up of high-dose chemotherapy with autologous stem-cell transplantation and response-adapted whole-brain radiotherapy for newly diagnosed primary CNS lymphoma: results of the multicenter Ostdeutsche Studiengruppe Hamatologie und Onkologie OSHO-53 phase II study. *Ann Oncol.* 2012;**23**:1809-12.
75. Schorb E, Kasenda B, Atta J, et al. Prognosis of patients with primary central nervous system lymphoma after high-dose chemotherapy followed by autologous stem cell transplantation. *Haematologica*. 2013;**98**:765-70.
76. Illerhaus G, Marks R, Muller F,et al. High-dose methotrexate combined with procarbazine and CCNU for primary CNS lymphoma in the elderly: results of a prospective pilot and phase II study. *Ann Oncol* 2009; **20**:319-25.
77. Laack NN, Ballman KV, Brown PB, et al. Whole-brain radiotherapy and high-dose methylprednisolone for elderly patients with primary central nervous system lymphoma: Results of North Central Cancer Treatment Group (NCCTG) 96-73-51. *Int J Radiat Oncol Biol Phys* 2006; **65**:1429-39.

78. Roth P, Martus P, Kiewe P, et al. Outcome of elderly patients with primary CNS lymphoma in the G-PCNSL-SG-1 trial. *Neurology*. 2012;**79**:890-96.
79. Omuro AM, Taillandier L, Chinot O et al. Temozolomide and methotrexate for primary central nervous system lymphoma in the elderly. *J Neurooncol* 2007;**85**:207-11.
80. Ney DE, Reiner AS, Panageas KS, et al. Characteristics and outcomes of elderly patients with primary central nervous system lymphoma: the Memorial Sloan-Kettering Cancer Center experience. *Cancer* 2010; **116**:4605-12.
81. Schuurmans M, Bromberg JE, Doorduijn J, et al. Primary central nervous system lymphoma in the elderly: a multicentre retrospective analysis. *Br J Haematol* 2010; 151:179-84.
82. Taoka K, Okoshi Y, Sakamoto N, Takano S, et al. A non radiation-containing, intermediate-dose methotrexate regimen for elderly patients with primary central nervous system lymphoma. *Int J Hematol* 2010; **92**:617-23.
83. Zhu JJ, Gerstner ER, Engler DA, et al. High-dose methotrexate for elderly patients with primary CNS lymphoma. *Neuro Oncol* 2009; **11**:211-15.
84. Kurzwelly D, Glas M, Roth P, et al. Primary CNS lymphoma in the elderly: temozolomide therapy and MGMT status. *J Neurooncol* 2010; **97**:389-92
85. Welch MR, Omuro A, DeAngelis LM. Outcomes of the oldest patients with primary CNS lymphoma treated at Memorial Sloan-Kettering Cancer Center. *Neuro Oncol* 2012; **14**:1304-11.
86. Omuro AM, Chinot O, Taillandier L, et al. Multicenter randomized phase II trial of methotrexate (MTX) and temozolomide (TMZ) versus MTX, procarbazine, vincristine, and cytarabine for primary CNS lymphoma (PCNSL) in the elderly: An Anocef and Goelams Intergroup study. *J Clin Oncol* **31**, 2013 (suppl; abstr 2032).
87. Jahnke K, Korfel A, Martus P, et al, German Primary Central Nervous System Lymphoma Study Group (G-PCNSL-SG). High-dose methotrexate toxicity in elderly patients with primary central nervous system lymphoma. *Ann Oncol*. 2005;**16**:445-49.
88. Correa DD, Shi W, Abrey LE, DeAngelis LM, et al. Cognitive functions in primary CNS lymphoma after single or combined modality regimens. *Neuro Oncol* 2012; 14:101-08
89. Hottinger AF, DeAngelis LM, Yahalom J et al. Salvage whole brain radiotherapy for recurrent or refractory primary CNS lymphoma. *Neurology* 2007;**69**: 1178-82.
90. Nguyen PL, Chakravarti A, Finkelstein DM et al. Results of whole-brain radiation as salvage of methotrexate failure for immunocompetent patients with primary CNS lymphoma. *J Clin Oncol* 2005;**23**:1507-13.
91. Reni M, Zaja F, Mason W et al. Temozolomide as salvage treatment in primary brain lymphomas. Br J Cancer. 2007;**96**:864-67
92. Fischer L, Thiel E, Klasen HA *et al.* Prospective trial on topotecan salvage therapy in primary CNS lymphoma. *Ann. Oncol* 2006*;* **17**:1141–45.
93. Raizer J J, Rademaker A, Evens A M et al.: Pemetrexed in the treatment of relapsed/refractory primary central nervous system lymphoma. *Cancer* 2012;**118**: 3743-48.
94. Chamberlain MC. Salvage therapy with bendamustine for methotrexate refractory recurrent primary CNS lymphoma: a retrospective case series. *J Neurooncol*. 2014 ; **118**:155-62
95. Herrlinger U, Brugger W, Bamberg M et al.: PCV salvage chemotherapy for recurrent primary CNS lymphoma. *Neurology* 2000; **54**: 1707-08.
96. Arellano-Rodrigo E, Lopez-Guillermo A, Bessell EM, et al. Salvage treatment with etoposide (VP-16), ifosfamide and cytarabine (Ara-C) for patients with recurrent primary central nervous system lymphoma. *Eur J Haematol*. 2003;**70**:219-24
97. Sierra del Rio M, Choquet S, Hoang-Xuan K et al. Platine and cytarabine-based salvage treatment for primary central nervous system lymphoma. *J Neurooncol.* 2011;**10**:409-14.
98. Plotkin SR, Betensky RA, Hochberg FH et al. Treatment of relapsed central nervous system lymphoma with high-dose methotrexate. *Clin Cancer Res* 2004;**10**:5643–46
99. Pentsova E, Deangelis LM, Omuro A. Methotrexate re-challenge for recurrent primary central nervous system lymphoma. *J Neurooncol*. 2014;**117**:161-65
100. Provencher S, Ferlay C, Alaoui-Slimani K et al. Clinical characteristics and outcome of isolated extracerebral relapses of primary central nervous system lymphoma: a case series. *Hematol Oncol.* 2011;**29**:10-16

Table 1: Consensus statements and recommendations for the general approach to patients with PCNSL including establishment of diagnosis, baseline work-up and response to treatment

Diagnosis

- Cranial MRI with FLAIR and T1 weighted sequences before and after contrast injection is the neuroimaging method of choice for the diagnosis and follow-up of PCNSL. Diffusion, dynamic susceptibility contrast, proton spectroscopy MRI, and FDG-PET can be useful in the differential diagnosis but are not specific (Good Practice Point).
- The diagnosis of PCNSL requires pathological confirmation before treatment (Good Practice Point).
- When PCNSL is suspected, the standard surgical procedure for diagnosis is a stereotactic or navigation guided needle biopsy (Good Practice Point, see section on surgery for discussion).
- Because it may prevent the histopathological diagnosis, it is recommended, if clinically possible, to avoid steroids before biopsy. In case of remission and/or unspecific inflammation in the tissue biopsied in steroid-pretreated patients, rebiopsy is recommended when close and careful follow-up with serial MRI indicates further tumor growth (Good Practice Point).
- PCNSL are diagnosed according to the WHO classification. Immunohistochemistry is required (Good Practice Point, see pathology section in the webappendix).
- Required immunohistochemical markers for the lymphoma cell characterization should include: pan-B cell markers (CD19,CD20,PAX5), BCL6, MUM1/IRF4, CD10 (Good Practice Point).
- PCR analysis of immunoglobuline gene families may contribute to diagnosis in difficult cases, in particular when inflammatory disorders such as multiple sclerosis or corticosteroid-mitigated PCNSL are considered. (Good Practice Point).
- In case of a suspicion of PCNSL, the work-up should include at least an HIV blood test, a lumbar puncture (if not contraindicated) and an ophthalmologic evaluation (with a fundoscopy and a slit lamp examination) in all patients, including those without ocular symptoms (Good Practice Point).
- The identification of lymphoma cells in the CSF or the vitreous may obviate the need for a stereotactic brain biopsy to confirm the diagnosis only in the setting of high clinical and radiological suspicion of PCNSL. As cytologic diagnosis may be difficult, a review by a specialist pathologist is recommended, and in any doubt a brain biopsy is required (Good Practice Point).
- Immunophenotyping by multiparameter flow cytometry of cells collected in the CSF or vitreous and immediately analyzed may add to diagnostic sensitivity.
- if B-cell monoclonality is shown in a sample with atypical/suspicious cells. PCR based analysis of immunoglobulin gene rearrangement in the CSF reportedly may show false positives. Therefore, evidence for the clonality of the lymphocytic cell population considered separately remains insufficient for the diagnosis for PCNSL except in case of high clinically documented suspicion of PCNSL (Good Practice Point).

Staging

- Systemic staging should include: physical examination, CT-scan of the chest, abdomen and pelvis, testicular sonography and bone marrow biopsy. FDG body PET may represent an improved alternative to total body CT-scan and testicular sonography (Good Practice Point).

Prognosis

- Age and performance status have been consistently identified as treatment-independent prognostic factors in PCNSL. Evaluating the individual risk of a PCNSL patient before treatment according to one of the existing prognostic scores is recommended (Good Practice Point).
- Age over 60-65 is used to define the elderly population in PCNSL (Good Practice Point).

Evaluation of response and follow-up

- The International Primary CNS Lymphoma Collaborative Group (IPCG) criteria (2005) combining MRI, eye examination, CSF analysis and steroid dose should be used to evaluate response to treatment (Good Practice Point).
- There is no evidence as yet that brain FDG PET can be used to assess response in PCNSL in the way that it is used for other lymphomas (Good Practice Point).
- Formal prospective neuropsychometric testing is recommended in the follow-up of patients treated in clinical trials on PCNSL (Good Practice Point).

Table 2: Consensus statements and recommendations for treatment of patients with PCNSL

Surgery

- Surgical resection may be considered in patients suffering from a large space occupying lesion with acute symptoms of brain herniation to reduce rapidly intracranial pressure (Good practice point).
- In patients with an unifocal and resectable lesion suspected of PCNSL, no consensus was met in the panel to recommend either surgical resection or biopsy

Chemotherapy

- CHOP-regimens and derivatives are not indicated in PCNSL (Level B).
- Chemotherapy should include MTX at HD ($\geq 3g/m^2$) both to cross the BBB and yield cytotoxic levels in the CSF. It should be delivered in 2-3 hour iv infusions for a minimum of 4-6 injections and at intervals that should not exceed 2-3 weeks (Good Practice Point).
- Combination of HD-MTX with other chemotherapeutic agents improves the response rates with respect to HD-MTX alone (Level B).
- Chemotherapeutic agents to combine with HD MTX should be selected among active drugs known to cross BBB, such as HD cytarabine (Level B).
- HD-MTX-chemotherapy is feasible in elderly patients with adequate performance status and renal function (Level B).
- BBBD followed by IA MTX is an alternative experimental approach appropriated for a selected group of patients that should be undertaken by trained teams only (Level B).
- The value of IT chemotherapy as prophylaxis is unclear. IT chemotherapy (intralumbar or preferably intraventricular through an Ommaya reservoir) can be proposed in case of documented meningeal involvement with insufficient response to iv HD MTX (>3g/ m2) based chemotherapy (Good Practice Point).
- Rituximab combined with a chemotherapy regimen is still an experimental regimen that has its main place in clinical trials (Level C).

Radiotherapy

- WBRT, HD MTX, and *a fortiori* combined treatment expose patients to an increased risk of neurotoxicity (Level A).
- The role of consolidation WBRT following HD-MTX based chemotherapy remains debated. In addition, the optimal dose is not yet defined, but it should be chosen on the base of 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 Gy dose /fraction appears advisable. With such doses, there is no evidence to add a focal boost on the enhancing lesions (Good Practice Point).
- In patients < 60 years who have achieved a CR to induction chemotherapy, the option of immediate WBRT (40 - 45 Gy in 1.8 - 2.0 Gy fractions) or WBRT omission should be discussed with the patient. Reduced dose WBRT consolidation (23.4 - 30 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 > 60 years, the risk of delayed neurotoxicity, after WBRT (doses >30 Gy in 1.8-2.0 Gy fractions) especially if following HDMTX , is unacceptably high and WBRT at this dose 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 PCNSL (Level B).
- HDC/ASCT should be reserved for patients < 60-65 years (Good Practice Point).
- High-dose thiotepa-based conditioning chemotherapy should be preferred over the BEAM regimen (Level C).
- HDC/ASCT as consolidation in first-line treatment remains experimental in PCNSL and should be restricted by selected trained centers (Good Practice Point).

Primary intraocular lymphoma (PIOL)

- PIOL may be treated by either HD-MTX-based chemotherapy (with or without WBRT) or by local therapy (intravitreal chemotherapy or ocular RT) (Good Practice Point).
- Local treatment (intravitreal chemotherapy or ocular RT) is a valid approach for patients with systemic chemotherapy contraindications or for elderly patients with relapsing intraocular disease (Good Practice Point).
- Concurrent intraocular and CNS lymphoma should be treated no differently from PCNSL (Good Practice Point).
- If consolidation WBRT is proposed, it should include both eyes (Good Practice Point).

- Refractory and relapsed IOL should be treated according to the patients' characteristics and prior treatments. Treatments include intravitreal injections of MTX, focal radiotherapy, WBRT, systemic chemotherapy and HDC/ASCT (Good Practice Point).

Salvage treatment

- Patients with relapsed / refractory PCNSL should be enrolled into phase I-II trials (Good Practice Point).
- The choice of the most appropriate salvage treatment should depend upon the patient's age, performance status, comorbidity, site of relapse, prior therapy, and duration of previous response. The expected side effects of the chosen drug must also be considered carefully (Good Practice Point).
- Salvage WBRT may be proposed in radiotherapy-naïve patients; it may be preceded by induction chemotherapy (Good Practice Point)
- HDC/ASCT is a valid therapeutic option in patients aged <60-65 years with chemosensitive relapsing PCNSL (Level B).
- Salvage chemotherapy can be delivered as induction therapy before WBRT or HDC/ASCT, or as exclusive treatment in patients not eligible for these therapies.
- MTX re-challenge should be considered in recurrent PCNSL patients who previously responded to HD MTX (Level C).
- Isolated extra-CNS relapses should be managed with anthracycline-based chemotherapy followed or not by HDC/ASCT (Good Practice Point)

WEBAPPENDIX

This webappendix summarizes evidences used for EANO`s recommendations for the general approach to PCNSL patients with coverage of diagnostic aspects – pathology and genetics, clinical presentation, pathological confirmation, neuropathology of corticosteroid-treated PCNSL, cerebrospinal fluid (CSF) analyses, vitreous analyses, staging,– as well as prognostic factors, response criteria to treatment, treatment related neurotoxicity and treatment of intraocular lymphoma.

Pathology and genetics

PCNSL is a mature B cell lymphoma corresponding to DLBCL of the CNS. Morphologically, haematopoietic tumor cells, mostly resembling centroblasts, are scattered throughout the brain tissue and also exhibit a marked angiotropism with sheets of tumor cells clustering within and around blood vessel wall. Immunohistochemistry is required for the diagnosis. In addition to the expression of pan-B cell markers (CD19, CD20, PAX5), the tumor cells of PCNSL are characterized by a $BCL6^{+}IRF/MUM1+CD10^{-}$ immunophenotype with high proliferative activity (Ki-67 indexes of 70-90%), together with high expression of the MYC and BCL2 proteins.[1-3] With rare exception, Epstein-Barr Virus (EBV) is absent from PCNSL of immunocompetent patients. Ongoing activity of the germinal center program and blocked terminal B cell differentiation together with pathways deregulated by genetic alterations (B cell receptor, toll like receptor, NF-kB pathways) may foster B cell activation and brisk proliferation and be of pathogenetic relevance.[4-9] Analysis of the molecular landscape of PCNSL indicates that aberrant somatic hypermutation which targets several genes (*PIM1, TTF, MYC, KLH14, OSPL10, SUSD2*) may play an important role in the pathogenesis of PCNSL, [9,10] and that alterations in genes of role in CNS development may facilitate DLBCL manifestation in the CNS.[10] Epigenetic studies revealed frequent gene silencing due to CpG island hypermethylation in individual genes including *MGMT, CDKN2A*, and *DAPK*.[11,12] Recurring chromosomal losses affected the 6q, 6p21.32 (*HLA* locus) and 9p21 (*CDKN2A* locus) regions.[5,13] However, to date, no specific molecular genetic signature distinguishes clearly PCNSL from non-CNS DLBCL, suggesting an important role of the microenvironement in explaining the peculiar behaviour of PCNSL. For research, collecting frozen samples and developing a network for PCNSL tumor banks should be encouraged.

Diagnosis

Clinical presentation

Presenting symptoms may include cognitive decline and/or personality changes, focal neurological deficits and increased intracranial pressure. Seizures are less frequent (10%). Ocular symptoms, due to an involvement of retina, choroid or vitreous, are represented by floaters and/or blurred vision; they can be either isolated (10%) or coexist with cerebral symptoms (10-20%). However, up to one-half of patients with PCNSL and ocular involvement have no visual symptoms. Insidious onset and delayed diagnosis of intraocular lymphoma are common.[14] In immunocompetent patients, cranial MRI with contrast enhancement typically shows intense and homogeneously enhancing single lesions (70%) or multiple lesions (30%) with modest surrounding edema, usually located in periventricular areas and/or deep gray matter.[15,16] Although suggestive, all these MRI findings are not specific. Advanced imaging techniques, especially FDG-PET, diffusion tensor imaging, dynamic susceptibility contrast MRI (DSC-MRI) and proton MR spectroscopy can increase the diagnostic accuracy and help in differentiating PCNSL from other brain tumors or non-tumor lesions.[17-26] However, although some signatures are highly suggestive of PCNSL, especially when present together (low regional cerebral blood volume ratios, high percentage of signal-intensity recovery at the end of the first pass of contrast agent relative to baseline, very high lipid resonances), they are not sufficiently specific in practice to replace pathological confirmation.

Pathological confirmation

Diagnosis always needs to be confirmed pathologically, according to the WHO classification in most cases by stereotactic needle biopsy.[1] In classical cases, combined histology and immunohistochemistry yields the diagnosis of PCNSL, i.e. DLBCL of the CNS. In such cases, molecular studies are not required. In equivocal cases PCR testing for clonality may aid the diagnosis.[27,28]

Neuropathology of corticosteroid-treated PCNSL

As the tumor cells of PCNSL are potentially highly sensitive to corticosteroids, they may undergo rapid apoptosis. Transient tumor shrinkage or disappearance of contrast enhancement may occur even after short

exposure to steroids in approximately 40% of PCNSL, coupled with significant neurological improvement.[29] Stereotactic or navigation guided needle biopsy in this setting may be non-diagnostic in up to 50% of cases.[30] In the absence of tumor blasts, resorptive changes with prominent infiltration of macrophages, T cells, reactive astrocytes , and prominent microglial activation may prevail. In some cases, a few enlarged B cells may persist, being suspicious of blast. In such cases, PCR analysis of immunoglobuline genes may demonstrate monoclonality. However, a small number of B cells may pretend monoclonality ("pseudoclonality"). Therefore, unless patients are rapidly deteriorating with suggestive radiological features of PCNSL, it is usually recommended to defer corticosteroids until histologic confirmation has been obtained. Clinicians referring from peripheral hospitals should discuss with the specialist neurosurgical centre before starting corticosteroids. If, nevertheless, corticosteroids have been given with a subsequent objective response, tapering corticosteroids within one or two weeks and delaying biopsy until tumor regrowth would be a reasonable option. Since regrowth occur in most cases within a few weeks after discontinuation corticosteroids, a serial MRI follow-up with one month interval may be recommended at least the first three months. If no significant changes in contrast enhancement or progression are observed, biopsy seems associated with a relatively good probability of yielding a diagnosis despite steroid pre-treatment.[31]

CSF analysis

The identification of lymphoma cells in the CSF or in a vitreous biopsy, when possible, may obviate the need for a brain biopsy for the diagnostic confirmation, only in the setting of high clinical and radiological suspicion of PCNSL. Frequently, CSF is characterized by elevated protein levels in 75% and mild pleiocytosis in 50% of patients. However, lymphoma cells are detected in only 10-30% in the CSF.[32,33] Cellular immunophenotyping by flow cytometry in the CSF and PCR analysis of immunoglobulin heavy and light chain genes may help to distinguish malignant cells from reactive lymphocytes by identifying clonal B-cell populations even when cytological examination is negative.[34,35] However, low cell numbers in the CSF sample are frequently found and may make flow cytometric analysis difficult. A relatively high ratio of PCR false negatives has been reported in PCNSL.[33,36] Different CSF molecular genetic markers and proteins including microRNA (miR-21, miR-19b, and miR-92),[37] soluble CD19,[38] antithrombin III,[39] free immunoglobulin light chains,[40] and interleukin-10 and CXCL13,[41] are potentially useful diagnostic biomarkers for PCNSL but require further validation before being used in routine practice. As cytologic diagnosis may be difficult, in any doubt or inconsistencies with the patient clinical setting, a pathological confirmation by a brain biopsy is recommended.

Vitreous analysis

Ophthalmologic evaluation includes fundoscopy and slit lamp examination. Fluorescein angiography may be useful for lymphomatous involvement of the retina.[14] Ophthalmologic involvement has to be confirmed by vitreous biopsy when eyes are the unique site of disease. Positive cytology is obtained in 70% of cases in trained pathology department. As for CSF, immunophenotyping and detection of IgH or T-cell receptor rearrangements by PCR analysis indicating monoclonality are helpful tools for diagnosis.[42,43] High levels of interleukin 10 (IL10) and/or high IL10 / IL6 ratio in ocular fluids are strongly suggestive of B-cell lymphomatous uveitis,[44] but are not diagnostic.

Staging

The aims of staging are both to specify the extent of the lymphoma within the CNS and to exclude the presence of the disease elsewhere. If not contraindicated and already performed at the diagnostic work-up, all patients should have a lumbar puncture for CSF cytology. Systemic involvement is present in up to 12% of the cases.[45,46] Since identification of a systemic site of the lymphoma has important implications for the treatment strategy, an international workshop to standardize baseline evaluation recommended performing at least a CT-scan of the chest, abdomen and pelvis, a bone marrow biopsy, a testicular ultrasound in elderly males.[47] FDG body PET, which is more sensitive than the body CT-scan,[48] is not yet an established routine diagnostic investigation, but is used in some European countries as an integral part of diagnostic work-up.

Prognostic factors

Age and performance status have been consistently recognized as the most important therapy-independent prognostic factors.[49-53] Based on retrospective cohorts of PCNSL, other variables including serum lactate dehydrogenase (LDH) levels, involvement of deep brain structures,[53-55] CSF protein levels,[50,53] and extent of lesions within the CNS (multifocal versus unifocal),[52] have been correlated with outcome, and some of them are integrated with age and performance status in different prognostic scoring systems. Hence, three clinically meaningful prognostic scores are available for PCNSL: the IELSG score,[53] the MSKCC score,[51] and the Nottingham-Barcelona score.[52] All of them distinguished 3 different risk groups. Using such scoring systems is useful to compare studies in order to avoid as much as possible selection biases. Since then, other prognostic

factors have been correlated with unfavorable outcome and need to be validated in independent series: elevated FDG uptake on PET,[56] chromosome 6q deletion or *CDKN2A* homozygous deletion in the tumor DNA,[5,57] and delayed response to initial chemotherapy, as compared to early response.[58] Several variables have yielded opposite results in retrospective studies, such as apparent diffusion coefficient (ADC) value derived from diffusion-weighted imaging,[59-61]BCL-6 expression analysis,[62-66] and MTX exposure reflected by MTX area under the curve (AUC).[67-70]

Response criteria

In 2005 the International Primary CNS Lymphoma Collaborative Group (IPCG) published a consensus opinion to standardize response criteria and outcome measures in immunocompetent patients with PCNSL.[47] These response criteria define CR as complete disappearance of contrast enhancement on MRI, no evidence of ocular lymphoma, negative CSF cytology and discontinuation of corticosteroid use for at least 2 weeks prior to the evaluation of response. Since corticosteroids may mask presence of residual disease its discontinuation is included as an essential requirement. The IPCG also delineated which findings are compatible with unconfirmed CR (CRu). It is important to sort out CRu from PR because the latter means failure of primary treatment. According to the IPCG outline CRu includes those cases who fulfill the criteria for CR with the following limitations: at time of evaluation the patient is still on any dose of corticosteroids, MRI continues to show small but persistent enhancing abnormalities related to biopsy/surgical site or to focal hemorrhage, and the follow-up ophthalmologic examination shows persistent minor abnormality which is unlikely to represent ocular lymphoma. PR is defined as 50% decrease in enhancing tumor or residual disease on eye examinations, or persistent or suspicious CSF cytology. Progressive disease (PD) is recognized as 25% increase in the enhancing lesion or appearance of any new site of disease in the CNS or as systemic disease, recurrent or new ocular disease, or recurrent or positive CSF cytology. Of note, these definitions do not take into account the non-enhancing lesion best visualized on T2-Flair MRI, whose differential diagnosis may be challenging since it could be treatment-related white matter changes (including leukoencephalopathy) but also correspond to infiltrative PD.[71] There no evidence as yet that brain FDG PET can be used to assess response in PCNSL in the way that it is used for other lymphomas.

Delayed neurotoxicity

Delayed treatment-related neurotoxicity has been systematically evaluated in few studies (Class II and III). However, there is a general perception and agreement, that the combination of HD MTX and WBRT is associated with disabling neurotoxicity with an incidence of 25% to 35% and related mortality of 30%.[50,72] This deleterious treatment complication typically occurs several months to years after successful treatment. Neuropsychological examination may confirm impaired psychomotor speed, executive function, attention and memory.[73] Affected patients show cortical/subcortical atrophy and leukoencephalopathy,[73-75] which may leave them demented, ataxic and incontinent. Median survival after onset of clinically-evident neurotoxicity is less than 1-2 years.[50,72,75] Autopsy findings include myelin and axonal loss, gliosis, spongiosis, thinning of white matter, small and large vessel disease, and necrosis.[75,76] Of note, imaging abnormalities may not always correlate with the neurologic impairment severity over time. In a retrospective mono-institutional series analysis of 183 patients, only the administration of WBRT was identified as an independent risk factor for the development of late neurotoxicity: in this series, 2% treated with chemotherapy alone developed clinically-evident neurotoxicity, while 33% treated with combination chemo-/radiotherapy were affected. The cumulative incidence of neurotoxicity for the whole group was 5% at 2 years and 24% at 5 years, with a substantially higher risk in patients ≥ 60 years (Class IIIb).[75] They are related to clinically and radiologically overt neurotoxicity. The prevalence of treatment-related "subtle" cognitive dysfunction amongst patients treated for PCNSL is probably largely underestimated as formal psychometric evaluationshave not been routinely performed in most prospective studies. Small case series identified WBRT, and not chemotherapy, as the primary cause of neurotoxicity in PCNSL.[76,77] These results have been confirmed by 3 long-term evaluations (Class IIIb). [78-80] In the most recent analysis of 80 long-term survivors of PCNSL, free of tumor and having completed treatment with different regimens at least two years prior to evaluation, those who had received WBRT showed significantly lower mean scores in attention and executive function, motor skills, and neuropsychological composite score, associated with poorer quality of life measures (Class IIIb).[80] Moreover, on brain imaging, mean areas of total T2 abnormalities in the WBRT group were more than twice the mean of any other non-WBRT group. These results caution against the routine administration of WBRT as part of upfront treatment and call for the implementation of formal neuropsychometric testing in clinical trials on PCNSL.[73]

Intraocular lymphoma

Intraocular infiltration can be the exclusive site of disease at presentation, the so-called primary intra-ocular lymphoma (PIOL), or as a part of PCNSL with concomitant brain or meningeal disease. The optimal treatment for intraocular lymphoma is not known. Data on therapy and outcome are scarce and limited to retrospective case reports or mostly small series with heterogeneous patient populations and treatments. As many as 90 % of patients with PIOL patients consequently develop brain involvement over the course of the disease and dissemination to the brain is the main cause of death.[14,81] The median survival of isolated PIOL is approximately 60 months.[81,82] Treatment may be focal, including ocular RT (historically, total dose of 35-40 Gy, 2 Gy per fraction using opposed lateral beams to include both globes) (Class IV) and intravitreal chemotherapy. [83-86] Uncontrolled series have reported clinical remission with repeated intravitreal MTX and more recently after rituximab injections (Class IV).[85,86] Treatment may be also extensive, including systemic chemotherapy and WBRT. Intraocular responses have been reported with HD MTX,[87] HD cytarabine,[88,89] ifosfamide, trofosfamide used as single agent,[90] with MTX-based polychemotherapy and after HDC/ASCT (Class IV).[91] A large retrospective multicenter study did not show any difference in PIOL between focal and extensive therapy in terms of disease control and survival (Class IIIb).[81] Unfortunately, this and other studies failed to provide reliable predictors of brain dissemination in PIOL patients; thus, some experts recommend local therapy for disease confined to the eyes, but others consider that initial treatment of PIOL should not differ from that of PCNSL i.e. high-dose MTX-based polychemotherapy followed, or not, by WBRT in order to eradicate possible concomitant microscopic disease in the brain and in the CSF responsible for relapse. In this case, local treatments would remain options for refractory or recurrent disease confined to the eyes. The management decision should take into account the individual risk of treatment toxicities (including those related to ocular treatment) and local expertise.[14,92] When intraocular lymphoma is concurrent with brain lesions, it has not been identified as an independent prognostic factor and the prognosis is similar to that of the PCNSL without intraocular disease (Class IIIb).[93] Accordingly, patients with concomitant intraocular and cerebral disease should be treated no differently from PCNSL**.** The value of additional local ocular treatment (i.e. intravitreal chemotherapy or ocular radiotherapy if WBRT has not been delivered) to systemic chemotherapy remains matter of debate, with conflicting results in two retrospective studies (Class IIIb). [93,94]

References

1. Kluin PM, Deckert M, Ferry JA. Primary diffuse large B-cell lymphoma of the CNS. In: Swerdlow SH, Campo E, Harris NL, editors. World Health Organisation Classification of Tumours Pathology and Genetics of Tumours of the Haematopoietic and Lymphoid Tissues. Lyon: IARC Press, 2008; 240–41.
2. Camilleri-Broet S, Criniere E, Broet P, et al. A uniform activated Bcell- like immunophenotype might explain the poor prognosis of primary central nervous system lymphomas: analysis of 83 cases. *Blood* 2006; **107**: 190–96.
3. Brunn A, Nagel I, Montesinos-Rongen M et al. Frequent triple-hit expression of *MYC, BCL2*, and *BCL6* in primary lymphoma of the central nervous system and absence of a favorable MYC(low)BCL2 (low) subgroup may underlie the inferior prognosis as compared to systemic diffuse large B cell lymphomas. *Acta Neuropathol* 2013; **126**:603-05
4. Deckert M, Montesinos-Rongen M, Brunn A, et al. Systems biology of primary CNS lymphoma: from genetic aberrations to modeling in mice. *Acta Neuropathol*. 2014 ;**127**:175-88
5. Gonzalez-Aguilar A, Idbaih A, Boisselier B, et al. Recurrent mutations of *MYD88* and *TBL1XR1* in primary central nervous system lymphomas. *Clin. Cancer Res*. 2012;**18**:5203–5211
6. Montesinos-Rongen M, Godlewska E, Brunn A, et al. Activating L265P mutations of the *MYD88* gene are common in primary central nervous system lymphoma. *Acta Neuropathol* 2011;**122**:791–92
7. Montesinos-Rongen M, Schäfer E, Siebert R, et al.. Genes regulating the B cell receptor pathway are recurrently mutated in primary central nervous system lymphoma. *Acta Neuropathol* 2012;**124**:905–06.
8. Montesinos-Rongen M, Schmitz R, Brunn A, et al. Mutations of *CARD11* but not *TNFAIP3* may activate the NF-kappaB pathway in primary CNS lymphoma. *Acta Neuropathol*. 2010;**120**:529–35.
9. Bruno A, Boisselier B, Labreche K, et al. Mutational analysis of primary central nervous system lymphoma. *Oncotarget* 2014;**5**:5065-75
10. Vater I, Montesinos-Rongen M, Schlesner M et al. The mutational pattern of primary lymphoma of the central nervous system determined by whole-exome sequencing. *Leukemia* 2014.doi: 10.1038/leu.2014.264
11. Chu LC, Eberhart CG, Grossman SA, et al. Epigenetic silencing of multiple genes in primary CNS lymphoma. *Int J Cancer* 2006; **119**: 2487–91.

12. Ferreri AJ, Dell'Oro S, Capello D, et al. Aberrant methylation in the promoter region of the reduced folate carrier gene is a potential mechanism of resistance to methotrexate in primary central nervous system lymphomas. *Br J Haematol* 2004; **126**: 657–64.

13. Braggio E, McPhail ER, Macon W, et al. Primary central nervous system lymphomas: a validation study of array-based comparative genomic hybridization in formalin-fixed paraffin-embedded tumor specimens. *Cancer Res*. 2011;**17**:4245–53

14. Chan CC, Rubenstein JL, Coupland SE, et al. Primary vitreoretinal lymphoma: a report from an International Primary Central Nervous System Lymphoma Collaborative Group symposium. *Oncologist*. 2011;**16**:1589-99

15. Bühring U, Herrlinger U, Krings T et al. MRI features of primary central nervous system lymphomas at presentation. *Neurology* 2001;**57**:393–96

16. Kuker W, Nagele T, Korfel A, et al: Primary central nervous system lymphomas (PCNSL): MRI features at presentation in 100 patients. *J Neurooncol* 2005; **72**:169-77

17. Kawai N, Okubo S, Miyake K, et al. Use of PET in the diagnosis of primary CNS lymphoma in patients with atypical MR findings. *Ann Nucl Med*. 2010; **24**:335-43

18. Yamashita K, Yoshiura T, Hiwatashi A, et al. Differentiating primary CNS lymphoma from glioblastoma multiforme: assessment using arterial spin labeling,diffusion-weighted imaging, and ^{1}□F-fluorodeoxyglucose positron emission tomography. *Neuroradiology*. 2013; **55**:135-43

19. Toh CH, Castillo M, Wong AM,et al.. Primary cerebral lymphoma and glioblastoma multiforme: differences in diffusion characteristics evaluated with diffusion tensor imaging. *AJNR*. 2008;**29**:471-75

20. Mangla R, Kolar B, Zhu T, et al. Percentage signal recovery derived from MR dynamic susceptibility contrast imaging is useful to differentiate common enhancing malignant lesions of the brain. *AJNR* 2011;**32**:1004-10

21. Radbruch A, Wiestler B, Kramp L,et al. Differentiation of glioblastoma and primary CNS lymphomas using susceptibility weighted imaging. *Eur J Radiol*. 2013;**82**:552-56.

22. Blasel S, Jurcoane A, Bähr O, Weise L, et al. MR perfusion in and around the contrast-enhancement of primary CNS lymphomas. *J Neurooncol*. 2013;**114**:127-34.

23. Toh CH, Wei KC, Chang CN, et al. Differentiation of primary central nervous system lymphomas and glioblastomas: comparisons of diagnostic performance of dynamic susceptibility contrast-enhanced perfusion MR imaging without and with contrast-leakage correction. *AJNR* 2013 ;**34**:1145-49

24. Kickingereder P, Sahm F, Wiestler B, et al. Evaluation of Microvascular Permeability with Dynamic Contrast-Enhanced MRI for the Differentiation of Primary CNS Lymphoma and Glioblastoma: Radiologic-Pathologic Correlation. *AJNR* 2014;**35**:1503-08

25. Chawla S, Zhang Y, Wang S, et al. Proton magnetic resonance spectroscopy in differentiating glioblastomas from primary cerebral lymphomas and brain metastases. *J Comput Assist Tomogr* 2010;**34**:836-41

26. Lu SS, Kim SJ, Kim HS, et al. Utility of proton MR spectroscopy for differentiating typical and atypical primary central nervous system lymphomas from tumefactive demyelinating lesions. *AJNR* 2014; **35**:270-77

27. Shaw A, Iyer V, Rooney N, et al. Diagnosis of primary cerebral lymphomas: possible value of PCR testing in equivocal cases requiring rebiopsy. *Br J Neurosurg* 2014: **28**:214-19

28. Deckert M, Brunn A, Montesinos-Rongen M et al. Primary lymphoma of the central nervous system--a diagnostic challenge. *Hematol Oncol* 2014;**32**:57-67

29. Pirotte B, Levivier M, Goldman et al. Glucocorticoid-induced long-term remission in primary cerebral lymphoma: case report and review of the literature. *J Neurooncol*. 1997;**32**:63-69

30. Brück W, Brunn A, Klapper W et al. Differential diagnosis of lymphoid infiltrates in the central nervous system: experience of the Network Lymphomas and Lymphomatoid Lesions in the nervous system. *Pathologe* 2013;**34**:186-97

31. Porter AB, Giannini C, Kaufmann T, et al. Primary central nervous system lymphoma can be histologically diagnosed after previous corticosteroid use: a pilot study to determine whether corticosteroids prevent the diagnosis of primary central nervous system lymphoma. *Ann Neurol* 2008;**63**:662-67

32. Balmaceda C, Gaynor JJ, Sun M, et al. Leptomeningeal tumour in primary central nervous system lymphoma: Recognition, significance, and implications. *Ann Neurol* 1995;**38**:202-09.

33. Korfel A, Weller M, Martus P, et al. Prognostic impact of meningeal dissemination in primary CNS lymphoma (PCNSL): experience from the G-PCNSL-SG1 trial. *Ann Oncol* 2013;**23**:2374-80

34. Hegde U, Filie A, Little RF, et al. High incidence of occult leptomeningeal disease detected by flow cytometry in newly diagnosed aggressive B-cell lymphomas at risk for central nervous system involvement: the role of flow cytometry versus cytology. *Blood* 2005; **105**:496-502

35. Schroers R, Baraniskin A, Heute C, et al.. Diagnosis of leptomeningeal disease in diffuse large B-cell lymphomas of the central nervous system by flow cytometry and cytopathology. *Eur J Haematol.* 2010;**85**:520-28

36. Fischer, L., Martus, P., Weller, M., et al. Meningeal dissemination in primary CNS lymphoma: prospective evaluation of 282 patients. *Neurology* 2008, **71**,1102–08.

37. Baraniskin A, Kuhnhenn J, Schlegel U, et al. Identification of microRNAs in the cerebrospinal fluid as marker for primary diffuse large B-cell lymphoma of the central nervous system. *Blood* 2011;**117**:3140-46.

38. Muñiz C, Martín-Martín L, López A, et al. Spanish Group for the Study of Central Nervous System Disease in Non-Hodgkin Lymphoma. Contribution of cerebrospinal fluid sCD19 levels to the detection of CNS lymphoma and its impact on disease outcome. *Blood* 2014; **123**:1864-69

39. Roy S, Josephson SA, Fridlyand, J, et al. Protein biomarker identification in the CSF of patients with CNS lymphoma. *J Clin Oncol* 2008, **26**,:96–105.

40. Schroers, R., Baraniskin, A., Heute, C, et al. Detection of free immunoglobulin light chains in cerebrospinal fluids of patients with central nervous system lymphomas. *Eur J Haematol* 2010; **85**: 236–42.

41. Rubenstein JL, Wong VS, Kadoch C, et al. CXCL13 plus interleukin 10 is highly specific for the diagnosis of CNS lymphoma. *Blood.* 2013 6;**121**:4740-48.

42. Shen DF, Zhuang Z, LeHoang P et al. Utility of microdissection and polymerase chain reaction for the detection of immunoglobulin gene rearrangement and translocation in primary intraocular lymphoma. *Ophthalmology* 1998;**105**:1664 –69.

43. Misotten T, Tielemans D, Bromberg JE et al. Multicolor flowcytometric immunophenotyping is a valuable tool for detection of intraocular lymphoma. *Ophtalmology* 2013;**120**:991-96

44. Cassoux N, Giron A, Bodaghi B et al. IL-10 measurement in aqueous humor for screening patients with suspicion of primary intraocular lymphoma. *Invest Ophthalmol Vis Sci* 2007;**48**:3253–59

45. O'Neill BP, Dinapoli RP, Kurtin PJ, et al. Occult systemic non-Hodgkin's lymphoma in patients initially diagnosed as primary central nervous system lymphoma: How much staging is enough? *J Neurooncol* 1995;**25**:67-71.

46. Ferreri AJ, Reni M, Zoldan MC, et al. Importance of complete staging in non-Hodgkin's lymphoma presenting as a cerebral mass lesion. *Cancer* 1996;**77**:827-33.

47. Abrey LE, Batchelor TT, Ferreri AJ, et al. Report of an international workshop to standardize baseline evaluation and response criteria for primary CNS lymphoma. *J Clin Oncol*. 2005;**23**:5034-43.

48. Mohile NA, Deangelis LM, Abrey LE. Utility of brain FDG-PET in primary CNS lymphoma. *Clin Adv Hematol Oncol.* 2008; **6** :818-20

49. Corry J, et al. Primary central nervous system lymphoma: age and performance status are more important than treatment modality. *Int J Radiat Oncol Biol Phys*. 1998;**41**:615-20.

50. Blay JY, Conroy T, Chevreau C, et al et al. High-dose methotrexate for the treatment of primary cerebral lymphomas: analysis of survival and late neurologic toxicity in a retrospective series. *J Clin Oncol* 1998; **16**:864-71.

51. Abrey LE, Ben-Porat L, Panageas KS, et al. Primary central nervous system lymphoma: the Memorial Sloan-Kettering Cancer Center prognostic model. *J Clin Oncol* 2006 ;**24**:5711-15.

52. Bessell EM, Graus F, Lopez-Guillermo A et al. Primary non-Hodgkin's lymphoma of the CNS treated with CHOD/BVAM or BVAM chemotherapy before radiotherapy: Long-term survival and prognostic factors. *Int J Radiat Oncol Biol Phys 2004*;**59**:501–08.

53. Ferreri AJ, Blay JY, Reni M, et al. Prognostic scoring system for primary CNS lymphomas: the International Extranodal Lymphoma Study Group experience. *J Clin Oncol*.2003 ;**21**:266-72

54. Ghesquières H, Drouet Y, Sunyach MP, et al. Evidence of time-dependent prognostic factors predicting early death but not long-term outcome in primary CNS lymphoma: a study of 91 patients. *Hematol Oncol* 2013;**31**:317-24

55. Iwadate Y, Suganami A, Ikegami S, et al. Non-deep-seated primary CNS lymphoma: therapeutic responses and a molecular signature. *J Neurooncol.*2014 ; **117**:261-68

56. Kasenda B, Haug V, Schorb E, et al. 18F-FDG PET is an independent outcome predictor in primary central nervous system lymphoma. *J Nucl Med* 2013;**54**:184-91.

57. Cady FM, O'Neill BP, Law ME, et al. Del(6)(q22) and BCL6 rearrangements in primary CNS lymphoma are indicators of an aggressive clinical course. *J Clin Oncol* 2008;**26**:4814-19.

58. Pels H, Juergens A, Schirgens I, et al. Early complete response during chemotherapy predicts favorable outcome in patients with primary CNS lymphoma. *Neuro Oncol* 2010;**12**:720-24.

59. Barajas RF Jr., Rubenstein JL, Chang JS, et al. Diffusion weighted MR imaging derived apparent diffusion coefficient is predictive of clinical outcome in primary central nervous system lymphoma. *AJNR* 2010;**31**:60–66.

60. Wieduwilt M, Valles F, Issa S et al. Immunochemotherapy with intensive consolidation for primary CNS lymphoma: a pilot study and prognostic assessment by diffusion-weighted MRI. *Clin Cancer Res* 2012; **18**: 1146-55

61. Morris PG, Correa DD, Yahalom J, et al. Rituximab, methotrexate, procarbazine, and vincristine followed by consolidation reduced-dose whole-brain radiotherapy and cytarabine in newly diagnosed primary CNS lymphoma: final results and long-term outcome. *J Clin Oncol*. 2013;**31**:3971-79

62. Braaten KM, Betensky RA, de Leval L, et al. BCL-6 expression predicts improved survival in patients with primary central nervous system lymphoma. *Clin Cancer Res* 2003; **9**: 1063–69.

63. Levy O, Deangelis LM, Filippa DA, et al. Bcl-6 predicts improved prognosis in primary central nervous system lymphoma. *Cancer* 2008; **112**: 151–56.

64. Lossos IS, Jones CD, Warnke R, et al. Expression of a single gene, BCL-6, strongly predicts survival in patients with diffuse large B-cell lymphoma. *Blood* 2001; **98**: 945–51.

65. Preusser M, Woehrer A, Koperek O, et al. Primary central nervous system lymphoma: a clinicopathological study of 75 cases. Pathology 2010;**42**:547-52.

66. Rubenstein JL, Hsi ED, Johnson JL, Jung SH, Nakashima MO, Grant B, et al. Intensive chemotherapy and immunotherapy in patients with newly diagnosed primary CNS lymphoma: CALGB 50202 (Alliance 50202). *J Clin Oncol* 2013 ;**31**:3061-68

67. Ferreri AJ, Guerra E, Regazzi M, et al. Area under the curve ofmethotrexate and creatinine clearance are outcome-determining factors in primary CNS lymphomas. *Br J Cancer* 2004;**90**: 353–58.

68. Joerger M, Huitema AD, Krahenbuhl S, et al. Methotrexate area under the curve is an important outcome predictor in patients with primary CNS lymphoma: pharmacokinetic pharmacodynamic analysis from the IELSG no. 20 trial. *Br J Cancer* 2010;**102**:673–77.

69. Blasco H, Senecal D, Le Gouge A, et al. Influence of methotrexate exposure on outcome in patients treated with MBVP chemotherapy for primary central nervous system lymphoma. *Br J Clin Pharmacol* 2010;**70**:367–75.

70. Morris PG, Abrey LE, Reiner AS, et al. Methotrexate area under the curve as a prognostic factor in primary CNS lymphoma treated with immunochemoradiotherapy. *Leuk Lymphoma*, 2011;**52**:1891-97

71. Fischer L, Koch A, Schlegel U, et al. Non-enhancing relapse of a primary CNS lymphoma with multiple diffusion-restricted lesions. *J Neurooncol* 2011;**102**:163-66.

72. Abrey LE, DeAngelis LM, Yahalom J. Long-term survival in primary CNS lymphoma. *J Clin Oncol* 1998; **16**:859-63

73. Correa DD, Maron L, Harder H, et al. Cognitive functions in primary central nervous system lymphoma: literature review and assessment guidelines. *Ann Oncol* 2007; **18**:1145-51

74. Wassenberg MW, Bromberg JE, Witkamp TD et al. White matter lesions and encephalopathy in patients treated for primary central nervous system lymphoma. *J Neurooncol* 2001; **52**:73-80

75. Omuro AM, Ben-Porat LS, Panageas KS *et al.* Delayed neurotoxicity in primary central nervous system lymphoma. *Arch Neurol* 2005; **62**:1595–600

76. Harder H, Holtel H, Bromberg JEC et al. Cognitive status and quality of life after treatment for primary CNS lymphoma. *Neurology* 2004;**62**:544-47

77. Correa DD, DeAngelis LM, Shi W. et al. Cognitive functions in survivors of primary central nervous system lymphoma. *Neurology* 2004;**62**:548-55

78. Jürgens A, Pels H, Rogowski S, et al. Long-term survival with favorable cognitive outcome after chemotherapy in primary central nervous system lymphoma. *Ann Neurol* 2010;**67**:182-89.

79. Correa DD, Shi W, Abrey LE, DeAngelis LM, et al. Cognitive functions in primary CNS lymphoma after single or combined modality regimens. *Neuro Oncol* 2012; **14**:101-08.

80. Doolittle ND, Korfel A, Lubow MA, et al. Long-term cognitive function, neuroimaging, and quality of life in primary CNS lymphoma. *Neurology* 2013; **81**:84-92

81. Grimm SA, Pulido JS, Jahnke K, Schiff D, et al. Primary intraocular lymphoma: an International Primary Central Nervous System Lymphoma Collaborative Group Report. *Ann Oncol* 2007 ;**18**:1851-55.

82. Hormigo A, Abrey L, Heinemann MH, DeAngelis LM. Ocular presentation of primarycentral nervous system lymphoma: diagnosis and treatment. *Br J Haematol* 2004;**126**:202-08

83. Margolis L, Fraser R, Lichter A, et al.. The role of radiation therapy in the management of ocular reticulum cell sarcoma. *Cancer.* 1980;**45**:688-92

84. Berenbom A, Davila RM, Lin HS, et al. Treatment outcomes for primary intraocular lymphoma: implications for external beam radiotherapy. *Eye* 2007;**21**:1198-201

85. Frenkel S, Hendler K, Siegal T, et al. Intravitreal methotrexate for treating vitreoretinal lymphoma: 10 years of experience. *Br J Ophthalmol* 2008;**92**:383-88

86. Hashida N, Ohguro N, Nishida K. Efficacy and Complications of Intravitreal Rituximab Injection for Treating Primary Vitreoretinal Lymphoma.*Transl Vis Sci Technol* 2012; **1**:1-11

87. Batchelor TT, Kolak G, Ciordia R, et al. High-dose methotrexate for intraocular lymphoma. *Clin Cancer Res* 2003;**9**:711-15.
88. Siegel MJ, Dalton J, Friedman AH, et al. Ten-year experience with primary ocular 'reticulum cell sarcoma' (large cell non-Hodgkin's lymphoma*). Br J Ophthalmol* 1989;**73**:342-46.
89. Strauchen JA, Dalton J, Friedman AH. Chemotherapy in the management of intraocular lymphoma. *Cancer* 1989;**63**:1918-21
90. Jahnke K, Thiel E, Bechrakis NE, Willerding G, et al. Ifosfamide or trofosfamide in patients with intraocular lymphoma. *J Neurooncol* 2009 ;**93**:213-17
91. Soussain C, Suzan F, Hoang-Xuan K, et al. Results of intensive chemotherapy followed by haematopoietic stem cell rescue in 22 patients with refractory or recurrent primary CNS lymphoma or intraocular lymphoma. *J Clin Oncol* 2001; **19**:742-49.
92. Rajagopal R, Harbour JW. Diagnostic testing and treatment choices in primary vitreoretinal lymphoma. *Retina* 2011;**31**:435–40
93. Grimm SA, McCannel CA, Omuro AM, et al. Primary CNS lymphoma with intraocular involvement: International PCNSL Collaborative Group Report. *Neurology* 2008 ;**71**:1355-60
94. Ferreri AJ, Blay JY, Reni M, et al. International Extranodal Lymphoma Study Group (IELSG). Relevance of intraocular involvement in the management of primary central nervous system lymphomas. *Ann Oncol* 2002;**13**:531-38