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Guideline SCT-8

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Management of Primary Central Nervous System Diffuse Large B-Cell Lymphoma

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An assessment conducted in February 2024 deferred the review of Guideline SCT-8. Minor modifications were made to recommendations 5, 6, and 7 to reflect current practice. The document remains current until it is assessed again next year. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol)

Guideline SCT-8 is comprised of 5 sections. You can access the summary and full report here:
https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/49406

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Management of Primary Central Nervous System Diffuse Large B-Cell Lymphoma

Section 1: Recommendations

This section is a quick reference guide and provides the guideline recommendations only. For key evidence associated with each recommendation, see Section 2.

GUIDELINE OBJECTIVES

To determine the most effective therapy for primary central nervous system diffuse large B-cell lymphoma (PCNS DLBCL) including primary intra-ocular lymphoma (PIOL).

TARGET POPULATION

Adult patients (≥18 years of age) with PCNS DLBCL including PIOL.

INTENDED USERS

This guideline is intended for clinicians involved in the management of PCNS lymphoma in Ontario, and for policy makers and program planners involved in stem cell transplant and systemic and radiation therapy.

RECOMMENDATIONS

Recommendation 1
Combination chemotherapy with high-dose methotrexate (HD-MTX), cytarabine (AraC), thiotepa, and rituximab (MATRix regimen) is recommended as first-line treatment of PCNS DLBCL for patients younger than 70 years with adequate renal function, and Eastern Cooperative Oncology Group (ECOG) performance status ≤3. Cyclophosphamide, doxorubicin, vincristine, prednisolone (CHOP)-like chemotherapy regimens are not recommended for treatment of PCNS DLBCL.

Qualifying Statements for Recommendation 1

- There is insufficient evidence to support or refute alternative multi-agent chemotherapy regimens that combine HD-MTX, rituximab, and additional drugs that cross the blood-brain barrier such as procarbazine or temozolomide. These regimens have not been evaluated in prospective randomized controlled trials published to date; thus, there remains uncertainty in the clinical benefit/risk compared with standard chemotherapy regimens including the MATRix regimen.
- CHOP-like chemotherapy regimens are not recommended for treatment of PCNS lymphoma because the chemotherapeutic agents demonstrate poor penetration across the blood-brain barrier.

Recommendation 2
Treatment with an HD-MTX-based regimen plus rituximab chemotherapy is a reasonable treatment option for elderly patients (>70 years) that have adequate renal function and ECOG performance status ≤3.

Qualifying Statements for Recommendation 2

- Prospective, randomized trials evaluating elderly patients with PCNS lymphoma are lacking; thus, the optimal chemotherapy regimen in this population is not clear. Single-agent HD-MTX and HD-MTX-based combination regimens, including the MATRix regimen, may be reasonable options particularly in fit patients with an ECOG performance status ≤3.
- Very elderly patients (age >80 years) and/or those with a poor performance status (ECOG 4) have a particularly poor prognosis and the decision to initiate treatment with chemotherapy must take a patient-centred approach that carefully weighs the risks versus benefits of chemotherapy.
- Elderly patients with PCNS lymphoma and reduced renal function are at increased risk for MTX-related toxicity. The use of MTX in patients with creatinine clearance lower than 50 ml/min has not been adequately evaluated in prospective studies. Physicians should consider the issue of renal function and the potential for increased HD-MTX toxicity in elderly patients.

Recommendation 3
Intrathecal chemotherapy does not need to be routinely added to first-line HD-MTX-based regimens.

Qualifying Statements for Recommendation 3

- There are insufficient data to support routine incorporation of intrathecal chemotherapy to first-line HD-MTX-based regimens. The members of the task force of the 2015 European Association for Neuro-Oncology, in their deliberation, as a good practice point, acknowledged that intrathecal chemotherapy may be considered in selected circumstances such as patients with leptomeningeal disease and an incomplete response to HD-MTX-based chemotherapy. The members of the Working Group agreed with this comment and support the consideration of intrathecal chemotherapy in selected cases. However, while there are clinical circunstances where intrathecal chemotherapy might be considered, the benefits and risks of its routine administration in all patients receiving aggressive systemic MTX-based regimens is unclear, and thus it is not recommended outside of clinical trials.

Recommendation 4
Blood-brain barrier disruption followed by intra-arterial (IA) MTX is not recommended for the treatment of PCNS DLBCL.

Qualifying Statements for Recommendation 4

- There is insufficient evidence to recommend blood-brain barrier disruption followed by IA MTX therapy in the treatment of patients with PCNS DLBCL. Blood-brain barrier disruption followed by IA MTX is still an experimental approach and, therefore, it is not recommended by the members of the Working Group outside clinical trials.

Recommendation 5 ***(Modified in 2020 – See Appendix 10)***

Whole brain radiotherapy (WBRT) or comfort-based palliative care are reasonable treatment options for patients who refuse aggressive chemotherapy or who are considered ineligible for HD-MTX-based, or alternative, chemotherapy regimens.

Qualifying Statements for Recommendation 5

- The clinical benefit of WBRT in this poor-risk population, compared with supportive care, has not been confirmed in prospective comparative clinical trials. WBRT as a single treatment modality is associated with a response rate of approximately 50% and median survival of approximately one year that is offset by a risk of neurotoxicity.

Recommendation 6 ***(Modified in 2020 – See Appendix 10)***

WBRT should not be routinely administered in patients who have achieved a complete remission (CR) following first-line HD-MTX-based chemotherapy.

Qualifying Statements for Recommendation 6

- For transplant eligible patients, autologous stem cell transplantation (ASCT) is a reasonable alternative consolidation treatment and patients should also be informed of this treatment option (see Recommendation 7).
- In patients who achieve a CR following first-line chemotherapy, consolidation with WBRT has not been clearly shown to improve overall survival when compared with no radiotherapy. The addition of WBRT is associated with an increased risk of neurotoxicity that may have a significant impact on quality of life. The risk of neurotoxicity is particularly high in patients older than 60 years of age. The role of WBRT in patients who have achieved a CR following first-line chemotherapy remains controversial; a patient-centred, multi-disciplinary approach is recommended to inform patients of the trade-off in risks and benefits associated with WBRT consolidation in this setting.
- WBRT is a reasonable consolidation option for patients in partial remission following first-line chemotherapy who are not eligible for ASCT.
- Reduced-dose WBRT consolidation (23.4 to 30.0 Gy in 1.8 to 2.0 Gy fractions) has not been adequately compared with the standard-dose WBRT (40 to 45 Gy in 1.8 to 2.0 Gy fractions) in a prospective randomized trial; thus, the risks and benefits associated with this approach are unclear and cannot be recommended outside a clinical trial.
- Hyperfractionated WBRT consolidation has not been adequately compared with the standard-dose WBRT in a randomized trial and, therefore, the optimal dose for hyperfractionated schedules remains unclear and cannot be recommended outside a clinical trial.
- Elderly patients (older than 60 years of age) have an increased risk of neurotoxicity when WBRT is combined with chemotherapy. If a CR is reached in this patient group, WBRT should be avoided.

Recommendation 7 ***(Modified in 2020 – See Appendix 10)***

High-dose thiotepa-based conditioning chemotherapy and ASCT should be considered as consolidation therapy for transplant-eligible patients with stable disease or better response following first-line HD-MTX-based chemotherapy for the treatment of PCNS lymphoma.

Qualifying Statements for Recommendation 7

Despite an absence of data indicating a survival advantage of ASCT over WBRT, ASCT is preferred because of the significant neurotoxicity of WBRT. The differences in toxicity and patient preference must be carefully considered and a patient-centred, multi-disciplinary approach should be implemented to inform patients of the benefits and differential risk associated with ASCT (complications related to myeloablative chemotherapy) and WBRT (neurotoxicity).

Recommendation 8
High-dose chemotherapy plus ASCT is a reasonable treatment option for eligible patients with chemotherapy-sensitive relapsed PCNS lymphoma. High-dose thiotepa-based conditioning chemotherapy is recommended over BEAM (carmustine, etoposide, AraC, and melphalan) or similar conditioning regimens.

Recommendation 9
In patients with PIOL who are candidates for chemotherapy, treatment that includes HD-MTX should be considered. Patients that are ineligible for systemic chemotherapy should be treated with a local approach, either intravitreal chemotherapy or ocular radiation.

Qualifying Statements for Recommendation 9

The optimal management of PIOL is not known due to a lack of prospective and comparative data. HD-MTX-based systemic chemotherapy and local approaches (intravitreal methotrexate, ocular radiation) are both reasonable options for treatment. Given the improvement in outcomes for patients with PCNS lymphoma treated with HD-MTX-based chemotherapy, and recognizing the relatively high relapse rates in PIOL treated with local approaches, the members of the Working Group suggest that HD-MTX-based chemotherapy should be considered for eligible patients with PIOL. However, in the absence of comparative, prospective studies, HD-MTX can not be recommended as a definitive standard of care and local approaches are a reasonable alternative.

Management of Primary Central Nervous System Diffuse Large B-Cell Lymphoma

Section 2: Guideline – Recommendations and Key Evidence

GUIDELINE OBJECTIVES

To determine the most effective therapy for primary central nervous system diffuse large B-cell lymphoma (PCNS DLBCL) including primary intra-ocular lymphoma (PIOL).

TARGET POPULATION

These recommendations apply to adult patients (≥18 years of age) with PCNS DLBCL including PIOL.

INTENDED USERS

Intended users of this guideline are clinicians involved in the management of PCNS DLBCL in the province of Ontario, and policy makers and program planners involved in stem cell transplant and systemic and radiation therapy.

RECOMMENDATIONS, KEY EVIDENCE, AND INTERPRETATION OF EVIDENCE

Recommendation 1

Combination chemotherapy with high-dose methotrexate (HD-MTX), cytarabine (AraC), thiotepa, and rituximab (MATRix regimen) is recommended as first-line treatment of PCNS DLBCL for patients younger than 70 years with adequate renal function, and Eastern Cooperative Oncology Group (ECOG) performance status ≤3.

Cyclophosphamide, doxorubicin, vincristine, prednisolone (CHOP)-like chemotherapy regimens are not recommended for treatment of PCNS DLBCL.

Qualifying Statements for Recommendation 1

- There is insufficient evidence to support or refute alternative multi-agent chemotherapy regimens that combine HD-MTX, rituximab, and additional drugs that cross the blood-brain barrier such as procarbazine or temozolomide. These regimens have not been evaluated in prospective randomized controlled trials published to date; thus, there remains uncertainty in the clinical benefit/risk compared with standard chemotherapy regimens including the MATRix regimen.
- CHOP-like chemotherapy regimens are not recommended for treatment of PCNS lymphoma because the chemotherapeutic agents demonstrate poor penetration across the blood-brain barrier.

Key Evidence for Recommendation 1

The MATRix recommendation is supported by evidence obtained from a randomized, open-label, multicentre phase 2 trial conducted by the International Extranodal Lymphoma Study Group-32 (IELSG32) [1]. Members of the Working Group endorse the recommendation against CHOP-like chemotherapy regimens from the 2015 recommendations contained in the European Association for Neuro-Oncology guideline.

- The international randomized phase 2 IELSG32 trial published in 2016 [1] addressed the tolerability and efficacy of adding rituximab with or without thiotepa to MTX-AraC combination therapy. At a median follow-up of 30 months, the authors reported an

incremental improvement in the outcomes of patients treated with additional rituximab (overall response rate [ORR], 74%; complete remission [CR], 30%; progression-free survival [PFS], 46%; overall survival [OS], 52%) or rituximab-thiotepa (ORR, 87%; CR, 49%; PFS, 61%; OS, 67%) when compared with methotrexate-AraC alone (ORR, 53%; CR, 23%; PFS, 36%; OS, 36%), with a statistical significant difference in favour of the MATRix therapy when compared with MTX-AraC alone in terms of ORR (hazard ratio [HR], 0.61; 95% confidence interval [CI], 0.49 to 0.77; p=0.00001), CR (HR, 0.46; 95% CI, 0.28 to 0.74; p=0.0007), PFS (HR, 0.38; 95% CI, 0.24 to 0.61; p=0.00089), and OS (HR, 0.41; 95% CI, 0.25 to 0.68; p=0.0015). Significant difference in favour of the MATRix therapy was also observed when compared with MTX-AraC plus rituximab in terms of CR (HR, 0.61; 95% CI, 0.40 to 0.94; p=0.02), but not in terms of PFS (p=0.12) and OS (p=0.12). Significant difference in favour of MTX-AraC plus rituximab was observed in terms of ORR (HR, 0.69; 95% CI, 0.54 to 0.88; p=0.01) and PFS (HR, 0.52; 95% CI, 0.32 to 0.86; p=0.05) when compared with MTX-AraC alone but not in terms of CR (HR, 0.74; p=0.29) and OS (HR, 0.63; p=0.095).

- The European Association for Neuro-Oncology Task Force on PCNS lymphoma [2] based the recommendation against CHOP-like chemotherapy regimens on results from three prospective phase II trials in which the CHOP regimen added to radiotherapy did not improve patient survival.

Interpretation of Evidence for Recommendation 1

The primary outcomes considered to inform this recommendation include OS, measures of disease control (response rates and PFS), and frequency of adverse events. It is the opinion of the members of the Working Group that these events and outcomes are highly valued by clinicians and patients.

The international IELSG32 trial is the first randomized trial in PCNS lymphoma to demonstrate that adding rituximab and thiotepa to conventional MTX-AraC significantly improve the outcomes (ORR, CR, PFS, OS) of patients with PCNS lymphoma. The MATRix regimen was associated with increased grade 3/4 neutropenia and thrombocytopenia compared with the control arm of MTX-AraC; however, there was no difference in any grade infections/febrile neutropenia. Adverse events were otherwise similar across the study arms.

The certainty of the evidence surrounding the MATRix regimen for patients with PCNS lymphoma is moderate because of imprecision: each outcome measure is represented in only one study, there was a relatively short follow-up period, and the number of events can be considered relatively low. This recommendation is generalizable to patients with PCNS DLBCL (aged 18 to 70 years) who had and ECOG ≤3, and adequate renal function.

Recommendation 2

Treatment with an HD-MTX-based regimen plus rituximab chemotherapy is a reasonable treatment option for elderly patients (>70 years) who have adequate renal function and ECOG performance status ≤3.

Qualifying Statements for Recommendation 2

- Prospective, randomized trials evaluating elderly patients with PCNSL are lacking; thus, the optimal chemotherapy regimen in this population is not clear. Single-agent HD-MTX and HD-MTX-based combination regimens, including the MATRix regimen, may be reasonable options particularly in fit patients with an ECOG performance status ≤3.
- Very elderly patients (age >80 years) and/or those with a poor performance status (ECOG 4) have a particularly poor prognosis and the decision to initiate treatment with

chemotherapy must take a patient-centred approach carefully weighing the risks versus benefits of chemotherapy.

- Elderly patients with PCNS lymphoma and reduced renal function are at increased risk for MTX-related toxicity. The use of MTX in patients with creatinine clearance lower than 50 ml/min has not been adequately evaluated in prospective studies. Physicians should consider the issue of renal function and the potential for increased HD-MTX toxicity in elderly patients.

Key Evidence for Recommendation 2

The data informing this recommendation are derived from the 2015 European Association for Neuro-Oncology Guidelines [2], a systematic review and individual patient data meta-analysis [3], a phase II trial [4], and generalized from the IESLG-32 trial [1].

- The European Association for Neuro-Oncology [2] recommends HD-MTX chemotherapy as a feasible therapeutic option for elderly patients with an adequate performance status and renal function. This guideline defined elderly patients as older than 60 years and assessed data from 18 single-arm trials. Four were prospective studies evaluating elderly patients, and seven prospective and seven retrospective studies included patients of all ages that reported on the elderly subset separately. Five of these studies measured and reported toxic effects of chemotherapy [5-9]. The study by Jahnke et al. [9] evaluated HD-MTX alone, while the other four studies evaluated toxicities related to HD-MTX in combination with other agents [5-8] (Appendix 7). Comparison with historical cohorts and limited data from cross-trial comparisons suggest that treatment with MTX-based chemotherapy is associated with improved outcomes compared with whole brain radiotherapy (WBRT). However, definitive assessment for toxicity is limited by the variability among trial designs. Treatment-related mortality was reported to range from 2% to 7% and grade 3/4 nephrotoxicity and liver toxicity was less than 10%.
- The systematic review and individual patient data meta-analysis conducted by Kassenda et al. [3] found a statistically significant benefit for elderly patients (age >60 years) with PCNS lymphoma after HD-MTX-based combination chemotherapy when compared with therapies without HD-MTX. In a multivariable Cox regression analysis, HD-MTX-based chemotherapy was associated with improved survival compared with treatment that did not include HD-MTX (HR, 0.70; 95% CI, 0.53 to 0.93; p=0.013). In addition, patients treated with HD-MTX in combination with other chemotherapeutic agents had prolonged survival compared with HD-MTX monotherapy (HR, 0.54; 95% CI, 0.35 to 0.84; p=0.006).
- The phase II trial from the Nordic Lymphoma Group focused on de-escalation of HD-MTX/high-dose AraC induction therapy followed by maintenance treatment in elderly patients (66 to 75 years) with PCNS lymphoma. The authors observed promising results at 22 months of follow-up when compared with patients aged 18 to 65 years in terms of PFS (33.1% versus 44.4%; p=0.74) and OS (60.7% versus 55.6%; p=0.40). Myelosuppression was the most common side effect after the AraC cycles, with grade 3/4 anemia, neutropenia, and thrombocytopenia reported in 16%, 89%, and 81% of the patients, respectively. HD-AraC-related toxicity was a concern in the elderly. Three of four treatment-related deaths occurred in this population due to neutropenia and sepsis-induced multi-organ failure, after the first course of HD-AraC. Therefore, the authors suggested either the omission of this agent from the regimen, or a further de-escalation of induction to reduce toxicity in older patients.
- Evidence for the incorporation of rituximab into HD-MTX-based regimens is generalized from the IELSG32 phase II trial [1]. In this trial, patients were randomly allocated to receive MTX-AraC combination with or without rituximab. The addition of rituximab to MTC-AraC regimen was associated with improved outcomes in terms of ORR (53% versus

74%; HR, 0.69; p=0.01), and PFS (36% versus 46%; HR, 0.52; 95% CI, 0.32 to 0.86, p=0.05) but not in OS (36% versus 52%; HR, 0.63; 95% CI, 0.42 to 1.02, p=0.095), when compared with a MTX-AraC regimen alone. Toxicity was similar in both arms (MTX-AraC versus MTX-AraC-rituximab: neutropenia 52% versus 56%, thrombocytopenia 71% versus 74%, anemia 32% versus 36%, febrile neutropenia 21% versus 13%, and nephrotoxicity 1% versus 2%).

Interpretation of Evidence for Recommendation 2

The primary outcomes to inform this recommendation include OS, PFS, and toxicity including neurotoxicity. It is the opinion of the members of the Working Group that these outcomes are highly valued by most patients and clinicians.

The body of evidence that informs this recommendation is from one practice guideline, one systematic review and individual patient data meta-analysis, and a randomized phase II trial in patients up to 70 years of age. The studies included in the practice guideline and in the systematic review are predominantly non-comparative, single-arm trials and, thus, the level of evidence supporting this recommendation was considered low. The members of the Working Group considered the quality of evidence for addition of rituximab to HD-MTX-based chemotherapy to be moderate to low because it is based on a single randomized phase II trial evaluating patients ≤70 years of age that was not powered to detect differences in survival.

Overall, rates of neurotoxicity were infrequently reported for patients treated with HD-MTX-based chemotherapy alone (i.e., without WBRT consolidation); however, most studies did not rigorously incorporate neuro-psychologic testing prospectively.

The recommended treatments are largely effective for all critical outcomes for HD-MTX-based regimens and the incorporation of rituximab. Compared with WBRT, these data suggest HD-MTX-based therapy is associated with significant improvement in OS and with manageable toxicity in eligible patients. Given the generally short survival time and significant neurotoxicity associated with WBRT, the reported improvement in survival and low rates of neurotoxicity with HD-MTX and rituximab-based chemotherapy represents a desirable benefit to risk ratio. Very few patients over age 75 are included in clinical trials evaluating front-line therapy in PCNS lymphoma; thus, it is difficult to generalize to this population and to patients with very poor performance status (ECOG 3 or 4).

The members of the Working Group generalized the incorporation of rituximab to HD-MTX-based regimens in patients older than 70 years of age based on several factors including the benefit observed in younger patients (IESLG-32 trial), and the well-tolerated nature of therapy in most patients.

Recommendation 3

Intrathecal chemotherapy does not need to be routinely added to first-line HD-MTX-based regimens.

Qualifying Statements for Recommendation 3

There are insufficient data to support routine incorporation of intrathecal chemotherapy to first-line HD-MTX-based regimens. The members of the task force of the 2015 European Association for Neuro-Oncology, in their deliberation, as a good practice point, acknowledged that intrathecal chemotherapy may be considered in selected circumstances such as patients with leptomeningeal disease and an incomplete response to HD-MTX-based chemotherapy. The members of the Working Group agreed with this comment and support the consideration of intrathecal chemotherapy in selected cases. Hoewever, while there are clinical circumstances where intrathecal chemotherapy might be considered, the benefits and risks of its routine administration in all patients receiving aggressive

systemic MTX-based regimens is unclear and, thus, it is not recommended outside clinical trials.

Key Evidence for Recommendation 3

This recommendation is the consensus of the Working Group, based on the recommendation from the 2015 European Association for Neuro-Oncology guideline [2].

- The European Association for Neuro-Oncology [2] assessed data from three retrospective and two consecutive single-arm studies. The three retrospective studies reported no benefit in survival of adding intrathecal MTX and AraC to HD-MTX-based regimens, while the two consecutive single-arm trials suggested additional benefit for the same regimen. In view of the low level of evidence, the multidisciplinary task force of the European Association for Neuro-Oncology does not recommend routine incorporation of intrathecal chemotherapy to systemic chemotherapy regimens.

Interpretation of Evidence for Recommendation 3

Incorporation of intrathecal chemotherapy to HD-MTX-based systemic therapy has not been adequately studied prospectively. The benefit and risks of routine administration of intrathecal chemotherapy are unclear and, thus, it is not recommended outside of clinical trials.

Recommendation 4

Blood-brain barrier disruption followed by intra-arterial (IA) MTX is not recommended for the treatment of PCNS DLBCL.

Qualifying Statements for Recommendation 4

There is insufficient evidence to recommend blood-brain barrier disruption followed by IA MTX therapy in the treatment of patients with PCNS DLBCL. Blood-brain barrier disruption followed by IA MTX is still an experimental approach and, therefore, it is not recommended by the members of the Working Group outside clinical trials

Key Evidence for Recommendation 4

This recommendation is the consensus of the Working Group, based on guidance provided by the 2015 European Association for Neuro-Oncology [2].

- The European Association for Neuro-Oncology Guidelines [2] recommends blood-brain barrier disruption followed by IA MTX as an alternative experimental approach that is appropriate for a selected group of patients, but should be undertaken only by teams with a high level of expertise. This recommendation is based on three single-arm, non-comparative studies. The largest of these, a retrospective multi-institution study that evaluated blood-brain barrier disruption and IA MTX in 149 patients, reported an ORR of 81.9%, median PFS of 1.8 years (95% CI, 1.3 to 2.8 years), five-year PFS of 31%, and median OS of 3.1 years (95% CI, 2.2 to 5.0 years). The treatment regimen consisted of two blood-brain barrier disruption treatments on consecutive days every four weeks for up to 12 months. Treatment-related adverse events included periprocedural focal seizures (33.6% of patients, 9.2% of procedures), and stroke (7.4% patients).

Interpretation of Evidence for Recommendation 4

Blood-brain barrier disruption by IA infusion of hypertonic mannitol followed by IA MTX has not been compared with current standard chemotherapy regimens in prospective randomized trials.

Recommendation 5 ***(Modified in 2020 – See Appendix 10)***

Whole brain radiotherapy (WBRT) or comfort-based palliative care are reasonable treatment options for patients who refuse aggressive chemotherapy or who are considered ineligible for HD-MTX-based, or alternative, chemotherapy regimens.

Qualifying Statements for Recommendation 5

The clinical benefit of WBRT in this poor-risk population, compared with supportive care, has not been confirmed in prospective comparative clinical trials. WBRT as a single treatment modality is associated with a response rate of approximately 50% and median survival of approximately one year that is offset by a risk of neurotoxicity.

Key Evidence for Recommendation 5

- There are limited data on which to base a recommendation regarding alternative treatment for patients who are not eligible for HD-MTX-based chemotherapy regimens.
- This recommendation was informed by expert opinion of the members of the Working Group.

Interpretation of Evidence for Recommendation 5

Many patients with PCNS lymphoma may refuse aggressive chemotherapy due to toxicity concerns or may not be eligible for HD-MTX-based chemotherapy regimens due to unfavourable prognostic factors for survival (e.g., advanced age, poor performance status, significant comorbidities/organ dysfunction) and the decision to use alternative treatments for these patients must take a patient-centred approach carefully weighing the risks versus benefits of available treatment options. It is the opinion of the members of the Working Group that WBRT or comfort-based palliative care are reasonable alternatives in patients who are considered ineligible and/or refuse HD-MTX-based chemotherapy regimens.

Recommendation 6 ***(Modified in 2020 – See Appendix 10)***

Whole brain radiation therapy (WBRT) should not be routinely administered in patients who have achieved a complete remission following first-line HD-MTX-based chemotherapy.

Qualifying Statements for Recommendation 6

- For transplant eligible patients, autologous stem cell transplantation (ASCT) is a reasonable alternative consolidation treatment and patients should also be informed of this treatment option (See Recommendation 7)
- In patients who achieve a CR following first-line chemotherapy, consolidation with WBRT has not been clearly shown to improve OS when compared with no radiotherapy. The addition of WBRT is associated with an increased risk of neurotoxicity that may have a significant impact on quality of life. The risk of neurotoxicity is particularly high in patients older than 60 years of age. The role of WBRT in patients who have achieved a CR following first-line chemotherapy remains controversial; a patient-centred, multi-disciplinary approach is recommended to inform patients of the trade-off in risks and benefits associated with WBRT consolidation in this setting.
- WBRT is a reasonable consolidation option for patients in partial remission following first line chemotherapy who are not eligible for ASCT.
- Reduced-dose WBRT consolidation (23.4 to 30.0 Gy in 1.8 to 2.0 Gy fraction) has not been adequately compared with the standard-dose WBRT (40 to 45 Gy in 1.8 to 2.0 Gy fraction) in a prospective randomized trial; thus, the risks and benefits associated with this approach are unclear and cannot be recommended outside a clinical trial.
- Hyperfractionated WBRT consolidation has not been adequately compared with the standard-dose WBRT in a randomized trial, and therefore the optimal dose for

hyperfractionated schedules remains unclear and cannot be recommended outside a clinical trial.

- Elderly patients (older than 60 years of age) have an increased risk of neurotoxicity when WBRT is combined with chemotherapy. If a CR is reached in this patient group, WBRT should be avoided.

Key Evidence for Recommendation 6

The recommendation represents the consensus of the Working Group after reviewing the evidence from the 2015 European Association for Neuro-Oncology Guidelines [2], one phase III randomized controlled trial [10], and a single-arm phase II trial .

- The 2015 European Association for Neuro-Oncology acknowledged the greater risks of neurotoxicity associated with WBRT, and concluded that consolidation WBRT after HD-MTX-based chemotherapy remains controversial. It is the opinion of the European task force that although the optimal dose has not yet been defined, it should be chosen on the basis of the response to primary chemotherapy. In patients younger than 60 years of age with progressive or residual disease after primary chemotherapy, a total dose of 40 to 45 Gy with 1.8 to 2.0 Gy dose per fraction was recommended. The decision to deliver WBRT to patients with CR should be discussed with the patient. The authors recommended that reduced-dose WBRT consolidation should only be investigated in clinical trials.
- The phase III randomized controlled trial [10] used a non-inferiority design to evaluate the role of WBRT in primary therapy of patients with PCNS lymphoma. Patients were randomly allocated to receive HD-MTX-based chemotherapy alone or followed by WBRT. The statistical proof of non-inferiority regarding survival was not proven because the lower limit of the confidence intervals crossed the a priori defined non-inferiority margin of 0.9. The authors reported comparable survival rates (32.4 versus 36.1 months; HR, 0.98; 95% CI, 0.79 to 1.26; p=0.98) after a follow-up of 81.2 months. Treatment-related neurotoxicity was more common in patients receiving WBRT than in those who did not receive WBRT (49% versus 26%; p=0.054 by clinical assessment, and 71% versus 46%; p=0.04 by neuroradiology assessment).
- The single-arm phase II trial [11], a prospective cooperative group study, reported on the use of MTX, rituximab, and temozolomide, followed by hyperfractionated WBRT and subsequent temozolomide for the treatment of patients with PCNS lymphoma. The authors reported significantly improved two-year PFS (63.6% versus 50%; p=0.03) and OS (80.8% versus 64%; p=0.006) when compared with historical controls from the RTOG-9310 trial.
- The recommendation for elderly patients represents the consensus of the members of the Working Group

Interpretation of Evidence for Recommendation 6

WBRT as consolidation treatment has not been clearly shown to improve overall survival in patients who have achieved a CR following first-line HD-MTX-based chemotherapy regimens. **Patients treated with WBRT following standard first-line chemotherapy regimens are at increased risk for developing clinical neurotoxicity including impaired cognition, dementia, ataxia, and incontinence.** It is the opinion of the members of the Working Group that a patient-centred, multi-disciplinary approach is recommended to inform patients of the trade-off in risks and benefits associated with WBRT consolidation in this setting. Elderly patients (>60 years) are at particularly high risk for neurotoxicity with WBRT consolidation following chemotherapy; therefore, it is the opinion of the Working Group that WBRT should be avoided in this patient group.

Recommendation 7 ***(Modified in 2020 - See Appendix 10)***

High-dose thiotepa-based conditioning chemotherapy and ASCT should be considered as consolidation therapy for transplant-eligible patients with stable disease or better response following first-line HD-MTX-based chemotherapy for the treatment of PCNS lymphoma.

Qualifying Statement for Recommendation 7

Despite an absence of data indicating a survival benefit for ASCT over WBRT, ASCT is preferred because of the significant neurotoxicity of WBRT. The differences in toxicity and patient preference must be carefully considered and a patient-centred, multi-disciplinary approach should be implemented to inform patients of the benefits and differential risk associated with ASCT (complications related to myeloablative chemotherapy) and WBRT (neurotoxicity).

Key Evidence for Recommendation 7

This recommendation is supported by two randomized phase II trials comparing consolidation chemotherapy with WBRT versus ASCT in patients with PCNS lymphoma [12,13]. Both trials compared sequential HD-MTX and AraC-based chemotherapy plus rituximab followed by WBRT or high-dose chemotherapy (HD-CT)/ASCT with two-year PFS as the primary endpoint. The conditioning regimen used by the two groups consisted of a high dose of carmustine and thiotepa [12], and thiotepa, busulfan, and cyclophosphamide [13]. These two trials have been published in abstract form.

- The IELSG32 trial reported on an intention-to-treat basis. They reported no statistically significant difference in two-year PFS between WBRT and ASCT (80 ± 5% after WBRT versus 70 ± 6% after ASCT). Multivariable analysis suggested no statistical difference in two-year OS between patients treated with WBRT and those treated with ASCT (85 ± 5% versus 71 ± 6%; p=0.12). Comparison of WBRT with ASCT reported significant impairment of attention/executive functions and non-significant trend to impaired memory in patients treated with WBRT, while improved functions were observed in patients treated with ASCT. Both consolidation therapies were reported to be associated with significant improvement in language and quality of life. Further information surrounding quality of life and neurotoxicity have not been reported, but are expected to be available when results from the second randomization addressing the role of consolidation therapy are fully published.
- At a median follow-up of 33 months, the Anocef-Goelams trial reported a two-year PFS for patients in the HD-CT/ASCT arm of 86.8% (95% CI, 76.6 to 98.3) compared with a two-year PFS for patients in the WBRT arm of 63.2% (95% CI, 49.5 to 80.5). Data regarding OS and neuropsychological evaluations have not yet been reported.

Interpretation of Evidence for Recommendation 7

The evidence considered to inform this recommendation derived from two prospective phase II trials reported in abstract form with a few limitations. The IELSG32 trial was not powered to detect a difference in OS (the primary endpoint of the second randomization was two-year PFS). Neither study was designed to determine whether ASCT has equivalent or non-inferior efficacy (non-inferiority design) to WBRT as the consolidation treatment for patient with PCNS lymphoma. As per above, ASCT is preferred because of the severe cognitive impairment and neurotoxicity associated with WBRT.

Recommendation 8
HD-CT plus ASCT is a reasonable treatment option for eligible patients with chemotherapy-sensitive relapsed PCNS lymphoma. High-dose thiotepa-based conditioning chemotherapy is recommended over BEAM (carmustine, etoposide, AraC, and melphalan) or similar conditioning regimens.
Key Evidence for Recommendation 8
This recommendation is supported by the evidence obtained from the 2015 European Association for Neuro-Oncology Guideline [2]. No additional studies to inform this recommendation were identified.
Interpretation of Evidence for Recommendation 8
The 2015 European Association for Neuro-Oncology Guideline included a review of three studies (two publications from one multicentre phase 2 trial and an independent retrospective single-centre series study) providing guidance for HD-CT plus ASCT in the treatment of patients with chemotherapy-sensitive relapsed or refractory PCNS lymphoma; these studies reported the benefit of the thiotepa, busulfan, and cyclophosphamide regimen followed by ASCT. A phase II trial from the Memorial Sloan Kettering Centre addressing BEAM-conditioned ASCT was also reviewed by the European Association for Neuro-Oncology Task Force which reported unsatisfactory results. The certainty of the evidence on the efficacy of HD-CT plus ASCT is low. However, due to the poor prognosis for patients with relapsed or refractory PCNS lymphoma, the members of the Working Group endorsed the recommendation from the 2015 European Association for Neuro-Oncology Guideline.

Recommendation 9
In patients with PIOL who are candidates for chemotherapy, treatment that includes HD-MTX should be considered. Patients that are ineligible for systemic chemotherapy should be treated with a local approach, either intravitreal chemotherapy or ocular radiation.
Qualifying Statement for Recommendation 9
The optimal management of PIOL is not known due to a lack of prospective ans comparative data. HD-MTX-based systemic chemotherapy and local approaches (intravitreal methotrexate, ocular radiation) are both reasonale options for treatment. Given the improvement in outcomes for patients with PCNSL treated with HD-MTX-based chemotherapy, and recognizing the relatively high relapse rates in PIOL treated with local approaches, the members of the Working Group suggest that HD-MTX-based chemotherapy should be considered for eligible patients with PIOL. However, in the absebce of comparative, prospective studies, HD-MTX can not be recommended as a definitive standard of care and local approaches are a reasonable alternative.
Key Evidence for Recommendation 9
The recommendation for the treatment of patients with PIOL represents the consensus of the Working Group based on consensus-based guidance from the 2015 European Association for Neuro-Oncology guideline [2]. No additional studies to inform this recommendation were identified.
Interpretation of Evidence for Recommendation 9
The 2015 European Association for Neuro-Oncology Guideline reviewed the evidence surrounding the treatment of PIOL and concluded that the evidence is scarce and limited to

retrospective case reports, mostly small series with heterogeneous patient populations and treatments. The level of the evidence for the treatment of patients with PIOL is low. However, since the optimal treatment for this condition remains unknown, the members of the Working Group endorsed the consensus-based recommendation from the 2015 European Association for Neuro-Oncology Guideline. The management decision should take into consideration the benefit and risks of the treatment options.

IMPLEMENTATION CONSIDERATIONS

Funding for rituximab and thiotepa should be considered to facilitate administration of optimal first-line chemotherapy for patients with PCNS lymphoma.

RELATED GUIDELINES

- The Role of IMRT in Central Nervous System Cancer, N. Laperriere, R.B. Rumble, P. Warde, and the Members of the IMRT Indications Expert Panel of Cancer Care Ontario's Program in Evidence-Based Care [Report Date: October 29, 2010]. Available at: https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/2191

Management of Primary Central Nervous System Diffuse Large B-Cell Lymphoma

Section 3: Guideline Methods Overview

This section summarizes the methods used to create the guideline. For the systematic review, see Section 4.

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-Based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO). The PEBC mandate is to improve the lives of Ontarians affected by cancer through the development, dissemination, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer control.

The PEBC supports the work of Guideline Development Groups (GDGs) in the development of various PEBC products. The GDGs are composed of clinicians, other healthcare providers and decision makers, methodologists, and community representatives from across the province.

The PEBC is a provincial initiative of CCO supported by the Ontario Ministry of Health and Long-Term Care (OMHLTC). All work produced by the PEBC is editorially independent from the OMHLTC.

JUSTIFICATION FOR GUIDELINE

The initiation of this guideline was prompted by the need to harmonize practice in Ontario around the management of PCNS DLBCL including PIOL. There is no clearly defined standard of care for patients with PCNS DLBCL, and substantial variability in practices exists within Ontario.

GUIDELINE DEVELOPERS

This guideline was developed by the PCNS Lymphoma (PCNSL) GDG (Appendix 1), which was convened at the request of the Stem Cell Transplant Steering Committee from CCO.

The project was led by a small Working Group of the PCNSL GDG, which was responsible for reviewing the evidence base, drafting the guideline recommendations, and responding to comments received during the document review process. The Working Group combined the expertise of neuro-oncology, hematology-oncology, radiation-oncology, stem cell transplant, and health research methodology. Other members of the PCNSL GDG served as the Expert Panel and were responsible for the review and approval of the draft document produced by the Working Group. Conflict of interest declarations for all GDG members are summarized in Appendix 2, and were managed in accordance with the *PEBC Conflict of Interest Policy*.

GUIDELINE DEVELOPMENT METHODS

The PEBC produces evidence-based and evidence-informed guidance documents using the methods of the Practice Guidelines Development Cycle [14,15]. This process includes a systematic review, interpretation of the evidence by the Working Group and draft recommendations, internal review by content and methodology experts and external review by Ontario clinicians and other stakeholders.

The PEBC uses the AGREE II framework [16] as a methodological strategy for guideline development. AGREE II is a 23-item validated tool that is designed to assess the methodological rigour and transparency of guideline development.

The currency of each document is ensured through periodic review and evaluation of the scientific literature and, where appropriate, the addition of newer literature to the original evidence-base. This is described in the *PEBC Document Assessment and Review Protocol*. PEBC guideline recommendations are based on clinical evidence, and not on feasibility of implementation; however, a list of implementation considerations such as costs, human resources, and unique requirements for special or disadvantaged populations is provided along with the recommendations for information purposes. PEBC guideline development methods are described in more detail in the *PEBC Handbook* and the *PEBC Methods Handbook*.

Search for Existing Guidelines

As a first step in developing this guideline, a search for existing guidelines was undertaken to determine whether an existing guideline could be adapted or endorsed. Only guidelines based on systematic review of the literature and published after 2013 were considered for endorsement or adaptation. To this end, the following sources were searched for existing guidelines that addressed the research questions:

- Practice guideline databases: the Standards and Guidelines Evidence Directory of Cancer Guidelines (SAGE), Agency for Healthcare Research and Quality (AHRQ) National Guideline Clearinghouse, and the Canadian Medical Association Infobase.
- Guideline developer websites: National Institute for Health and Care Excellence (NICE), Scottish Intercollegiate Guidelines Network (SIGN), American Society of Clinical Oncology (ASCO), and National Health and Medical Research Council - Australia.

Four guidelines that focussed on the management of the CNS cancers including PCNS lymphoma [17-20] were located in the targeted search of known guideline developers and professional organizations. Two of these guidelines were produced by the British Committee for Standards in Hematology; one focused on secondary CNS lymphoma [20], and one was produced in 2007 and likely to be out of date [18]. Two additional guidelines, one from the United States [17] and one from Canada [19], have recently been published, and they focused on the management of patients with PCNS lymphoma; however, either their recommendations were based on expert opinion and a consensus process [17], or a clear systematic review methodology was not presented. Therefore, none of these guidelines was considered for endorsement or adaptation. One additional guideline from the European Association for Neuro-Oncology that significantly overlapped in scope with the objectives and the research questions of the present document was later found when searching the electronic databases MEDLINE (OVID) and EMBASE (OVID) [2]. The identified guideline was evaluated by three independent methodologists (NPV, CZ, FB) using the AGREE II framework. The guideline was also reviewed by members of the PCNSL Working Group and agreement with the recommendations contained in the European Association for Neuro-Oncology guideline led to the Working Group members' decision to use its recommendations as a basis for the present document. It was the opinion of the members of the Working Group that current evidence from phase II and III trials may lead to a change of some of the recommendations. The AGREE scores are presented in Appendix 3, and a brief description of the retained guideline is presented below.

European Association for Neuro-Oncology [2]

The 2015 European guideline was developed by the European Association for Neuro-Oncology Task Force on PCNS lymphoma with the support of the review committee of specialists in the management of PCNS lymphoma. The task force represents European-based medical

experts including neurologists, hematologists, medical oncologists, neurosurgeons, pathologists, ophthalmologists, and radiation oncologists from 11 countries. The guideline was developed with the aim to establish evidence-based recommendations and consensus expert opinion for the management of immunocompetent adult patients with PCNS lymphoma. Evidence-based recommendations were based on literature obtained through a systematic review of the literature from 1980 to September 2014.

The 2015 European recommendations regarding the treatment of patients with PCNS lymphoma and related to our research questions are presented in Table 3-1.

Table 3-1. The 2015 Recommendations from the European Association for Neuro-Oncology Task Force on PCNS Lymphoma

Indication	Recommendations [2]	Level of Evidence*
Chemotherapy	• CHOP regimens and derivatives are not recommended for treatment of PCNS lymphoma	B
	• HD-MTX (≥3 g/m^2): at least 4-6 IV infusion for 2-3 h at intervals that should not exceed 2-3 weeks	GPP
	• Combination of HD-MTX with other CT agents improves responses compared with HD-MTX alone	B
	• Chemotherapeutic agents to be used in combination with HD-MTX should be selected from active drugs known to cross the blood-brain barrier, such as HD-cytarabine (AraC)	B
	• HD-MTX CT is feasible in elderly patients with an adequate performance status and renal function	B
	• Blood-brain barrier disruption followed by intra-arterial MTX is an alternative experimental approach that is appropriate for a selected group pf patients but should be undertaken only by teams with a high level of expertise	GPP
	• The value of intrathecal CT as prophylaxis is unclear. Intrathecal CT (intralumbar or preferably intraventricular through an Ommaya reservoir) can be proposed whenever meningeal involvement is documented, together with an insufficient response to intravenous HD-MTX-based CT (at least 3 g/m^2)	C
	• Rituximab combined with a CT regimen is recommended only as an experimental regimen within clinical trials	
Radiotherapy	• WBRT, HD-MTX, and combined treatments expose patients to greater risks of neurotoxic effects	A
	• Consolidation WBRT after HD-MTX-based CT remains controversial. The optimal dose is not yet defined but should be chosen on the basis of the response to primary CT	GPP
	• In patients with progressive or residual disease after primary CT, a total dose of 40-45 Gy with 1.8-2.0 Gy dose per fraction	GPP

	is advisable. When these doses are used, there is no evidence for the use of a focal boost on the enhanced lesions	GPP
	• In patients younger than 60 years of age, who have achieved a CR to induction CT, the decision for immediate WBRT (40-50 Gy in 1.8-2.0 Gy fractions) or omission of WBRT should be discussed with the patient. Reduced-dose WBRT consolidation (23.4-30.0 Gy in 1.8-2.0 Gy fractions) is a therapeutic option that should be investigated in a clinical trial	B
	• In patients older than 60 years, the risk of delayed neurotoxic effects with WBRT (doses greater than 30 Gy in 1.8-2.0 Gy fractions), especially after HD-MTX, is too high. WBRT at these doses should be deferred or avoided	
High-dose chemotherapy with autologous stem-cell transplantation (HDCT-ASCT)	• HDCT-ASCT is an efficient treatment in relapsed or refractory PCNS lymphoma	B
	• HDCT-ASCT should be reserved for patients less than 60-65 years of age	GPP
	• HD thiotepa-based conditioning CT should be preferred over the BEAM regimen	C
	• HDCT-ASCT as consolidation for first-line treatment is experimental in PCNS lymphoma and should be used only in clinical centres that have had sufficient training	GPP
	• HDCT-ASCT is a valid therapeutic option in patients younger than 60-65 years with chemosensitive relapsing PCNS lymphoma	B
Primary Intraocular Lymphoma	• PIOL can be treated either HD-MTX-based CT (with or without WBRT) or by locally applied therapy (intravitreal CT or ocular RT)	GPP
	• Local treatment (intravitreal CT or ocular RT) is a valid approach for patients with systemic CT contraindications or for elderly patients with relapsing intraocular disease	GPP
	• If consolidation WBRT is proposed, it should include both eyes	GPP

Abbreviations: ASCT (autologous stem cell transplantation); BEAM (carmustine, etoposide, cytarabine, and melphalan); CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone); CR (complete response); CT (chemotherapy); GPP (good practice point); HD-MTX (high-dose methotrexate); HDCT (high-dose chemotherapy; GPP (good practice point); PIOL (primary intraocular lymphoma); WBRT (whole-brain radiotherapy).

[*] A (at least one randomized phase 3 clinical trial or two consistent randomized phase 2 trials); B (at least randomized phase 2 trial or several phase 2 trials, prospective, and retrospective studies); C (at least two consistent prospective or retrospective studies); GPP (insufficient evidence to categorize the recommendation on levels A-C, and if recommendation agreed by all members of the task force).

GUIDELINE REVIEW AND APPROVAL

Internal Review

For the guideline document to be approved, 75% of the content experts who comprise the GDG Expert Panel must cast a vote indicating whether or not they approve the document, or abstain from voting for a specified reason, and of those that vote, 75% must approve the document. In addition, the PEBC Report Approval Panel (RAP), a three-person panel with methodology expertise, must unanimously approve the document. The Expert Panel and RAP members may specify that approval is conditional, and that changes to the document are required. If substantial changes are subsequently made to the recommendations during external review, then the revised draft must be resubmitted for approval by RAP and the GDG Expert Panel.

External Review

Feedback on the approved draft guideline is obtained from content experts and the target users through two processes. Through the Targeted Peer Review, several individuals with content expertise are identified by the GDG and asked to review and provide feedback on the guideline document. Through Professional Consultation, relevant care providers and other potential users of the guideline are contacted and asked to provide feedback on the guideline recommendations through a brief online survey. This consultation is intended to facilitate the dissemination of the final guidance report to Ontario practitioners.

PATIENT AND CAREGIVER-SPECIFIC CONSULTATION GROUP

Two patients participated as Consultation Group members for the PCNSL Working Group. The patient representatives reviewed copies of the project plan and draft recommendations and provided feedback on their comprehensibility, appropriateness, and feasibility to the Working Group's Health Research Methodologist (NPV). The Health Research Methodologist (NPV) relayed the feedback to the Working Group for consideration.

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- Ananya Nair for conducting a data audit.
- Sara Miller for copy editing.

Management of Primary Central Nervous System Diffuse Large B-Cell Lymphoma

Section 4: Systematic Review

INTRODUCTION

PCNS DLBCL is a rare and aggressive B-cell malignancy defined by involvement of the brain, leptomeninges, eyes, or spinal cord in the absence of systemic disease. Based upon Surveillance, Epidemiology, and End Results (SEER) database estimates, the incidence of PCNS lymphoma in the United States is approximately 0.47/100,000 person-years [21]. It accounts for approximately 3% to 4% of all CNS malignancies, 1% of all cases of DLBCL, and has a median age at diagnosis of approximately 60 years [22,23]. Risk factors for the development of PCNS DLBCL include increasing age and immunocompromised states, in particular acquired immunodeficiency syndrome (AIDS), which has been reported to be associated with a 3600-fold increased risk compared with the general population [24]. The assessment of newly diagnosed patients should include full assessment of the neuro-axis (magnetic resonance imaging scans of the brain/spinal column, examination of the cerebrospinal fluid [CSF] by lumbar puncture, slit lamp examination to assess for ocular involvement), and full staging investigations to rule out systemic lymphoma (computed tomography scans of the chest/abdomen/pelvis, bone marrow aspirate and biopsy, testicular ultrasonography). A retrospective, multivariable analysis by the IELSG identified age greater than 60 years, ECOG performance status greater than 1, lactate dehydrogenase greater than the upper limit of normal, increased CSF protein levels, and involvement of deep brain structures (periventricular regions, cerebellum, basal ganglia, brain stem) as independent poor prognostic markers and incorporated them in a prognostic model that is now commonly incorporated into clinical trials and can be easily incorporated into clinical practice.

Left untreated, the expected survival for patients with PCNS DLBCL is approximately two to three months. Historically, WBRT is associated with a median survival of approximately one year. Survival is poorer for patients with PCNS DLBCL compared with patients with systemic DLBCL. Several factors likely contribute to poor outcomes, including (1) poor CNS penetration of most chemotherapeutic agents used to treat systemic DLBCL; (2) poor performance status of many patients as a consequence of their presenting neurologic deficits, age, and co-morbidities; and (3) the negative impact of disease rarity on the conduct of prospective-comparative clinical trials needed to advance patient outcomes. There are very few completed randomized controlled trials to help guide optimal treatment for patients with PCNS DLBCL. In addition, prospective and retrospective cohort studies usually have small sample sizes and are subject to a significant risk of bias in outcomes, making cross-cohort comparisons particularly uncertain. As a consequence, considerable uncertainty exists regarding optimal management of patients with PCNS DLBCL. The Stem Cell Transplant Steering Committee believes strongly that a systematic review and development of evidence based recommendations was both appropriate and necessary to try and inform a consistent and optimized approach to management.

During the initial literature search, a systematic review and guideline recommendations from the European Association for Neuro-Oncology was found which significantly overlapped in scope with the objectives and the research questions of the present document [2]. Their literature search included publications between 1980 and September 2014. The identified guideline was evaluated by three independent methodologists (NPV, CZ, FB) using the AGREE II framework. The guideline was also reviewed by members of the PCNSL Working Group who

believed it was well conducted and that the resources required to repeat the literature search would be of limited value. There was general agreement with the recommendations contained in the European Association for Neuro-Oncology guideline and this led to the Working Group members' decision to use its recommendations as a basis for the present document. It was the opinion of the members of the Working Group that a literature search should be conducted from September 2014 until present because this may lead to a change of some of the recommendations contained within the European Association for Neuro-Oncology guideline document.

The Working Group of the PCNSL GDG developed this evidentiary base to inform recommendations as part of a clinical practice guideline. Based on the objectives of this guideline (Section 2), the Working Group derived the research questions outlined below.

RESEARCH QUESTION(S)

1. What is/are the optimal chemotherapy regimen(s) for the first-line treatment of PCNS DLBCL?
2. Does chemotherapy combined with radiation therapy improve the outcome of patients with PCNS DLBCL when compared with chemotherapy alone, and if so, what is the optimal radiation dose and schedule?
3. Does HD-CT plus ASCT improve the outcome of patients with PCNS DLBCL when compared with standard-dose chemotherapy with or without radiation therapy in the:
    a. Front-line setting
    b. In the setting of relapsed/refractory disease

METHODS

This evidence review was conducted in two planned stages: a search for systematic reviews followed by a search for primary literature. These stages are described in subsequent sections.

Search for Existing Systematic Reviews

A search was conducted for existing systematic reviews. The website of the Cochrane Database of Systematic Reviews (CDSR) (www.cochrane.org/evidence), along with the electronic databases MEDLINE (OVID) and EMBASE (OVID) were searched from January 2000 to May 2016. The full literature search strategy used to identify potential relevant systematic reviews from OVID MEDLINE and EMBASE is presented in Appendix 4. The website of the CDSR was searched using the keyword "Primary Central Nervous System Lymphoma".

Systematic reviews were included if:

1. The systematic review searched for studies assessing any of the following indications in the management of primary central nervous system lymphoma: chemotherapy regimens as a single modality treatment; chemotherapy combined with radiotherapy for the first-line treatment; HD-CT plus ASCT in either, the first-line setting or relapsed/refractory disease.
2. The existing systematic review reported the sources searched as well as the dates that were searched.

Any identified systematic review that addressed the research question was assessed, based on their clinical content and relevance, using A Measurement Tool to Assess Systematic Reviews (AMSTAR) [25]. The results of the AMSTAR assessment were used to determine whether any existing review could be incorporated as part of the evidentiary base.

Search for Primary Literature

A systematic review of the primary literature was planned if no suitable guidelines or systematic reviews were identified. If a suitable guideline or systematic review was found, a systematic review of the primary literature would be conducted from the end date of the reported search to update the evidence from the identified guidelines(s) and/or systematic review(s). In the case that missing information was identified from the reporting of any suitable guideline or systematic review, original studies would be retrieved and appropriate information extracted.

Literature Search Strategy

The electronic databases MEDLINE (OVID) and EMBASE (OVID) were searched for relevant articles from the completion date of the search for the 2015 European Association for Neuro-Oncology guideline (2014) to July 2016, and updated in December 2016. The search strategy included a logical combination of terms for the condition (PCNS lymphoma), the intervention (chemotherapy, radiotherapy, ASCT), and studies of interest (all but phase I trials, comment, letter, editorial, newspaper, case report or historical article). The full literature search strategy used to retrieve potential relevant studies is presented in Appendix 4.

Study Selection Criteria and Process

Inclusion Criteria

Articles identified in this systematic review were eligible for inclusion if they met all of the following criteria:

1. Published full-report articles or abstracts of phase II and phase III randomized and non-randomized trials evaluating any of the following indications in the management of PCNS lymphoma: chemotherapy, radiotherapy, or HD-CT plus ASCT. Primary prospective studies with a sample size of at least 30 participants were also included.
2. Reported the outcomes of interest; namely, ORR, complete response rates (CRR), overall survival (OS), event-free survival (EFS), PFS, quality of life (QoL), or toxicity (including neurotoxicities).
3. Published in 2014 or later to update the evidence from the European guideline used as a baseline of this evidentiary base.

Exclusion Criteria

Studies were excluded if they were:

1. Letters, case reports, comments, books, notes, or editorial publication types.
2. Articles published in a language other than English due to unavailability of translation services.

A review of the titles and abstracts that resulted from the search was done by one reviewer (NPV). For items that warranted full-text review, one reviewer (NPV) reviewed each item and consulted members of the Working Group whenever there was uncertainty.

Search for Abstracts

The American Society of Clinical Oncology (ASCO), the American Society of Hematology (ASH), and the International Conference on Malignant Lymphoma were searched for meeting abstracts of randomized control trials on the management of PCNS lymphoma from 2014 through 2016. A sample size of at least 30 participants was required.

Data Extraction

Data extraction was conducted by one author (NPV), and a data audit was conducted by a second independent individual (AN) to verify the accuracy of extracted data.

For primary studies, key characteristics, including author/trial sponsor, publication year, years of data collection, country, study design, protocol, diagnosis of PCNS lymphoma, sample size, recruitment method, inclusion criteria, interventions, and primary and secondary endpoints were extracted. Outcomes of interest including CRR and ORR, PFS, OS, toxicities including neurotoxicities, and quality of life were extracted when available.

Ratios, including hazard ratios, were expressed with a ratio <1.0 indicating that the intervention/experimental procedure had a better outcome than the comparison group.

Assessment of Study Quality and Potential for Bias

The quality of the systematic reviews identified in the literature search was appraised using the AMSTAR tool [25].

Clinical trials were assessed for quality by examining the following criteria: method of randomization, reporting on allocation concealment, reporting of blinding, the power and sample size calculation, reporting details of the statistical analysis, reporting on baseline characteristics, and reporting on losses to follow-up. Single-arm evidence was assessed according to full reporting of the patient selection criteria, the interventions each patient received, and all relevant outcomes. All authors reviewed and discussed a draft of this guideline with the aim of assessing the quality of the evidence as a whole, without the use of a scoring system or cut-offs.

RESULTS

Search for Existing Systematic Reviews

A search for systematic reviews was conducted to update the 2015 recommendations from the European Association for Neuro-Oncology. Four citations were identified as potentially relevant. From these, one systematic review with individual patient data meta-analysis investigating the prognosis and effects of first-line treatment for elderly patients with newly diagnosed PCNS lymphoma was included [3]. This systematic review not only contains information from trials that were not considered in the European guideline [2], but also provides a comprehensive summary of the best available evidence up to 2014 focused in the treatment of elderly patients diagnosed with PCNS lymphoma. The list of the studies included in the individual patient data meta-analysis and its indication of inclusion in the European guideline is presented in Table 4-1.

Table 4-1. Studies included in the Systematic Review and Meta-Analysis Evaluating the Management of Primary Central Nervous System Lymphoma

Individual Patient Data Meta-Analysis [3]	European Association for Neuro-Oncology [2]
Freilich et al., 1996	Not included
Fritsch et al., 2011	✓
Ghesquieres et al., 2010	✓
Hoang-Xuan et al., 2003	✓
Illerhaus et al., 2009	✓
Kurzwelly et al., 2010	✓

Laack et al., 2006	✓
Lee et al., 2014	Not included
Makino et al., 2015*	Not included
Ney et al., 2010	✓
Ng et al., 2000	Not included
Olivier et al., 2014	Not included
Omuro et al., 2007	✓
Omuro et al., 2013	✓
Pulczynski et al., 2014	Not included
Roth et al., 2012	✓
Schlegel et al., 2012	Not included
Schuurmans et al., 2010	✓
Welch et al., 2012	✓
Zhu et al., 2009	✓

*PDF format publication date (formerly Epub 2014 Apr 11)

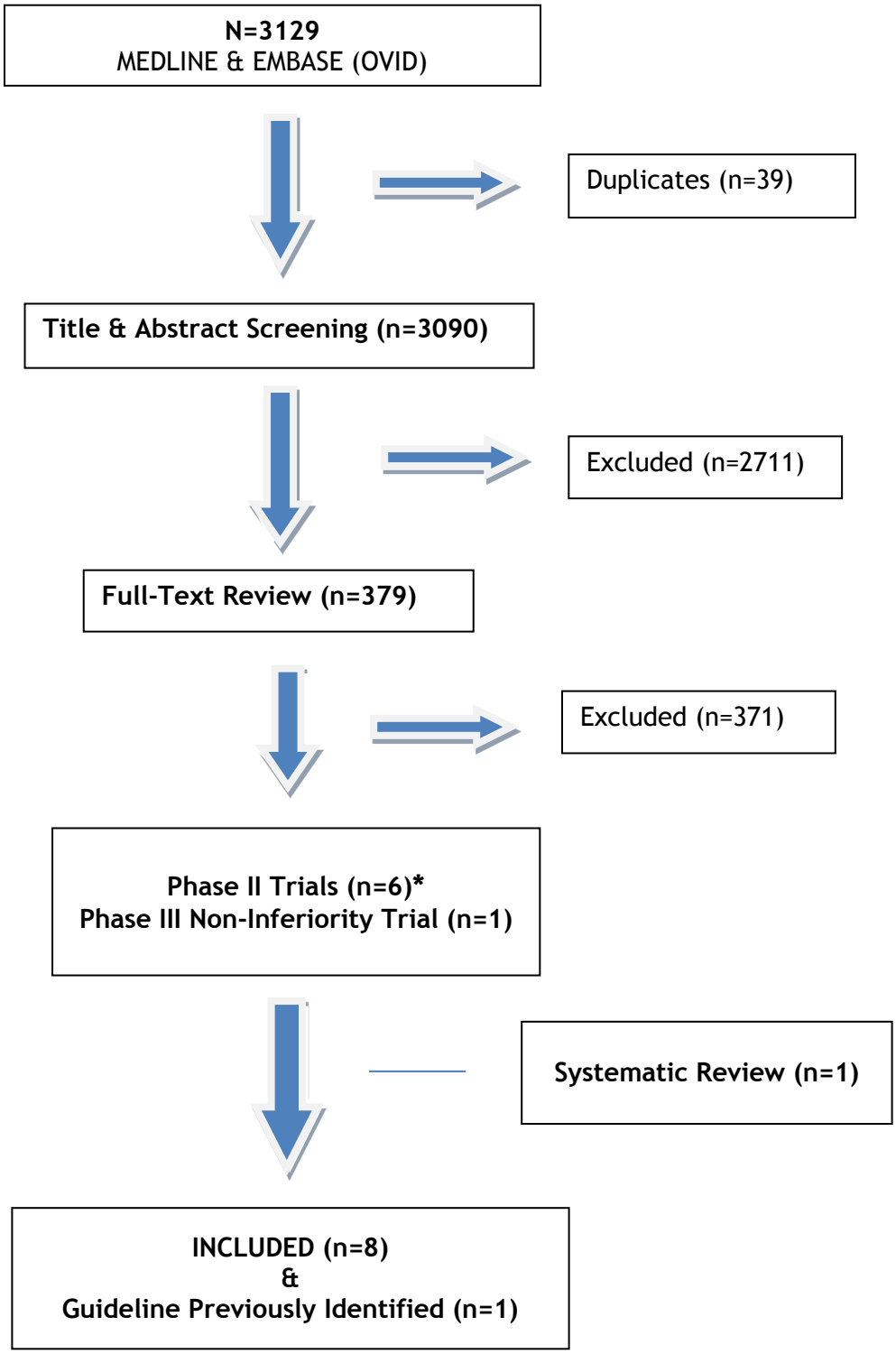
Search for Primary Literature

The primary literature review was used to address domains and/or outcomes of interest not covered by the included guideline and systematic review; therefore, only primary literature published from 2014 was considered because it corresponds to the end date of the search in the identified guideline (September 2014) and systematic review (November 2014).

Literature Search Results

As presented in Figure 4-1, of the 3129 titles and abstracts identified in the search of MEDLINE and EMBASE, 3090 appeared potentially eligible on initial review, and 379 of these were verified to be eligible for full-text review. From these, eight full-report publications were identified that evaluated treatment modalities for PCNS lymphoma, and reported the outcomes of interest. The remaining 371 publications were excluded because they failed to pass the inclusion criteria. Studies selected for inclusion are listed in Table 4-2.

Figure 4-1. Literature Search Flow Diagram of Included Studies Addressing Treatment Strategies for the Management of Adults with Primary Central Nervous System Lymphoma



*Two phase II trials reported in abstract form

Table 4-2. Studies Selected for Inclusion

Question	Number of Included Studies (ref)
1. Chemotherapy regimens for the first-line treatment of PCNS lymphoma	1 Guideline [2] 1 Systematic review [3] 2 Phase II trials [1,4]
2. Chemotherapy combined with radiotherapy compared with chemotherapy alone	1 Guideline [2] 1 Phase III non-inferiority randomized trial [10] 1 Phase II trial [11]
3. High-dose chemotherapy plus ASCT compared with standard-dose chemotherapy ± radiotherapy	1 Guideline [2] 3 Phase II trial [12,13,26]

Abbreviations: ASCT (autologous stem cell transplantation); PCNS (primary central nervous system)

Study and Patients Characteristics

This systematic review identified studies assessing treatment modalities that include chemotherapy, radiotherapy, and ASCT in the management of patients with PCNS lymphoma, and reporting the outcomes of interest. One systematic review with meta-analysis [3], six phase II trials [1,4,11-13,26], and one non-inferiority randomized phase III trial [10] were identified. See Table 4-3 for details. One guideline that had been previously identified in the search for existing guidelines [2] was also included.

Table 4-3. Summary of Included Studies

RQ 1. Chemotherapy Regimens						
Author Study/Trial, Country	**Design**	**Recruitment**	**Inclusion Criteria**	**Interventions**	**Primary Endpoint**	**Secondary Endpoint**
Kasenda, 2015 [3] Switzerland	Systematic review with individual patient data meta-analysis	Anonymized individual patient data of elderly patients with PCNS lymphoma (published and unpublished)	Studies focused on first-line therapy exclusively for ≥60-year-old patients with PCNS lymphoma	▪ HD-MTX-based therapy* vs. no HD-MTX† ▪ HD-MTX monotherapy vs. HD-MTX plus any other CT ▪ HD-MTX plus oral CT vs. HD-MTX plus at least two other IV aggressive agents ▪ HD-MTX-based CT plus WBRT vs. HD-MTX w/o WBRT	OS, PFS, CR	
Ferreri, 2016 IELSG32 [1] Switzerland	Randomized phase II trial with a double randomization	Fifty-three centres from five countries (Italy, United Kingdom, Germany, Denmark, Switzerland)	18-70 years of age, histologically proven B-cell PCNS lymphoma, no previous treatment, and an ECOG performance of ≤3 (or ≤2 for patients 66-70 years old)	1st Randomization MTX, AraC MTX, AraC, RTX MTX, AraC, RTX, THIO	CR	OR, PFS, OS, toxicity
Pulczynski, 2015 NLG [4] Nordic countries	Multicentre, single-arm phase II trial with two populations (patients aged 18-65 and those aged 66-75 years)	Twelve centres in Sweden, Norway, Denmark, and Finland	18-75 years of age, histologically confirmed PCNS lymphoma, regardless of ECOG performance score	Patients 18-65 years old RTX, MTX, IFO, DEXA, VCR, DepoCyt, CPH, AraC, VDS Patients 66-75 years old RTX, MTX, IFO, DEXA, DepoCyt, TMZ, AraC, VDS	OS	RR, PFS, systemic toxicity, neurotoxicity

RQ 2. Chemotherapy Alone vs. Chemotherapy plus Radiotherapy						
Author Study/Trial Country	**Design**	**Recruitment**	**Inclusion Criteria**	**Interventions**	**Primary Endpoint**	**Secondary Endpoint**
Korfel, 2015 G-PCNSL-SG1 [10] Germany	Non-inferiority randomized phase III trial	Seventy-five centres in Germany	≥18 years with PCNS lymphoma confirmed by histology, cytology, or immunochemistry from CSF, no previous treatment, a KPS <50% if not related to PCNS lymphoma, and or <30% if related to PCNS lymphoma	HD-MTX + WBRT vs. WBRT	OS	CR (with first-line chemotherapy, WBRT, or high-dose AraC), PFS, toxicity, delayed neurotoxicity
Glass, 2016 RTOG0227 [11] USA	Single-arm phase II trial	Participating institutions not listed	≥18 years of age with PCNS lymphoma confirmed by brain biopsy, CSF cytology, or vitrectomy	MTX, TMZ, RTX, followed by hyperfractionated WBRT and subsequent TMZ	2-year OS	Pre-irradiation CR and OR, PFS, neurologic toxicities, quality of life

RQ 3. High-Dose Chemotherapy plus Autologous Stem Cell Transplant						
Author Study/Trial Country	**Design**	**Recruitment**	**Inclusion Criteria**	**Interventions**	**Primary Endpoint**	**Secondary Endpoint**
Omuro, 2015 MSKCC [26] USA	Single-arm phase II trial	Single centre (Memorial Sloan Kettering Cancer Center, NY, USA)	18-72 years with PCNS lymphoma confirmed by MRI and histology, no previous treatment, and regardless of performance status	R-MPV (RTX, MTX, PCV, VIN) HD-CT (THIO, CTX, BUS)+ ASCT	1-year PFS	OS, toxicities, response rate after R-MPV and after HD-CTCT plus ASCT
Ferreri, 2016 IELSG32 [12] Switzerland [Abstract]	Randomized phase II trial with a double randomization	Fifty-three centres from five countries (Italy, United Kingdom, Germany, Denmark, Switzerland)	18-70 years of age, histologically proven B-cell PCNS lymphoma, no previous treatment, and an ECOG performance of <3 or lower (or ≤2 for patients 66-70 years old)	2nd Randomization WBRT HD-CT, ASCT (BCNU-thiotepa conditioned/ASCT)	2-year PFS	OS, Toxicities

RQ 3. High-Dose Chemotherapy plus Autologous Stem Cell Transplant						
Author Study/Trial Country	**Design**	**Recruitment**	**Inclusion Criteria**	**Interventions**	**Primary Endpoint**	**Secondary Endpoint**
Houillier, 2016 Anocef-Goelams [13] France [Abstract]	Randomized phase II trial	Twenty-three French centres	18-60 years of age with newly diagnosed PCNS lymphoma and measurable disease	Induction chemotherapy (R-MBVP, R-AraC) plus WBRT or intensive chemotherapy + ASCT	2-year PFS	Response rate after induction therapy, and PFS after consolidation therapy

Abbreviations: AraC (cytarabine); ASCT (autologous stem cell transplantation); BCNU (carmustine); BUS (busulfan); CPH (cyclophosphamide); CR (complete remission); CTX (cyclophosphamide); DEXA (dexamethasone); ECOG (Eastern Cooperative Oncology Group); HD-CT (high-dose chemotherapy); IFO (ifosfamide); IV (intravenous); KPS (karnofsky performance score); MRI (magnetic resonance imaging); MTX (methotrexate); OR (overall response); OS (overall survival); PCV (procarbazine); PFS (progression-free survival); R-AraC (rituximab, cytarabine); R-MBVP (rituximab, methotrexate, prednisone); RTX (rituximab); THIO (thiotepa); TMZ (temozolomide); VCR (vincristine); VDS (vindesine); VCR (vincristine); WBRT (whole brain radiation therapy).

* Defined as any therapy that contained HD-MTX-based therapies
† Including those only receiving WBRT

Study Design and Quality

The identified systematic review was assessed for quality using the AMSTAR criteria described at www.amstar.ca. The systematic review scored well. It provided valuable evidence as it focused on the optimal chemotherapy regimen for the first-line treatment of PCNS lymphoma in the elderly population, and therefore included in this review. The results of the AMSTAR assessment are presented in Appendix 5.

Only primary literature published from 2014 was considered because it corresponds to the end date of the search in the identified guideline and systematic review. Two phase II trials were also included in this review to inform recommendations surrounding the optimal chemotherapy regimen for the first-line treatment of patients with PCNSL [1,4]. The trial reported by Ferreri et al. [1] was a randomized phase II multicentre trial with random allocation schemes, and involved 227 patients with histologically confirmed PCNSL lymphoma from five countries and 53 centres. Patients were stratified according to risk score (low, intermediate, high) to ensure balance across group of homogeneous risk, and a computer-generated randomization list was used within each stratum to preserve allocation concealment. The trial met the sample size requirement of at least 42 participants per group to achieve 80% power to measure a 20% difference (45% versus 65%) in CR rates which was the primary endpoint. The statistical analysis was done by modified intention-to-treat (patients who post-hoc objectively did not meet the eligibility criteria at the time of randomization were excluded). The study reported by Pulcznski et al. [4] fully described the study design, selection criteria, the interventions, and the relevant primary and secondary outcomes. It involved 66 patients with histologically confirmed PCNS lymphoma from four countries and 12 centres, and an intention-to-treat analysis with no losses to follow-up; no additional details were reported.

Two additional studies, a single-arm phase II trial [11] and a non-inferiority randomized phase III trial [10], were included in this review to inform the recommendations surrounding chemotherapy with or without radiation for the first-line treatment of patients with PCNS lymphoma. The study reported by Glass et al. [11] included 53 participants, and reported an intention-to-treat analysis with 9% lost to follow-up. Results from this study were compared with a pre-specified cohort from trial RTOG 9310, which reported a median and two-year OS of 37 months and 64%, respectively. The non-inferiority trial reported by Korfel et al. [10] involved 410 participants from 75 centres in Germany. Patients were randomly allocated to treatment in a 1:1 ratio with block randomization using a self-written computer program, and stratified according to age (<60, ≥60), and institution. This non-inferiority trial met the sample size requirement of at least 151 participants per group to achieve 60% power to prove non-inferiority of omission of WBRT with a HR of 1.2 for WBRT versus no WBRT. Both intention-to-treat and per-protocol analyses were reported, with an 8% and 9% loss to follow-up for WBRT and non-WBRT arms, respectively.

One single-arm phase II trial [26] and two randomized phase II trials reported in abstract form [12,13] were also included in this review to inform the recommendations surrounding ASCT for the management of PCNS lymphoma. The selection criteria, the interventions, and the relevant outcomes were fully described in these trials. See Table 4-4 for study design characteristics and Appendix 6 for details on quality assessment.

Table 4-4. Study Design Characteristics of the Studies Evaluating Therapies for the Treatment of PCNS Lymphoma

RQ 1. Chemotherapy Regimens				
Author Study/Trial Period	**Method/Protocol**	**Diagnosis of PCNSL**	**N***	**Doses and Schedule**
Kasendra, 2015 [3] 1966 – Nov 2014	A systematic review of studies of first-line therapy in immunocompetent patients ≥60 years with PCNS lymphoma and an individual patient data meta-analysis from eligible studies and international collaboration		Total = 783† (33% from prospective and 67% from retrospective studies) ▪ HD-MTX-based therapy‡ vs. no HD-MTX§ : 573 vs. 210 ▪ HD-MTX monotherapy vs. HD-MTX plus any other CT: 72 vs. 501 ▪ HD-MTX plus oral CT vs. HD-MTX plus at least two other IV aggressive agents: 195 vs. 146	Median dosages/Median number of applications HD-MTX-based CT (n=573): 3 g/m^2 (1-8 g/m^2)**/4 (1-29) WBRT (n=276): 36 Gy (28.5-70 Gy)
Ferreri, 2016 IELSG32 [1] Feb 2010-Aug 2014	Phase II trial evaluating the potential clinical benefit of adding rituximab with or without thiotepa to the methotrexate-cytarabine combination backbone (first randomization)	Histologically confirmed	Total = 227 MTX, AraC: 75 MTX, AraC, RTX: 74 MTX, AraC, RTX, THIO: 78	First Randomization: Four IV cycles (every 3 weeks) MTX: 3.5 g/m^2 (0.5 g/m^2 in 15 min, followed by 3 g/m^2 in 3-h infusion) on day 1 ARA-C: 2 g/m^2 in 1 h infusion, twice a day every 12 h on days 2-3 RTX: 375 mg/m^2 as a conventional infusion on days -5 & 0 THIO: 30 mg/m^2 in 30 min infusion on day 4

RQ 1. Chemotherapy Regimens				
Author Study/Trial Period	**Method/Protocol**	**Diagnosis of PCNSL**	**N***	**Doses and Schedule**
Pulczynski, 2015 NLG [4] May 2007-Oct 2010	Multicentre, single-arm phase II trial with 2 populations, to investigate the efficacy and safety of HD-MTX/HD-AraC-based multi-agent immunotherapy regimen with CSF targeted treatment but without radiotherapy Populations: patients aged 18-65 years and patients aged 66-75 years)	Histologically confirmed	Patients 18-65 years old RTX, MTX, IFO, DEXA, VCR, DepoCyt, CPH, AraC, VDS: 39 Patients 66-75 years old RTX, MTX, IFO, DEXA, DepoCyt, TMZ, AraC, VDS: 26	Patients aged 18-65 (six cycles; 3-week interval between cycles) RTX: 375 mg/m^2 IV on day 1 (cycle 1) MTX††: 5.0 g/m^2 IV on day 1 (cycle 1,2,4, and 5) IFO: 800 mg/m^2 IV on days 2-5 (cycle 1 and 4) DEXA: 10 mg/m^2 PO on days 2-5 (cycle 1, 2, 4, and 5) and on days 3-7 (cycle 3 and 6) VCR: 2 mg IV on day 1 (cycle 2 and 5) DepoCyt: 50 mg ISP on day 2 (cycle 1, 2, 4, and 5) CPH: 200 mg/m^2 IV on days 2-5 (cycle 2 and 5) AraC: 1.5 g/m^2 X 2 IV on day 1-2 (cycle 3 and 6) VDS: 5 mg IV on day 1 (cycle 3 and 6) Patients aged 66-75 (six cycles; 3-weeks interval between cycles) RTX: 375 mg/m^2 IV on day 1 (cycle 1) MTX: 3 g/m^2 IV on day 1 (cycle 1, 2, 4, and 5) IFO: 800 mg/m^2 IV on days 2-5 (cycle 1) DEXA: 10 mg/m^2 PO on days 2-5 (cycle 1, 2, 4, and 5) and on days 3-7 (cycle 3 and 6) DepoCyt: 50 mg ISP on day 2 (cycle 1, 2, 4, and 5) TMZ: 150/m^2 mg PO on days 2-6 (cycle 2, 4 and 5) AraC: 1g/m^2 X 2 IV on day 1-2 (cycle 3 and 6) VDS: 5 mg IV on day 1 (cycle 3 and 6) Maintenance Treatment: TZM 150/m^2 days 1-5 at an interval of 28 days. Started one month after completion of induction therapy and continued for one year or until relapse/progression.

Abbreviations: AraC (cytarabine); BCNU (carmustine); CPH (cyclophosphamide); CSF (cerebrospinal fluid); DEXA (dexamethasone); HD-AraC (high-dose cytarabine); HD-MTX (high-dose methotrexate); IC-SCT (intensive chemotherapy and hematopoietic stem cell transplantation); IFO (ifosfamide); ISP (intraspinally); IV (intravenous); MTX (methotrexate); PCNS (primary central nervous system); R-MPV (rituximab, methotrexate, procarbazine, vincristine); RTX (rituximab); THIO (thiotepa); TMZ (temozolomide); VCR (vincristine); VDS (vindesine); WBRT (whole brain radiation therapy);

* As randomized, unless otherwise specified
† 405 individual patient data from identified studies, and 378 published and unpublished patient data from 6 other databases (Milan, Boston, Tel Aviv from Israel, Rochester)
‡ Defined as any therapy that contained HD-MTX-based therapies
§ Including those only receiving WBRT
** 77% of the patients received ≥3g/m^2
†† Infusion time was reduced from 24 to 3 h as it has been reported that a higher drug penetration is achieved by a shorter infusion time (Hiraga et al., 1999)

RQ 2. Chemotherapy Alone vs. Chemotherapy plus Radiotherapy				
Author Study/Trial Period	**Method/Protocol**	**Diagnosis of PCNSL**	**N***	**Doses and Schedule**
Korfel, 2015 G-PCNSL-SG1 [10] 1999 – 2009	Non-inferiority design with a margin of 0.9† to test the hypothesis that first-line HD-MTX-based chemotherapy alone is not inferior to primary chemotherapy followed by WBRT	Confirmed by histology, cytology, or immunocytoch emistry from CSF	Total = 410 HD-MTX, WBRT: 202 HD-MTX: 208	First-Line Chemotherapy - HD-MTX: 4 g/m^2 over 4 h within 14 days (six 14-day intravenous cycles) Arm A (WBRT: 45 Gy in 1.5 Gy daily) o If CR achieved: 4-7 weeks after completion of first-line CT o Not CR: As a rescue in patients without CR Arm B (No WBRT) o If CR achieved: No further treatment o Not CR: Second-line CT with HD-AraC (3 g/m^2 over 3 h/day 1-2; four 21-day cycle)
Glass, 2016 RTOG 0227 [11]	Phase II trial to investigate the efficacy of induction chemotherapy with MTX, TMZ, and RTX, followed by hyperfractionated WBRT and subsequent TMZ	Brain biopsy, cerebrospinal fluid cytology, or vitrectomy confirmed	Total = 53	Pre-RT Chemotherapy RTX: 375 mg/m^2, 3 days prior first cycle of MTX MTX‡: 3.5 g/m^2 on weeks 1, 3, 5, 7, 9 (5 cycles) TMZ: 100 mg/m^2§ daily for 5 days, week 4 and 8 RT – hyperfractionated WBRT WBRT: 1.2 Gy twice-daily fractions, 5 days per week on weeks 11, 12, 13 for a total of 36 Gy Post-RT Chemotherapy TMZ: 200 mg/m^2 daily for 5 days on weeks 14, 18, 22, 26, 30, 34, 38, 42, 46, 50 (10 cycles)

Abbreviations: AraC (cytarabine); BCNU (carmustine); CPH (cyclophosphamide); DEXA (dexamethasone); HD-AraC (high-dose cytarabine); HD-MTX (high-dose methotrexate); IC-SCT (intensive chemotherapy and hematopoietic stem cell transplantation); IFO (ifosfamide); MTX (methotrexate); PCNS (primary central nervous system); R-MPV (rituximab, methotrexate, procarbazine, vincristine); RT (radiation therapy); RTX (rituximab); THIO (thiotepa); TMZ (temozolomide); VCR (vincristine); VDS (vindesine); WBRT (whole brain radiation therapy).

* As randomized, unless otherwise specified

† First-lime HD-MTX chemotherapy alone was defined as non-inferior to WBRT if the lower 95% confidence interval of the Hazard Ratio of WBRT vs. first-lime HD-MTX chemotherapy without WBRT was not below 0.9

‡ Each dose was followed 24 hours later by leucovorin 25 mg IV every 6 hours

§ Maximum tolerated dose (MTD) from phase I study

RQ 3. High-Dose Chemotherapy plus Autologous Stem Cell Transplant				
Author Study/Trial Period	**Method/Protocol**	**Diagnosis of PCNSL**	**N***	**Doses and Schedule**
Omuro, 2015 MSKCC [[26]] Jun 2005-Sept 2011	Single-centre phase II trial of high-dose chemotherapy with ASCT as an alternative to address chemo-resistance and overcome the blood-brain barrier	Confirmed by MRI and histology	Total = 33 R-MPV (32)† HDC+ASCT (26/31)‡ (HDC: THIO, CTX, BUS)	R-MPV Induction (1 cycle = 14 days) RTX: 500 mg/m^2 IV on day 1 MTX: 3.5 mg/m^2 IV on day 2, over 2 hours VCR: 1.4 mg/m^2 (capped at 2.8 mg) PCZ: 100 mg/m^2 per day on days 2 to 8 during odd cycles Harvesting and HSCT: Patients in CR/PR only THIO: 250 mg/m^2 IV on days -9, -8 and -7 BUS: 3.2 mg/Kg IV on days -6, -5, and -4 CTX: 60 mg/kg IV on days -3 and -2 Stem cell Infusion: On day 0
Ferreri, 2016 IELSG32 [12] Feb 2010-Aug 2014 [Abstract]	Phase II trial evaluating the efficacy and neurotolerability of ASCT, as an alternative to WBRT as consolidation (second randomization)	Histologically confirmed	Total = 118 WBRT: 55 ASCT: 58	Second Randomization WBRT: by two opposite lateral fields including the first two cervical vertebrae and the posterior two-thirds of the orbits with 36 ± 9 Gy ASCT BCNU: 400 mg/m^2 on day -6 THIO: 5 mg per kg every 12 h on days -5 and -4 ASCT
Houillier, 2016 Anocef-Goelams [13] [Abstract]	Randomized phase II trial evaluating the efficacy and toxicity of a standard chemo-immunotherapy followed by either WBRT or IC-SCT	NR	Total = 140 WBRT = 70 IC + SCT = 70	Induction Chemotherapy: 2 cycles of R-MBPV & 2 cycles of R-AraC R-MBVP RTX (375 mg/m^2 D1); MTX (3 g/m^2 D1, D15); VP16 (100 mg/m^2 D2) BCNU (100 mg/m^2 D3); Prednisone (60 mg/kg/day on D1-D5) R-AraC RTX (375 mg/m^2 D1); AraC (3 g/m^2 D1, D2) Consolidation Therapy: WBRT or IC-SCT as follows: THIO: 250 mg/mg/m2/day on D -9 through -7 Busulfan: 10 mg/kg (total dose) days -6 through -4 CPH: 60 mg/kg/day D -3 and -2

Abbreviations: AraC (cytarabine); BCNU (carmustine); CPH (cyclophosphamide); CR (complete response); DEXA (dexamethasone); HD-AraC (high-dose cytarabine); HD-MTX (high-dose methotrexate); HSCT (hematopoietic stem cell transplantation); IC-SCT (intensive chemotherapy and hematopoietic stem cell transplantation); IFO (ifosfamide); MRI (magnetic resonance imaging); MTX (methotrexate); R-MBPV (rituximab, methotrexate, etoposide, carmustine, prednisone); VDS (vindesine); R-MPV (rituximab, methotrexate, procarbazine, vincristine); RTX (rituximab); THIO (thiotepa); TMZ (temozolomide); VCR (vincristine); VP16 (etoposide).

* As randomized, unless otherwise specified

† Patients in partial response (PR) or stable disease (SD) received 2 additional cycles and proceed with HDC+ASCT if PR/CR was observed; otherwise, t
‡ Five patients did not undergo transplant because of refusal (n=2) or physician's decision (n=3) and were removed from the study (no harvesting failu

Outcomes: Chemotherapy Regimens as a Single Modality Treatment

1. Optimal Chemotherapy Regimen(s) for the First-Line Treatment of Patients with PCNS lymphoma (Table 4-5; RQ 1)

Systematic Reviews

One systematic review with an individual patient data meta-analysis was identified that investigated prognosis and treatment strategies for elderly patients (≥60 years) with newly diagnosed PCNS lymphoma [3]. The systematic review identified 20 eligible studies (one randomized phase II trial and 19 single-arm studies) published between 1996 and 2014 including 1103 patients. From the identified studies, individual patient data from 405 (40%) patients were available for meta-analysis and pooled with published and unpublished patient data from 378 patients from six other databases (international collaborators), for a total of 783 patients. Most of the data were collected retrospectively (67%). Median age for the entire cohort was 68 years and 37% were >70 years old. In a multivariable Cox regression analysis after a median follow-up of 40 months (95% CI, 36 to 47), HD-MTX-based chemotherapy was associated with improved survival compared with treatment that did not include HD-MTX (HR, 0.70; 95% CI, 0.53 to 0.93; p=0.013). Patients treated with HD-MTX in combination with other chemotherapeutic agents had prolonged PFS and OS compared with HD-MTX monotherapy (PFS: HR, 0.39; 95% CI, 0.27 to 0.58; p<0.001; and OS: HR, 0.54; 95% CI, 0.35 to 0.84; p=0.006). Therapies with HD-MTX plus at least two other intravenous agents were not associated with improved PFS or OS when compared with HD-MTX plus oral chemotherapy.

Primary Literature

One international randomized phase II trial by Ferreri et al. [1] and one multicentre single-arm phase II trial by Pulczynski et al. [4], published between 2014 and 2016, were identified that investigated the efficacy of systemic chemotherapy regimens in the treatment of patients with PCNS lymphoma.

The randomized phase II trial by Ferreri et al. [1] was published on behalf of the IELSG32. This is the first prospective randomized comparison of first-line combination chemotherapy regimens incorporating rituximab and a CNS-penetrating alkylating agent (thiotepa) in combination with HD-MTX and cytarabine. In this randomized, open-label, multicentre trial, untreated HIV-negative patients (age 18 to 70 years, ECOG ≤3) with PCNS lymphoma were randomly allocated to receive four cycles of HD-MTX plus cytarabine combination chemotherapy in one of three study arms: HD-MTX plus AraC alone; HD-MTX and AraC plus rituximab; or HD-MTX, AraC, and rituximab, plus thiotepa. Patients with a response assessed as stable disease or better were eligible for a second randomization between WBRT (36 Gy with a 9 Gy boost in partial responders) and ASCT (carmustine, thiotepa conditioning). The primary endpoint at first randomization was centrally assessed CRR and at second randomization was two-year PFS. Secondary endpoints included toxicity, OS, relapse rates, and neurotoxicity (assessed prospectively using the Mini-Mental State Examination (MMSE) and a panel of neuropsychiatric tests). At a median follow-up of 30 months, a statistically significant improvement in CRR, PFS, and OS were observed in patients treated with MTX-AraC-rituximab and thiotepa when compared with MTX-AraC combination therapy (CR, 0.46; 95% CI, 0.28 to 0.74; p=0.0007; PFS, 0.38; 95% CI, 0.24 to 0.61; p=0.00089; and OS, 0.41; 95% CI, 0.25 to 0.68; p=0.0015). Hematological toxicity was more common in patients treated with rituximab and thiotepa (67%) than in patients treated with MTX and AraC with or without rituximab (56% and 5%, respectively). Infective complications were similar across groups, and non-hematological toxicities were rare (Appendix 8). Results from the second randomization and neurocognitive outcomes have been reported in abstract form and summarized below.

The study by Pulczynski et al. [4] investigated the efficacy and safety of HD-MTX/HD-AraC-based therapy in two populations: patients aged 18 to 65 years and patients aged 66 to 75 years. The treatment was age-adjusted: patients older than 65 years received temozolomide instead of cyclophosphamide, and only ifosfamide cycle 1; vincristine was not used as part of the chemotherapy regimen in the elderly population. Maintenance treatment with temozolomide was also administered to improve disease control among patients older than 65 years who responded to reduced-intensity induction therapy. The ORR was 73.8% (69.2% in the younger and 80.8% in the elderly population); CRR were 59% and 57.7% for the younger and the elderly populations, respectively. The authors reported comparable PFS and OS rates for both the patients aged 18 to 65 years and patients older than 65 years (PFS: 33.1% versus 44.4%, p=0.74; OS: 60.7% versus 55.6%; p=0.40). Although the authors concluded that de-escalation of the induction therapy followed by maintenance treatment seems to be a promising strategy for the treatment of elderly patients with PCNS lymphoma, they recognized that HD-AraC toxicity is still of concern in this population and propose either the omission of this agent from the regimen, or a further de-escalation of induction in elderly patients to reduce toxicity.

2. *Chemotherapy with or without Radiation Therapy for the First-Line Treatment of Patients with PCNS lymphoma (Table 4-5; RQ 2)*

Two of the studies reported on strategies including chemotherapy and radiotherapy for the first-line treatment of patients with PCNS lymphoma, a non-inferiority randomized phase III trial by Korfel et al. [10] and a single arm-phase II trial by Glass et al. [11]. The study by Korfel et al. [10] hypothesized that the omission of WBRT in the treatment of patients with PCNS lymphoma receiving chemotherapy based on HD-MTX would not compromise OS. OS results at a shorter median follow-up (53.7 months) and as per-protocol analysis have been previously reported by Thiel et al. [27], and were considered in the recommendations from the European Association for Neuro-Oncology guideline. Korfel et al. (2015) presented an updated and final analysis including an intention-to-treat and a new as-treated analysis after a follow-up of 81.2 months. Results reported in the first publication were confirmed by the final report. Although the intention-to-treat analysis indicated a statistically significant improvement in PFS of patients receiving WBRT when compared with those treated without WBRT (15.4 versus 9.9 months; HR, 0.79; 95% CI, 0.64 to 0.98; p=0.034), comparable survival rates were reported (32.4 versus 36.1 months; HR, 0.98; 95% CI, 0.79 to 1.26; p=0.98). Statistical proof that WBRT can be omitted from first-line treatment of PCNS lymphoma without compromising OS using a non-inferiority design was not given; the study design stated that the 95% CI of the HR of WBRT versus no WBRT should be below 0.9 to prove non-inferiority. According to the authors, this study provides class II evidence that the OS of patients treated for PCNS lymphoma with HD-MTX-based chemotherapy does not significantly increase with the addition of WBRT in the treatment regimen; however, they also recognized the need of a randomized controlled trial to establish whether reduced-dose WBRT is safe and/or necessary for improved outcome in such populations.

Glass et al. [11] investigated whether PFS and OS of patients with PCNS lymphoma would be prolonged when treated with MTX, temozolomide, and rituximab, followed by hyperfractionated WBRT and subsequent temozolomide maintenance therapy. Complete remission was observed in 51% of assessable patients (18 of 35). The authors reported improved two-year PFS (63.6%; HR, 0.52; 95% CI, 0.30 to 0.89; p=0.018) and OS rates (80.8%; HR, 0.44; 95% CI, 0.25 to 0.80; p=0.007) when compared with historical controls from the RTOG 9310 trial (PFS, 50% and OS, 64%) which prospectively studied the efficacy of HD-MTX, vincristine, and procarbazine followed by WBRT and cytarabine [28]. Most of the reported toxicities were grade 3 occurring before radiation therapy; hematological toxicities were mainly attributed to chemotherapy. The median Spitzer quality of life scores increased in assessable patients from

baseline of 6 to 7 after radiation therapy, to 8 at six months, and to 10 at three years. The median baseline MMSE score was 28, and increased to 29 at each of the follow-up points (post-radiation, six months, and three years). The mean improvement in MMSE score was 2.1 after WBRT, 2.0 at six months after diagnosis, and 1.4 at year 3. Significant declines in MMSE score were seen in 3% (one of 33 assessable patients) post-radiotherapy and in 2.6% (one of 38 assessable patients) six months post-radiotherapy. An increase in MMSE score at three years was more pronounced in patients aged ≥60 years.

3. High-Dose Chemotherapy plus Autologous Stem Cell Transplantation for both the First-Line Treatment of Patients with PCNS lymphoma, and the Treatment of Patients with Relapsed/Refractory CNS lymphoma (Table 4-5; RQ 3)

One single-arm phase II trial by Omuro et al. [26] and two randomized phase II trials in abstract form [12,13] reported on outcomes from patients newly diagnosed with PCNS lymphoma and treated with HD-CT and ASCT. The single-arm phase II trial by Omuro et al [26] reported a treatment plan of five to seven cycles of chemotherapy with rituximab, MTX, procarbazine, and vincristine (R-MPV) as induction therapy; those with complete or partial remission proceeded with consolidation HD-CT with thiotepa, cyclophosphamide, and busulfan, followed by ASCT. The ORR defined as CR, unconfirmed complete response, or partial response after induction therapy was 97% (95% CI, 83 to 100). The reported two-year PFS and OS in transplanted patients was 81% (95% CI, 60 to 92) for both. Medians for PFS and OS were not reached. Induction therapy was well tolerated. Two patients died from transplant-related complications and another patient aged 61 developed a fatal chronic colitis of undetermined etiology. Self-reported quality of life significantly improved over baseline Functional Assessment of Cancer Therapy-Brain scores with slowed improvement by 12 to 18 months post-transplant. The authors reported no clinical neurotoxicities (neurologic deterioration in the absence of disease progression). Continuous improvement in scores from baseline over time were reported; however, the rate of cognitive improvement slowed by 12 to 18 months post-transplant. Analysis of white matter abnormalities showed an improvement after R-MPV, with 81% of patients displaying scores of 2 to 3 at baseline, compared with 19% after R-MPV (p=0.002). Following transplant, there was an increase in white matter abnormalities, with 44% of patients with scores of 2 to 3 (p=0.046), which then remained stable over time. No scores above 3 were seen at any time.

Ferreri et al. [12] reported the results of the second randomization from the international randomized phase II IELSG32 trial, comparing consolidation chemotherapy with WBRT versus ASCT in patients with PCNS lymphoma (age 18 to 70 years, ECOG ≤3). The IELSG32 trial randomly allocated 118 patients with responsive or stable disease after chemoimmunotherapy (MATRix regimen) between WBRT (36±9 Gy) and ASCT (59 patients per group). Per-protocol groups consisted of 55 patients treated with WBRT and 58 with ASCT. The authors reported comparable two-year PFS and OS rates for both the patients treated with WBRT and patients treated with ASCT (PFS: 80±5% versus 70±6%; OS: 85±5% versus 71±6%, p=0.12). Comparison of WBRT with ASCT reported significant impairment of attention/executive functions and non-significant trend to impaired memory in patients treated with WBRT, while improved functions were observed in patients treated with ASCT. Both consolidation therapies were reported to be associated with significant improvement in language and quality of life. Further information surrounding quality of life and neurotoxicity have not been reported, but are expected to be available when results from the second randomization addressing the role of consolidation therapy are fully published.

The Anocef-Goelams trial [13] randomized patients treated with rituximab, methotrexate, and prednisone (R-MBVP) and rituximab and cytarabine (R-AraC) as induction chemotherapy to receive WBRT or ASCT as consolidation treatment. WBRT was given to 53

patients and intensive chemotherapy plus ASCT was given to 44 patients. Overall response rate after consolidation treatment was 71% and 67% for WBRT and intensive chemotherapy-ASCT, respectively. Relapses after the end of the treatment occurred in 16 patients treated with WBRT in five treated with ASCT, with a median time to relapse of 15.1 and 8.5 months, respectively. At a median follow-up of 33 months, two-year PFS was 86.8% (95% CI, 76.6 to 98.3) and 63.2% (95% CI, 49.5 to 80.5) for patients in the ASCT and WBRT arm, respectively. The neurological evaluations have not yet been reported.

Table 4-5. Outcomes

RQ 1. Chemotherapy Regimens						
Author Study / Trial	**Intervention (n)**	**Complete Remission**	**Overall Remission***	**PFS**	**OS**	**Toxicities**
Kasenda, 2015 [3]	HD-MTX-based therapy vs. Therapies without HD-MTX	73% 55% p=NS.		HR: 0.80 [0.61-1.04] p=0.100	HR: 0.70 [0.53-0.93] p=0.013	
	HD-MTX plus other CT vs. HD-MTX monotherapy	73% 68% p=Significant		HR: 0.39 [0.27-0.58] p<0.001	HR: 0.54 [0.35-0.84] p=0.006	
	HD-MTX plus at least 2 other IV aggressive agents vs. HD-MTX plus oral CT		73% 75%	HR: 1.26 [0.80-1.99] p=NS	HR: 1.39 [0.90-2.15] p=0.143	
	Follow-up: 40 (36-47) mo.					

RQ 1. Chemotherapy Regimens						
Author Study / Trial	**Intervention (n)**	**Complete Remission**	**Overall Remission***	**PFS**	**OS**	**Toxicities**
Ferreri, 2016 IELSG32 [1]	A: MTX, AraC (75)	23%; $HR_{(A\ vs\ B)}$: 0.74 [0.43-1.29] p=0.29	53%; $HR_{(A\ vs\ B)}$: 0.69 [0.54-0.88] p=0.010	2-year 36%; $HR_{(A\ vs\ B)}$: 0.52 [0.32-0.86] p=0.051	36%; $HR_{(A\ vs\ B)}$: 0.63 [0.42-1.02] p=0.095	Grade 4 hematological toxicities were more common in patients treated with RTX and THIO than in patients treated with two other groups; infective complications were similar in the 3 groups; and grade 4 non-hematological toxicities were rare (see Appendix 8 for further details).
	B: MTX, AraC, RTX (69)	30%; $HR_{(B\ vs\ C)}$: 0.61 [0.40-0.94] p=0.020	74%; $HR_{(B\ vs\ C)}$: 0.89 [0.76-1.03] p=0.053	46%; $HR_{(B\ vs\ C)}$: 0.72 [0.46-1.13] p=0.12	52%; $HR_{(B\ vs\ C)}$: 0.78 [0.48-1.26] p=0.12	
	C: MTX, AraC, RTX, THIO (75)	49%; $HR_{(A\ vs\ C)}$: 0.46 [0.28-0.74] p=0.0007	87%; $HR_{(A\ vs\ C)}$: 0.61 [0.49-0.77] p=0.00001	61%: $HR_{(A\ vs\ C)}$: 0.38 [0.24-0.61] p=0.00089	67%; $HR_{(A\ vs\ C)}$: 0.41 [0.25-0.68] p=0.0015	
	Follow-up: 30 (12-66) mo.	$OR_{(C\ vs\ A)}$: 3.32 [1.64-6.72] p=0.00083				
		$OR_{(C\ vs\ B)}$: 2.23 [1.12-4.41] p=0.021				
Pulczynski, 2015 NLG [4]	18-65 years old RTX, MTX, IFO, DEXA, VCR, DepoCyt, CPH, AraC, VDS (39)	59.0%	69.2% Median: 10 mo.	2-year 33.1% [19.1-47.9]	2-year 60.7% [43.3-74.2] Median not reached	**Hematological** HD-AraC-related: myelosuppression with gr 3-4 anemia (16.1%), neutropenia (89.3%), and thrombocytopenia (80.9%).
	66-75 years old RTX, MTX, IFO, DEXA, DepoCyt, TMZ, AraC, VDS (26)	57.7%	80.8% Median not reached	44.4% [25.6-61.8] p=0.74	55.6% [35.2-71.8] p=0.40 Median not reached	Four patients died after the first course due to neutropenia and sepsis-induced multi-organ failure (aged 64, 66, 73, 74 years).
	Follow-up: 22 (1-57) mo.		Entire cohort: 73.8%	Entire cohort: 37.8% [26.3-49.3]	Entire cohort: 58.7% [45.8-69.5]	HD-MTX-related: Relatively well tolerated with 1.5% anemia, 25.8% gr 3-4 neutropenia, and 10.6% thrombocytopenia. See Appendix 9.

Note: OR comparisons are in opposite order to the rest of the data

RQ 2. Chemotherapy Regimens with or without Radiation Therapy

Author Study / Trial	Intervention (n) Follow-up	PFS	OS	Toxicities
Korfel, 2015 G-PCNSL-SG1 [10]	**Per-Protocol** First-Line treatment (HD-MTX) with WBRT (n=154) ○ CR (56) ○ No CR (98) First-Line treatment (HD-MTX) without WBRT (n=166) ○ CR (96) ○ No CR (70) Follow-up: 81.2 mo.	**Per-Protocol Analysis** <u>ALL Patients</u> ○ Overall 18.2 vs. 11.9 mo. HR: 0.83 [0.65-1.06] p=0.14 ○ Post-first-line CT† 25.5 vs. 12.0 mo HR: 0.65 [0.5-0.83] p=0.001 <u>Patients with CR</u> ○ Overall 42.5 vs. 22.3 mo. HR: 0.69 [0.46-1.03] p=0.065 ○ Post-first-line CT 40.1 vs. 19.1 mo. HR: 0.68 [0.46-1.01] p=0.057 <u>Patients without CR</u> ○ Overall 5.0 vs. 2.9 mo. HR: 0.6 [0.43-0.83] p=0.002 ○ Post-first-line CT 16.1 vs. 2.9 mo. HR: 0.41 [0.29-0.57] p<0.001 **As-Treated Analysis** <u>Patients with CR</u> ○ Post-first-line CT 33.8 vs. 19.0 mo HR: 0.64 [0.44-0.94] p=0.025 <u>Patients without CR</u> Post-first-line CT ○ With WBRT: 15.9 ○ Second-line CT: 3.2 ○ No further Therapy: 8.9 HR: 0.47 [0.35-0.62] p<0.001	**Per-Protocol Analysis** <u>ALL Patients</u> ○ Overall 35.6 vs 37.1 mo. HR: 1.03 [0.79-1.35] p=0.82 ○ Post-first-line CT 25.5 vs. 12.0 mo HR: 0.65 [0.5-0.83] p=0.001 <u>Patients with CR</u> ○ Overall 44.2 vs. 59.0 mo. HR: 1.06 [0.69-1.63] p=0.78 <u>Patients without CR</u> ○ Overall 27.4 vs. 18.2 mo. HR: 0.76 [0.54-1.08] p=0.119 **As-Treated Analysis** <u>Patients with CR</u> ○ Overall 51.9 vs. 59.0 mo. HR: 0.93 [0.68-1.53]‡ p=0.95 <u>Patients without CR</u> Post-first-line CT ○ With WBRT: 23.8 ○ Second-line CT: 14.8 ○ No further Therapy: 27.5 HR: 0.76 [0.56-1.02] p=0.172	<u>Hematological§</u> <u><60 yrs. vs. ≥60 yrs.</u> Leukopenia 14% vs. 29% Infections 18% vs. 32% Anemia 8% vs. 17% Thrombocytopenia 5% vs. 15% Elevation of urea or creatinine: 2% vs. 4% <u>Neurotoxicity WBRT vs. No WBRT</u>: • Clinical assessment 49% vs. 26% (p=0.054) • Neuroradiology assessment (MRI or CT) 71% vs. 46% (p=0.04) Neurotoxicity data were available for 79 patients, at a median follow-up of 49.2 mo (45 pts receiving WBRT with a median age of 62 yrs, and 34 pts not receiving WBRT with a median age of 63 yrs.)

RQ 2. Chemotherapy Regimens with or without Radiation Therapy						
Author Study / Trial	**Intervention (n) Follow-up**	**PFS**		**OS**		**Toxicities**
Korfel, 2015 G-PCNSL-SG1 [10]	**Intention-to-Treat** First-line treatment (HD-MTX) with WBRT (n=202) ○ CR: 87 ○ No CR:115 First-line Treatment (HD-MTX) without WBRT (208) ○ CR: 97 ○ No CR:111	**Intention-to-Treat** ALL Patients ○ Overall 15.4 vs. 9.9 mo. HR: 0.79 [0.64-0.98]	p=0.034	**Intention-to-Treat** ALL Patients ○ Overall 32.4 vs. 36.1 mo. HR: 0.98 [0.79-1.26]	p=0.98	
		○ Post-first-line CT** 19.4 vs. 11.9 mo HR: 0.72 [0.58-0.89]	p=0.003			
		Patients with CR ○ Overall 29.9 vs. 25.7 mo. HR: 0.85 [0.6-1.2]	p=0.35	Patients with CR ○ Overall 51.3 vs. 61.0 mo. HR: 1.13 [0.77-1.66]	p=0.53	
		○ Post-first-line CT 27.8 vs. 23.4 mo. HR: 0.84 [0.6-1.19]	p=0.33			
		Patients without CR ○ Overall 4.7 vs. 2.9 mo. HR: 0.67 [0.51-0.89]	p=0.004	In non-CR Patients ○ Overall 20.7 vs. 18.6 mo. HR: 0.86 [0.64-1.16]	p=0.32	
		○ Post-first-line CT 15.5 vs. 5.7 mo. HR: 0.58 [0.44-0.77]	p<0.001			

RQ 2. Chemotherapy Regimen with or without Radiation Therapy						
Trial	**Intervention Follow-up**	**Complete Remission**	**Overall Remission††**	**PFS**	**OS**	**Toxicities**
Glass, 2016 RTOG 0227 [11]	RTX, MTX, TMZ, WBRT, TMZ (53) Follow-up: 3.6 years	Pre-Irradiation CT Assessable: 35 Incomplete data: 18 CR: 51% (18/35)	Pre-Irradiation CT Assessable: 35 Incomplete data: 18 OR: 86% (30/35)	2-year: 63.6% Median 5.4 years [1.8-7.3]	2-year: 80.8% Median: 7.5 years [4.3-not reached]	Most toxicities were grade 3, occurring before radiation therapy (11 hematological, 6 hepatic, 6 metabolic, 5 neurological, and 3 renal/GU). Hematologic toxicities that occurred during hWBRT (n=6) were attributed to prior chemotherapy. Late radiotherapy toxicity was low • Grade 3: 1 brain, 1 hearing loss, and 1 leukoencephalopathy . • Grade 4: 1 thrombocytopenia).

* Complete response plus partial response
† PFS was calculated from termination of first-line chemotherapy to progression or death to better assess the role of second-line chemotherapy (HD-AraC or WBRT); patients in complete remission were compared to patients in partial remission, stable disease, and progressive-disease pooled)
‡ It is not clear to which comparison the HR is referring to
§ Results reported in previous publication
** To better assess the role of second-line chemotherapy (HD-AraC or WBRT), PFS was calculated from termination of first-line chemotherapy to progression or death (Patients in complete remission were compared to patients in partial remission, stable disease, and progressive-disease pooled)
†† Complete response plus partial response

RQ 3. High-Dose Chemotherapy Regimen plus Autologous Stem Cell Transplant					
Author Study / Trial	**Intervention Follow-up**	**Overall Remission***	**PFS**	**OS**	**Toxicities**
Front Line Setting					
Omuro, 2015 MSKCC [26]	R-MPV (32)[†]	Objective OR[§]: 31/32 97% [83-100]	**Entire Cohort n=32** Median PFS was not reached 1-year PFS: 82% [62-92] 2, 3, 5-year PFS estimates: 79% [58-90]	**Entire Cohort n=32** Median OS was not reached 1-year PFS: 88%[70-95] 2, 3, 5-year PFS estimates: 81% [63-91]	Induction R-MPV was well tolerated, with no treatment-related deaths and no treatment discontinuation because of toxicity. Three patients died from transplant-related complication (Stevens-Jonson syndrome, septic shock , and colitis
	HD-CT (THIO, CTX, BUS) + ASCT (26/31[‡]) Follow-up: 45 (27-86) mo.		**Transplanted n=26** Median PFS was not reached 1-year PFS: 85% [64-94] 2, 3, 5-year PFS estimates: 81% [60-92]	**Transplanted n=26** Median OS was not reached 1-year PFS: 88%[68-96] 2, 3, 5-year PFS estimates: 81%[60-92]	
Ferreri, 2016 IELSG32 [12] [Abstract]	WBRT		2-year ITT: 80 ± 5% PP: 76 ±6%	2-year 85 ± 5% (42 pts. alive)	WBRT vs. ASCT: Neutropenia 5% vs. 71%, thrombocytopenia 2% vs. 72%, toxic deaths 0 vs. 2.
	BCNU-thiotepa conditioned / ASCT		2-year ITT: 70 ± 6% PP: 75 ± 6%	2-year 71 ±6% (37 pts. alive) *P*=0.12	Significant impairment of attention/executive functions vs. improved functions
Houillier, 2016 Anocef-Goelams [13] [Abstract]	WBRT (53)	71%	2-year WBRT: Pending results	NR	Three treatment-related deaths were reported after IC+SCT. Other two deaths occurred during induction chemotherapy in the group assigned to receive WBRT. Neuropsychological evaluation is pending
	IC + SCT (44) Follow-up WBRT: 27.2 mo IC+SCT: 28.6mo	67%	IC+SCT: 86.8% [76.6-98.3]		

Abbreviations: AraC (cytarabine); BUS (busulfan); CPH (cyclophosphamide); CT (chemotherapy); CTX (cyclophosphamide); DEXA (dexamethasone); GU (genitourinary); HD-AraC (high-dose cytarabine); HD-MTX (high-dose methotrexate); HR (hazard ratio); hWBRT (hyperfractionated whole brain radiation therapy); IFO (ifosfamide); ITT (intention-to-treat);

mo (month); MTX (methotrexate); NR (not reported); OR (odds ratio); OS (overall survival); PFS (progression-free survival); PP (per-protocol); R-MPV (rituximab, methotrexate, procarbazine, vincristine); RTX (rituximab); THIO (thiotepa); TMZ (temozolomide); VCR (vincristine); VDS (vindesine); WBRT (whole brain radiation therapy).

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* Complete response plus partial response
† Induction R-MPV was well tolerated, with no treatment-related deaths and no treatment discontinuation because of toxicity
‡ Five patients did not undergo transplant because of refusal (n=2) or physician's decision (n=3) and were removed from the study (no harvesting failures)
§ Objective response rate is defined as CR, CRu, or PR after 5 or 7 cycles in eligible patients with measurable disease

Search for Ongoing Trials

The clinical trials registry (www.clinicaltrials.gov) was searched for information on relevant studies using the terms "Primary central nervous system lymphoma" and "treatment" on September 6, 2016. A total of 145 trials were identified, but only 11 met the inclusion criteria for this evidentiary base; their details are given in Table 4-6.

Table 4-6. Ongoing Trials Surrounding the Treatment for Central Nervous System Lymphoma

Protocol ID	Title, details
Chemotherapy Regimens	
NCT01960192	*Title:* The Prospective Study of FVD* Program and HD-MTX-Ara-C Program Contrast in the Treatment of PCNS Lymphoma *Status:* Recruiting participants *Estimated Completion Date:* June 2020 *Updated:* August 2016 (Source: University Zhengzhou, China)
NCT00293475	*Title:* A Phase I/II Trial Study of Patients with Newly Diagnosed Primary Central Nervous System Lymphoma Treated with Methotrexate/BBBD, and Adding Rituximab (an Anti CD-20 Antibody) and Carboplatin, to the Treatment Regimen *Status:* Recruiting participants *Estimated Completion Date (final data collection date for primary outcome measure):* January 2017 *Updated:* May 2016
NCT02657785	*Title:* Treatment of PCNS Lymphoma with Systemic R-IDARAM Chemotherapy and Intrathecal Immunotherapy *Status:* *Estimated Completion Date (final data collection for primary outcome measure):* December 2018 *Updated:* February 2016
NCT02836158	*Title:* Therapeutic Effects of R-IDARAM and Intrathecal Immunochemotherapy on Elderly Patients with PCNS Lymphoma *Status:* Recruiting participants *Estimated Completion Date (final data collection for primary outcome measure):* December 2025 *Updated:* July 2016
NCT02313389	*Title:* Phase III Trial Evaluating Maintenance Treatment versus Observation in Elderly Patients Suffering from Primary Central Nervous System Lymphoma in Complete Remission after High Dose Methotrexate Based Chemotherapy in First Line *Status:* Recruiting participants *Estimated Completion Date (final data collection for primary outcome measure):* June 2019 *Updated:* May 2016
Chemotherapy Regimens with or without Radiotherapy	
NCT02655744	*Title:* Prospective Neurobehavioral Outcomes Follow-up in PCNS Lymphoma Patients Treated with Cranial Radiotherapy Combined with or without MTX-based Chemotherapy According to the Multidisciplinary Treatment Guidelines Implemented at a Single Institution

	Status: Recruiting participants *Estimated Completion Date (final data collection for primary outcome measure):* December 2018 *Updated:* January 12, 2016
High-Dose Chemotherapy plus Autologous Stem Cell Transplantation	
NCT01011920	*Title:* Randomized Phase II Trial on Primary Chemotherapy with High-Dose Methotrexate and High-Dose Cytarabine with or without Thiotepa, and with or without Rituximab, Followed by Brain Irradiation vs. High-Dose Chemotherapy Supported by Autologous Stem Cells Transplantation for Immunocompetent Patients with Newly Diagnosed PCNS Lymphoma. *Status:* Ongoing, not recruiting participants *Estimated Completion Date (final data collection for primary outcome measure):* December 2016 *Updated:* July 26, 2016
NCT02531841	*Title:* High-Dose Chemotherapy and Autologous Stem Cell Transplant or Consolidating Conventional Chemotherapy in PCNS Lymphoma – Randomized Phase III Trial *Status:* Recruiting participants *Estimated Completion Date (final data collection for primary outcome measure):* November 2017 *Updated:* August 2015
NCT00863460	*Title:* Prospective, Multicentric, Randomized Phase II Study, Evaluating the Role of Cranial Radiotherapy or Intensive Chemotherapy with Hematopoietic Stem Cell Rescue after Conventional Chemotherapy for Primary Central Nervous System in Young Patients *Status:* Ongoing, not recruiting participants *Estimated Completion Date:* February 1, 2017 (Source: covalentDATA) *Updated:* September 2014
NCT02399189	*Title:* MT-R Followed by Autologous Stem Cell Transplantation in Newly-Diagnosed Primary Central Nervous System Lymphoma *Status:* Recruiting participants *Estimated Completion Date (final data collection for primary outcome measure):* April 2017 *Updated:* April 10, 2015
NCT00596154	*Title:* Rituximab, Methotrexate, Procarbazine and Vincristine Followed by High-dose Chemotherapy with Autologous Stem-Cell Rescue in Newly-diagnosed PCNS Lymphoma (PCNSL) *Status:* Ongoing trial, no recruiting participants *Estimated Completion Date (final data collection for primary outcome measure):* December 2017 *Updated:* August 2016
NCT01235793	*Title:* A Phase 2a Study of the Addition of Temozolomide to a Standard Conditioning Regimen for Autologous Stem Cell Transplantation in Relapsed and Refractory Central Nervous System (CNS) Lymphoma *Status:* Recruiting participants *Estimated Completion Date (final data collection for primary outcome measure):* December 2018 *Updated:* April 2016

NCT01182415	*Title:* Phase II Trial of High-Dose Thiotepa, Busulfan, Cyclophosphamide, and Rituximab with Autologous Stem Cell Transplantation for Patients with CNS involvement by Non-Hodgkin's Lymphoma or PCNS Lymphoma *Status:* Ongoing, no recruiting participants *Estimated Completion Date:* December 2016 *Updated:* January 14, 2016
NCT01511562	*Title:* A Randomized Phase II Trial of Myeloablative versus Non-Myeloablative Consolidation Chemotherapy for Newly Diagnosed PCNS B-Cell Lymphoma *Status:* Recruiting participants *Estimated Completion Date (final data collection for primary outcome measure):* October 2026 *Updated:* June 2016

* Fotemustine, teniposide, and dexamethasone)

DISCUSSION

This document represents a review of the evidence regarding the management of PCNS DLBCL with a specific focus on: (i) optimal chemotherapy and radiotherapy regimens to be used in the first-line setting and (ii) the role of thiotepa-based ASCT in both the front-line and relapsed setting. Apart from the role of ASCT, management of relapsed/refractory PCNS lymphoma was determined to be beyond the scope of this guideline.

Historically, clinical research in PCNS lymphome has been challenging and progress has been slow. Patient outcomes have been poor compared with systemic DLBCL and PCNS lymphoma represents a major unmet clinical need within the spectrum of lymphoid malignancies. Clinical practices have varied widely across geographical regions both nationally and internationally. This relates primarily to a lack of large, prospective, randomized clinical trials evaluating important clinical endpoints in specific patient populations. Disease rarity and clinical heterogeneity have posed challenges to timely study accrual and generalizability. Prospective trials have rarely been powered to detect important differences in survival or quality of life and rigorous prospective evaluations of neurologic toxicities of therapy have generally not been incorporated to trial design. Recently, multi-centre, international collaborative efforts have led the way to the development of larger randomized controlled trials incorporating prospective evaluation of neurologic toxicity utilizing formal neuro-psychologic assessments rather than relatively insensitive tools such as the MMSE. Elderly patients, and those with poor performance status or significant comorbidities, are under-represented in published studies to date and determining optimal approaches in clinical practice is particularly difficult because there may be important differences in toxicities including neurotoxicity and treatment-related mortality.

The introduction of HD-MTX-based chemotherapy into first-line treatment of PCNS lymphoma is now considered standard for eligible patients. Through sequential randomized phase II trials, the IESLG has confirmed the improved efficacy of HD-MTX–based combination regimens compared with single-agent HD-MTX. The IESLG 20 trial (Ferreri et al. Lancet 2009) established HD-MTX plus cytosine arabinoside (MA) as a standard treatment option based on improved ORR and CR rate compared with HD-MTX alone and provided the basis for MA as the control arm for the IESLG32 trial included in our updated literature search. We feel the results of the IESLG32 trial are important for several reasons. The MATRix regimen demonstrated

improved ORR, CR, PFS, and OS compared with standard MA chemotherapy. This is the first randomized trial to show a survival benefit in PCNS lymphoma and provides the strongest evidence to date that rituximab should be incorporated into front-line therapy in this population. Eligibility was restricted based on age and performance status ((ECOG ≤3 for patients aged ≤65 years, and ≤2 for patients 66 to 70 years of age). However, this trial included a second randomization to WBRT versus high-dose chemotherapy and ASCT; thus, the restriction in age and performance status is consistent with established transplant eligibility criteria. The Working Group reached consensus that the results of the first randomization may be generalizable to selected patients older than 70 years (i.e., transplant ineligible) with good performance status. Alternative HD-MTX-based regimens have been developed that incorporate a CNS-penetrating alkylating agent and rituximab (e.g., R-MPV); however, these regimens have not been evaluated in prospective, randomized clinical trials thus their relative efficacy and toxicity compared with other HD-MTX-based combinations including MATRix are not known.

The evidence to inform optimal front-line chemotherapy in elderly patients and those deemed less fit or with poor performance status is generally of low quality, consists primarily of pooled retrospective data and single-arm studies, or must be generalized from studies evaluating younger patients. Available data suggest HD-MTX-based chemotherapy is superior to WBRT and that HD-MTX-based combination regimens are associated with improved outcomes compared with HD-MTX alone. These observations are consistent with results from randomized controlled trials evaluating primarily younger patients. However, limited data suggest HD-MTX-based chemotherapy may be associated with increased rates of serious toxicity including therapy-related mortality in patients >70 years of age or with poor performance status. Taken together, treatment with a HD-MTX-based regimen is considered a reasonable option in this population; however, the optimal regimen has not been clearly defined and the decision to initiate therapy requires consideration of patient functional status, co-morbidities, and a patient-centred discussion regarding the benefits and potential for serious toxicity associated with treatment.

The optimal role for radiotherapy in the management of PCNS lymphoma has been controversial and continues to evolve as standard and high-dose chemotherapeutic approaches improve. WBRT, in the doses utilized to treat PCNS lymphoma, is associated with a risk for development of neurologic toxicity that may have a significant impact on cognitive functioning and quality of life. The risk is increased in patients ≥60 years of age and those with prior exposure to HD-MTX-based chemotherapy. The German PCNS lymphoma SG-1 trial results were updated within our literature review. This was a large, phase III randomized controlled trial testing WBRT versus no further therapy following HD-MTX induction within a non-inferiority design with OS as the primary endpoint. Omission of WBRT was found to be not non-inferior compared with WBRT. Strictly speaking, the interpretation that 'WBRT does not improve survival' is incorrect within the non-inferiority design even though the point estimates for OS in the two arms are similar. Additional methodological limitations included a high burden of patient drop-out that complicated the analysis of this trial. Furthermore, transplant-eligible patients may now be faced with a choice of therapy in the front-line setting (thiotepa-based conditioning and ASCT versys WBRT). The decision to consolidate with WBRT or SCT will be driven largely by differences in the toxicity profile; in particular, the trade-off between radiation-induced neurotoxicity and the short-term risks related to SCT. Radiotherapy is also considered a reasonable option for the treatment of non-transplant-eligible patients in less than CR after chemotherapy, patients with chemotherapy-resistant disease, or those who are deemed ineligible for chemotherapy.

High-dose chemotherapy and ASCT has been the standard of care for relapsed systemic DLBCL for approximately 20 years. Unfortunately, conditioning regimens used in that population have yielded disappointing results when applied to patients with PCNS lymphoma.

Novel thiotepa-based conditioning regimens, evaluated in single-arm, prospective studies in both the front-line and relapsed/refractory settings, demonstrated improved outcomes compared with historical controls. These data provided a strong rationale for the development of two randomized controlled trials evaluating ASCT versus WBRT as consolidation therapy following an induction course of chemotherapy. Preliminary results of these studies have been published in abstract form. In the IELSG32 trial, patients with stable disease or better were randomly allocated to WBRT or ASCT following thiotepa plus carmustine conditioning. No statistically significant difference in two-year PFS and OS was found, although the trial was underpowered to detect a difference in survival. Toxicity was consistent with the known toxicity profiles of the two approaches; transplantation was associated with a treatment-related mortality of 2% and minimal neurologic toxicity while WBRT was associated with the development of neurotoxicity. Longer follow-up and full publication of the data will be important in defining the risks and benefits of the two approaches. Nonetheless, the reported two-year PFS was excellent in both arms (80% versus 70% in the WBRT versus SCT). The preliminary results of the Anocef-Goelams trial have also been reported and demonstrated a two-year PFS of 87% in the transplant arm (thiotepa plus busulphan plus cyclophosphamide conditioning) versus 63% with WBRT; survival and toxicity data are not yet published. Although these randomized data are very preliminary, particularly regarding neurotoxicity, the results are consistent with single-arm phase II trials and compare very favourably with historical controls. Relapsed/refractory PCNS lymphoma is associated with a very poor prognosis. Prospective phase II data have demonstrated prolonged disease control and survival, particularly in patients that demonstrate chemosensitivity prior to SCT. Based on these data, ASCT with a thiotepa-based conditioning regimen is considered a reasonable option for the management of PCNS lymphoma in both relapsed/refractory and front-line disease. Most studies evaluating transplant have used either thiotepa plus busulphan- or thiotepa plus carmustine-based conditioning. In the absence of a direct comparison, the optimal salvage regimen is not yet clear. The Working Group acknowledged that other factors such as drug cost or availability may drive the decision to use one regimen over another.

Management of Primary Central Nervous System Diffuse Large B-Cell Lymphoma

Section 5: Internal and External Review

INTERNAL REVIEW

The guideline was evaluated by the GDG Expert Panel and the PEBC RAP (Appendix 1). The results of these evaluations and the Working Group's responses are described below.

Expert Panel Review and Approval

Of the eight members of the GDG Expert Panel, seven members cast votes and one abstained, for a total of 87.5% response in March 2017. Of those that cast votes, seven approved the document (100%). The main comments from the Expert Panel and the Working Group's responses are summarized in Table 5-1.

Table 5-1. Summary of the Working Group's responses to comments from the Expert Panel

Comments	Responses
1. The recommendation for the MATRix regimen is supported by a study comparing three arms. The authors need to clarify under the key evidence and interpretation of the evidence for this recommendation, the arms they are referring to.	The members of the Working Group agreed with this comment, and it is reflected in the document.
2. Recommendation 1 against CHOP-like chemotherapy regimens seems somewhat obvious. Did sthe earch come across data regarding the CHOP regimen in PCNS lymphoma? Or are you stating this because such data are in fact absent?	The members of the Working Group endorsed the recommendation against CHOP-like chemotherapy from the 2015 recommendations contained in the guideline from the European Association for Neuro-Oncology. It has been clarified under the key evidence for the recommendation.
3. Treatment with an HD-MTX-based regimen plus rituximab has been recommended as a reasonable option for elderly patients that have adequate renal function. However, it would be most helpful to provide some guidance as to the creatinine clearance that the authors think is safe.	The members of the Working Group agreed with this comment, and it is now documented under the "qualifying statement" for Recommendation 2 that HD-MTX can be safely used in the elderly if doses are reduced according to the creatinine levels calculated before each treatment cycle. It has also documented that patients with creatinine clearance lower than 50 ml/min shouldn't be treated with HD-MTX.
4. Under interpretation of the evidence for Recommendation 2, the authors mention short survival and significant neurotoxicity associated with WBRT. It would be important to mention other toxicities from this therapy, i.e., renal, others? Mortality risk?	It has been stated under the key evidence that assessment of toxicity is limited by the variability among trial designs. Treatment-related mortality was reported to range from 2% to 7% and grade 3/4 nephrotoxicity and liver toxicity was less than 10%
5. Results from the study by Pulczynski et al., 2015 is not included in the evidence summary.	This study has now been included in the evidence summary/recommendations.

6. According to the European Association for Neuro-Oncology, intrathecal chemotherapy may be considered in patients with leptomeningeal disease and an incomplete response to HD-MTX-based chemotherapy. If this is the case, was there consideration of a second part to Recommendation 3?	The members of the Working Group did not include any recommendation for leptomeningeal disease due to the lack of evidence base that inform a formal recommendation. The statement surrounding intrathecal chemotherapy for patients with leptomeningeal disease is based on expert opinion to clarify the original recommendation. This statement is now presented under the "Qualifying Statement" for Recommendation 3.
7. Under interpretation of the evidence for Recommendation 6, the authors recommend a patient-centred multi-disciplinary approach to inform patients of the trade-off in risks and benefits associated with WBRT consolidation. Should this not be an option in the recommendation itself?	The members of the Working Group agreed with this comment, and it is now documented under the recommendation.
8. Treatment-related toxicities should be included so the reader is able to appreciate the magnitude of the risk versus the benefit.	Treatment-related toxicities are now documented.
9. The authors did not include relapse treatment with chemotherapy for elderly patients who are not transplant candidates, and may be able to tolerate MTX again.	This document provides recommendations for the optimal first-line treatment for PCNS lymphoma. Further chemotherapies intended to treat relapse were considered by the members of the Working Group to be beyond the scope of this guideline.
10. Results of the second randomization of the IELSG32 trial have been presented at ASH in December 2016. Although it is abstract data, it should not be ignored.	Abstract data from the second randomization of the IELSG32 trial have been included in this document, under the key evidence for Recommendation 7.
11. The authors mentioned for Recommendation 7 that rates of two-year PFS between WBRT and ASCT were comparable. Somehow the authors need to comment on power since 15% difference will not look "comparable" to many readers.	The statement has been changed to better reflect the results from the IELSG32 trial. The statement now reads as: the IELSG32 trial reported on intention-to-treat basis no statistically significant differences in two-year PFS between WBRT and ASCT. Also, under the interpretation of the evidence it has been clarified that the trial was not powered to detect a difference in OS.
12. Do the authors need to address dosing of the rituximab? My understanding was that previous studies have suggested using a dose of 500 mg/m^2 instead of the one used in the MATRix study of 375 mg/m^2	There are no comparable data to define optimal doses for rituximab, and it is not clear that dose-intensity in the rituximab improves the outcomes of patients with PCNS lymphoma. The members of the Working Group feel that the MATRix study is the best available evidence nowadays for managing PCNS lymphoma. The study reported survival benefit in patients treated with doses of 375 mg/m^2 and, therefore, the members of the Working Group believe that the recommended dosage of rituximab is 375 mg/m^2.
13. The comments that the authors may get back from practitioners relate to the relevance of the Recommendation 1, in that	This guideline is intended to provide an evidence-based opinion on the most effective first-line therapy for patients with PCNS lymphoma. Further direction is considered by the members of the

thiotepa is not funded by CCO and hence not available to most centres.	Working Group to be beyond the scope of this document.
14. Depending on each physician's comfort in the manner in which the Rituxan funding approval forms are filled out, it could be questioned whether Rituxan is CCO covered for PCNS lymphoma.	This guideline is intended to provide an evidence-based opinion on the most effective first-line therapy for patients with PCNS lymphoma. Further direction is considered by the members of the Working Group to be beyond the scope of this document.
15. Not sure if systemic therapy should be recommended for the management of intraocular lymphoma; radiotherapy or intraocular therapy is generally how the disease is treated in some institutions.	There are no comparative clinical trials evaluating local approaches with systemic chemotherapy in patients with PIOL. However, local approaches for treating other presentations of PCNS lymphoma are considered inferior; therefore, it is the opinion of the members of the Working Group that it is reasonable to generalize the data to PIOL as these patients were eligible in trials evaluating therapies including MTX for the treatment of PCNS lymphoma.
16. According to Table 3-1, intrathecal chemotherapy (intralumbar or preferably intraventricular through an Ommaya reservoir) can be proposed whenever meningeal involvement is documented, together with an insufficient response to intravenous HD-MTC-based chemotherapy (at least 3 g/m^2). Do the authors need to make a comment regarding intrathecal chemotherapy (intralumbar or preferably intraventricular through an Ommaya reservoir)?	Table 3-1 listed the recommendations from the 2015 European Association for Neuro-Oncology guideline. The members of the Working Group recommend against the use of intrathecal chemotherapy due to the lack of evidence base that inform a formal recommendation. This statement has been presented under "interpretation of the evidence" for Recommendation 3.
17. Is the European guideline search strategy clear and acceptable to the authors, so that they feel that the result of the 2000 literature does not need to be evaluated?	Although the European Association for Neuro-Oncology Task Force did not report a search strategy in sufficient detail to allow reproducibility, the members of the Working Group believe that the reporting is acceptable and, therefore, decided to use its recommendations as a basis for the present guideline. There was also a willingness to retrieve and review original articles when missing evidence was identified in the reporting of the European guideline (i.e., treatment-related toxicities).

RAP Review and Approval

Three RAP members, including the PEBC Director, reviewed this document in March 2017. The RAP approved the document on March 13, 2017. The main comments from the RAP and the Working Group's responses are summarized in Table 5-2.

Table 5-2. Summary of the Working Group's responses to comments from RAP

Comments	Responses
1. In Recommendation 5, would it be appropriate to include "patient preference" as a reason why people may not get aggressive chemotherapy	The members of the Working Group agreed with this comment, and it is now documented.

EXTERNAL REVIEW
External Review by Ontario Clinicians and Other Experts

Targeted Peer Review

Seven targeted peer reviewers from Ontario, Quebec, and British Columbia who are considered to be clinical and/or methodological experts on the topic were identified by the PCNSL Working Group. Five agreed to be the reviewers (Appendix 1). Three responses were received. Results of the feedback survey are summarized in Table 5-3. The comments from targeted peer reviewers and the Working Group's responses are summarized in Table 5-4.

Table 5-3. Responses to nine items on the targeted peer reviewer questionnaire.

	Reviewer Ratings (N=3)				
Question	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the guideline development methods.				1	2
2. Rate the guideline presentation.		1			2
3. Rate the guideline recommendations.			1	1	1
4. Rate the completeness of reporting.			1		2
5. Does this document provide sufficient information to inform your decisions? If not, what areas are missing?			1	1	1
6. Rate the overall quality of the guideline report.			1		2
	Strongly Disagree (1)	(2)	Neutral (3)	(4)	Strongly Agree (5)
7. I would make use of this guideline in my professional decisions.				2	1
8. I would recommend this guideline for use in practice.				2	1
9. What are the barriers or enablers to the implementation of this guideline report?	Funding for some pf the recommended treatments may be limited in Ontario and other jurisdicions. In particular, funding for thiotepa and rutiximab as per the MATRIix regimen may be limited. Also, HD-MTX-based regimens and ASCT require expensive resources that go beyond the cost of the drug, such as in-patient admission, supportive care, and management of complications.				

Table 5-4. Responses to comments from targeted peer reviewers

Comments	Responses
1. There is no guidance given for consolidation radiation therapy in the setting of a CR and the use of hyperfractionated versus standard fraction radiation therapy. For patients in a CR, the literature (primarily based on RTOG studies) would support 36 Gy/18 fractions as a reasonable consolidiative regimen for a patient in CR and 45 Gy/25 fractions for patients in partial remission. Thus, I think the guideline would be enhanced by clarifying recommended dose ranges for consolidative radiation therapy by setting. In my opinion, 36-40 Gy in CR setting and 40-45 Gy in the partial remission setting, both at 1.8 to 2.0 Gy/day are reasonable dose regimens.	A qualifying stament has been added for Recommendation 6 to clarify that there is no comparable data to define optimal doses for hyperfractionated consolidiative regiments, and therefore the member of the Workig Group cannot recommend dose ranges for consolidative radiation therapy.
2. I agree with Recommendation 6 that *WBRT should not be routinely administered in patients who have achieved a CR following first-line chemotherapy*. However, Recommendation 6 appears to contradict Recommendation 7, which recommends ASCT for these patients. It almost sound like authors have chosen ASCT over radiation therapy, and have left WBRT as the preferred option for those not eligible for ASCT. There are phase 2 studies showing excellent outcomes for both consolidative ASCT (Omuro, Blood 2015) and WBRT (Morris, JCO 2013), which does not help inform this decision. Until we see more mature results from IELSG32, one cannot choose one over the other.	The members of the Working Group agreed ith this comment, and it is now documented under the qualifying statemet for Recommendation 7. The stament "WBRT is a reasonable consolidation option for patients in partial remission who are not eligible for ASCT" has been removed from Recommendation 7 and incorporated under the qualifying stamen for Recommendation 6.
3. The qualifying statement for Recommendation 3 makes it sound like intrathecal chemotherapy is only appropriate in the scenario of patients who have persistent leptomeningeal disease after HD-MTX. However, intrathecal chemotherapy may be clinically appropriate in other scenarios such as patients with symptomatic leptomeningeal disease receiving HD-MTX. There are no trials and there will never be any trials looking at this. Thus, there is equipoise as to the role of intrathecal chemotherapy, and writing very restrictive guidelines has the potential to deprive selected patients of a treatment that may be helpful in the short term even when it may not be helpful in the long term. To say that intrathecal chemotherapy is not	The members of the Working Group agreed with this comment, and the recommendation has been softened to clarify that the recommendation is not against intrathecal chemotherapy. The qualifying statement has also been clarified.

recommended outside of clinical trials (interpretation of evidence for Recommendation 3) is similarly problematic.	
4. May patients with PIOL benefit from intraocular treatments in the short term, even when they are receiving concurrent HD-MTX. Available literature is limited, but authors have chosen to be restrictive and only recommend intraocular therapies for patients ineligible for HD-MTX. There is equipoise and the recommendations and qualifying statement should reflect this.	A qualifying statement has been included for Recommendation 9 to address this comment.
5. The payor viewpoint was not considered. In many cases, there is significant doubt amongapproaches that likely have quite different cost profiles. Regimen/strategy should have been singled out as the primary recommendation for Ontario. When alternatives are presented, reasons anybody would select those alternatives are unclear. The cost-benefit ratio of the treatments is not presented	This document is intended to provide an evidence-based opinion on the most effective first-line therapy for patients with PCNS lymphoma. Further direction such as cost-benefit analysis is considered by the members of the Working Group to be beyond the scope of this document.
6. I disagree with qualifying statement for Recommendation 5. WBRT is associated with a risk of neurotoxicity. The clinical benefit of WBRT in this poor-risk population, compared with supportive care, has not been confirmed in prospective comparative clinical trials. Obviously, the management should be discussed with patients on a case-by-case basis but the toxicity of "palliative: WBRT without chemotherapy should not be exaggerated and the high clinical and radiological response rates should not be underestimated (not to mention the occasional durable disease control). I would also suggest that six months of memantine should be considered in all patients receiving WBRT based on prospective randomized evidence.	The qualifying statement for this Recommendation has been modified to address this comment.
7. Recommendation 6 is difficult to interpret. WBRT should not be used following a CR to HD-MTX (a coherent recommendation based on current data) but if used, only the highest dose should be used?	This comment has been addressed under the qualifying statement for Recommendation 6. In summary, there is no evidence to make recommendations regarding dosing schedules.

Professional Consultation

Feedback was obtained through a brief online survey of healthcare professionals and other stakeholders who are the intended users of the guideline. All medical oncologists in the PEBC database with an interest in PCNS lymphoma were contacted by email to inform them of the survey. Seventy-seven oncologists were contacted and one response was received. Another oncologist stated that he did not have interest in the area. The results of the feedback survey

from the participant are summarized in Table 5-5. There were no comments from the professional consultant.

Table 5-5. Responses to four items on the professional consultation survey

	Number (N=1)				
General Questions: Overall Guideline Assessment	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the overall quality of the guideline report.				1	
	Strongly Disagree (1)	(2)	(3)	(4)	Strongly Agree (5)
2. I would make use of this guideline in my professional decisions.				1	
3. I would recommend this guideline for use in practice.				1	
4. What are the barriers or enablers to the implementation of this guideline report?	The participant did not identify any				

PATIENT AND CAREGIVER-SPECIFIC CONSULTATION GROUP

Two patient participants reviewed copies of the project plan and draft recommendations and provided feedback on their comprehensibility, appropriateness, and feasibility. The comments/feedback from patients representatives and the Working Group's responses are summarized in Table 5-6.

Table 5-6. Summary of the Working Group's responses to comments from the Consultation Group

Comments	Responses
The patient representatives think that the guideline topic is very important to patients, and also that the guideline background and the current practice standards description are clear and directly related to the research questions. The timeline set up for the completion of this guideline was also thought to be reasonable. One patient representative was not sure why the population of interest included patients with PIOL.	In response to the patient representative concern surrounding PIOL, it was clarified that PIOL is a subset of PCNS lymphoma that either occurs independently to, or in association with, PCNS lymphoma and for that reason the population of interest was defined as patients with PCNS lymphoma including PIOL.

CONCLUSION

The final guideline recommendations contained in Section 2 and summarized in Section 1 reflect the integration of feedback obtained through the external review processes with the document as drafted by the GDG Working Group and approved by the GDG Expert Panel and the PEBC RAP.

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Appendix 1: Primary Central Nervous System Lymphoma Guideline Development Group

Primary Central Nervous System - Working Group	
Name	Affiliation
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Appendix 2: Conflict of Interest Declarations

In accordance with the PEBC Conflict of Interest (COI) Policy, the guideline authors (Working Group and Expert Panel members), and internal and external reviewers were asked to disclose potential COIs. Seven members of the Working Group declared no conflicts and one declared potential conflicts (LH). LH declared that she had received research grant support from CIHR/Gilead Sciences.

For the Expert Panel, four Internal Reviewers declared no conflicts and three declared potential conflicts (MC, WM, DS). MC reported receiving funding for clinical trials support from Janssen Ortho, Novartis, Celgene, Lilly, and Roche Canada. WM reported that he had received $5000 or more in a single year from Merck Sharpe and Dhome Roche for acting in a consulting capacity. DS declared that he has authored two publications involving chemotherapy and ASCT for PCNS lymphoma.

Members of the RAP declared they had no conflicts of interest.

Two Targeted Peer Reviewers indicated no interests to declare, and one declared potential COIs (DR). DR declared honoraria from Accuray, Siemens Healthineers, Varian Medical Systems, and BrianLab.

The COIs declared above did not disqualify any individuals from performing their designated role in the development of this guideline, in accordance with the PEBC COI Policy. To obtain a copy of the policy, please contact the PEBC office by email at ccopgi@mcmaster.ca.

Appendix 3: AGREE II Scores

European Association for Neuro-Oncology Guideline

Domains	*Score (3 reviewers)*
Scope and purpose	72%
Stakeholder involvement	54%
Rigor of development	52%
Clarity of presentation	85%
Applicability	11%
Editorial independence	42%

Appendix 4: Literature Search Strategies

Systematic Reviews

*Database(s): **EBM Reviews - Cochrane Database of Systematic Reviews** 2005 to July 01, 2016, **Embase** 1996 to 2016 Week 27, **Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)** 1946 to Present*

1	exp primary central nervous system lymphoma/
2	((central nervous system or cns or brain or spinal cord or brain stem or intramedullary or intradular or extramedullary) adj2 (neoplasm$ or lymphom$ or tumor$ or tumour$)).tw,ti,kf.
3	or/1-2
4	exp meta analysis/
5	exp "meta analysis (topic)"/
6	exp meta-analysis as topic/
7	exp "systematic review"/
8	exp "systematic review (topic)"/
9	(exp "review"/ or exp "review literature as topic"/ or review.pt.) and ((systematic or selection criteria or data extraction or quality assessment or jaded scale or methodologic$ quality or study) adj selection).tw.
10	meta-analysis.mp.
11	(meta-analy: or metaanaly: or meta analy:).tw.
12	(systematic review or systematic overview).mp.
13	((cochrane or medline or embase or cancerlit or hand search$ or hand-search$ or manual search$ or reference list$ or bibliograph$ or relevant journal$ or pooled analys$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or quantitative synthes?s or quantitative overview$ or systematic) adj2 (review$ or overview$)).tw.
14	(medline or med-line or pubmed or pub-med or embase or cochrane or cancerlit).ab.
15	or/4-14
16	exp phase 3 clinical trial/
17	exp "phase 3 clinical trial (topic)"/
18	exp clinical trial, phase iii/
19	exp clinical trials, phase iii as topic/
20	exp phase 4 clinical trial/
21	exp "phase 4 clinical trial (topic)"/
22	exp clinical trial, phase iv/
23	exp clinical trials, phase iv as topic/
24	exp randomized controlled trial/
25	exp "randomized controlled trial (topic)"/
26	exp controlled clinical trial/
27	exp randomized controlled trials as topic/
28	exp randomization/
29	exp random allocation/

30 exp double-blind method/
31 exp single-blind method/
32 exp double blind procedure/
33 exp single blind procedure/
34 exp triple blind procedure/
35 exp placebos/
36 exp placebo/
37 exp phase 2 clinical trial/
38 exp "phase 2 clinical trial (topic)"/
39 exp clinical trial, phase ii/
40 exp clinical trials, phase ii as topic/
41 exp clinical trial/
42 exp prospective study/
43 exp controlled clinical trial/
44 or/16-43
45 exp evidence based practice/
46 exp practice guideline/
47 exp consensus development conference/
48 guideline.pt.
49 practice parameter$.tw.
50 practice guideline$.mp.
51 (guideline: or recommen: or consensus or standards).ti.
52 (guideline: or recommend: or consensus or standards).kw.
53 or/45-52
54 (comment or letter or editorial or news or newspaper article or case reports or historical article or narrative review).pt.
55 3 and (15 not (44 or 53 or 54))
56 animal/ not (exp human/ or humans/)
57 55 not 56
58 limit 57 to english language [Limit not valid in CDSR; records were retained]
59 limit 58 to yr="2000 -Current"
60 remove duplicates from 59

Primary Literature

Database(s): ***Embase*** *1996 to 2016 Week 27****, Ovid MEDLINE(R) without Revisions*** *1996 to June Week 4 2016****, Ovid MEDLINE(R) Daily Update*** *July 01, 2016****, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations*** *July 01, 2016****, Ovid MEDLINE(R) Epub Ahead of Print*** *July 01, 2016*

1	exp primary central nervous system lymphoma/ or PCNSL.mp. or PIOL.mp. or exp intraocular lymphoma/
2	((central nervous system or CNS or brain or spinal cord or intramedul?ar: or intradul?ar: or intradural: or extramedul?ar: or intraocular or intra-ocular or PCNS).mp. or (exp central nervous system neoplasms/ or exp eye neoplasms/)) and ((lymphom: or NHL or DLBCL).mp. or exp lymphoma/)
3	or/1-2
4	(comment or letter or editorial or news or newspaper article or case reports or historical article).pt.
5	exp phase 1 clinical trial/
6	exp "Phase 1 clinical trial (topic)"/
7	exp clinical trial, phase 1/
8	exp phase i clinical trial/
9	exp clinical trial, phase i/
10	exp clinical trials, phase i as topic/
11	or/4-10
12	3 not 11
13	exp stem cell transplantation/ or (SCT or stem cell transplant: or ASCT).mp.
14	exp radiotherapy/ or exp chemoradiotherapy/ or exp adjuvant chemoradiotherapy/ or (radiotherapy: or radiation: or radiolog: or chemoradiation: or chemoradiotherapy or radiochemotherapy).mp.
15	exp chemoradiotherapy/ or exp chemotherapy, adjuvant/ or exp neoadjuvant therapy/ or exp adjuvant therapy/ or exp cancer adjuvant therapy/ or exp cancer combination chemotherapy/ or exp antineoplastic agents/ or (adjuvant or neoadjuvant or chemotherapy).mp.
16	or/13-15
17	12 and 16
18	animal/ not (exp human/ or humans.mp.) [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, nm, kf, px, rx, ui]
19	17 not 18
20	19 and (201409* or 201410* or 201411* or 201412*).dd.
21	19 and (201409* or 201410* or 201411* or 201412*).ed.
22	20 or 21
23	limit 19 to yr="2015 -Current"
24	22 or 23
25	remove duplicates from 24

Appendix 5: Quality Assessment of Included Systematic Review (AMSTAR)

(Yes/No/CA)

AMSTAR Tool		Kasenda et al.[3]
Q1.	Was an '*a priori*' design provided?	Yes
Q2.	Was there duplicate study selection and data extraction?	Yes
Q3.	Was a comprehensive literature search performed?	Yes
Q4.	Was the status of the publication used as an inclusion criterion?	CA
Q5.	Was a list of studies (included and excluded) provided?	No
Q6.	Were the characteristics of the included studies provided?	Yes
Q7.	Was the scientific quality of the included studies assessed and documented?	Yes
Q8.	Was the scientific quality of the included studies used appropriately in formulating conclusions?	Yes
Q9.	Were the methods used to combine the findings of studies appropriate?	Yes
Q10.	Was the likelihood of publication bias assessed?	No
Q11.	Was the conflict of interest stated?	Yes

Abbreviations: CA (can't answer)

Appendix 6: Quality assessment for included studies

Author Trial [Country]	Randomization	Allocation Concealment	Blinding	Power	Analysis	Confounding	Follow-Up
Kasenda, 2015 [3]	N/A	N/A	N/A	N/A	Kaplan-Meier plots, logistic, and Cox regression models. Each analysis was adjusted for age, KPS (≥70% vs. <70%), and random effect for study /database added		
Ferreri, 2016 IELSG32 Phase 2 Trial [1,12] [Switzerland]	Random allocation in a 1:1:1 ratio with permuted blocks, and stratified by risk score (low, intermediate, high) to ensure balance across group of homogeneous risk	A computer-generated randomization list (IELSG, Bellinzona, Switzerland) was used within each stratum	Investigators were blinding to randomization sequence. Open-label design: The investigators assessing the outcomes and analysing results were not blinded to treatment allocation, nor were the patients blinded to assigned treatment	One-sided test, type I error 5%, power 80%. Corresponding sample size of at least 42 patients per group was achieved	Modified intention-to-treat (all randomly assigned patients were considered for analysis, except those who did not meet the eligibility criteria at the time of randomization*)	Baseline characteristics were well balanced across groups, although high serum lactate dehydrogenase level was more common in the MTX, AraC (46%) group than in the other 2 groups (38% and 33% for MTX, AraC, RTX and MTX, AraC, RTX, THIO, respectively)	No losses to follow-up
Pulczynski, 2015 NLG [4]	N/A†	N/A	N/A	NR	Intention-to-treat	Median ECOG performance status was 1 (range 0-4)	No losses to follow-up

Author Trial [Country]	Randomization	Allocation Concealment	Blinding	Power	Analysis	Confounding	Follow-Up
Glass, 2016 RTOG 0227 [11]	Non-randomized	Single group assignment	Open-label design	N/A	Per-protocol	Baseline characteristics were well balanced with Zubrod performance statues ranging 0-2	There were 9% lost to follow-up
Korfel, 2015 G-PCNSL-SG1 [10] [Germany]	Random allocation to treatment in a 1:1 ratio with block randomization, and stratified by age (<60, ≥60) and institution	Self-written computer program (Department of Biostatistics and Clinical Epidemiology, Charrité Berlin, Berlin, Germany)was used	Open-label design: Physicians and patients were not blinded to treatment allocation because sham radiotherapy was not feasible and physicians were responsible for both treatment and assessment	One-sided test, designed to have 60% power to prove non-inferiority of omission of WBRT with a HR of 1.2 for WBRT vs. no WBRT. Corresponding sample size of at least 151 patients per group was achieved	Intent-to-treat, and by the treatment that was actually given (as-treated)‡	Baseline characteristics were well balanced between both arms (no statistically significant differences were detected by the X^2 and Mann-Whitney *U* tests)	There were 8% lost to follow-up in the HD-MTX + WBRT arm, and 9% lost to follow-up in the HD-MTX without WBRT arm
Omuro, 2015 MSKCC [26]	N/A§	N/A	N/A	Exact binomial test with a nominal 0.05 one-sided significance level and 90% power		Baseline characteristics were well balanced among participants	There were 3% lost to follow-up
Houillier, 2016 Anocef-Goelams [13] [Abstract]	Random allocation in 1:1 ratio with stratification according to performance status	NR	NR	Either of the two arms would be deemed effective if >24/38 patients are free of disease at 2-year follow-up with no major side effects	Intent-to-treat	NR	There were 1.4% lost to follow-up

Abbreviations: AraC (cytarabine); CR (complete remission); IELSG (International Extranodal Lymphoma Study Group); MTX (methotrexate), N/A (not applicable); NLG (Nordic Lymphoma Group); NR (not reported); RTX (rituximab); THIO (thiotepa).

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* Eight patients were excluded because of misdiagnosis, systemic lymphoma, concomitant cancer, or treated before registration.
† This is a single arm phase II study with 2 populations (patients 18-65 years old and patients 66-75 years old)
‡ Patients in CR after HD-MTX-based primary chemotherapy received consolidating WBRT or no further treatment. Patients without CR received WBRT or second-line chemotherapy (HD-AraC)
§ This is a single-arm phase II study

Appendix 7: Toxicities in Elderly Patients Reported from Studies Included in the 2015 Guideline from the European Association for Neuro-Oncology*

Author	n	Median age yrs. [range]	Design	Chemotherapy	Toxicities
Illerhaus et al., 2009 [5]	28	70 [57-79]	Open-label, prospective phase II trial	HD-MTX, PCV and CCNU	Grade 3 and 4 Toxicities • Neutropenia: 64% • Thrombocytopenia: 29% • Anemia: 32% • Grade 3 transient ALT and GGT elevation without liver dysfunction: 7% • Infections during neutropenia: 28% Treatment-related Mortality : 7% 1 thrombocytopenic cerebral hemorrhage, and 1 cardiac failure
Ghesquiéres et al., 2010 [7]	36	66 [61-70]	Open-label, prospective multicentric phase II study (GELA)	COP, MCOPA, CYM MCVP	Grade 4 Toxicities • Neutropenia: 90% • Infection: 19% Deaths: 27% 3 septic shock, 1 intracranial and pulmonary abscesses, 1 arrhythmia, 2 acute renal failure, 1 lethal abdominal bleeding with grade 4 thrombopenia in a context of Varicella-zoster virus infection, and 2 unknown cause
	18	73 [71-82]			Grade 4 Toxicities • Neutropenia: 63% • Infection: 6% Deaths: 17% 1 septic shock, 1 cardiac complication, 1 global deterioration of PS
Hoang-Xuan et al., 2003 [6]	50	72 [60-81]	Open-label, prospective multicenter phase II study (EORTC)	HD-MTX, CCNU, PCV, MP, and intrathecal chemotherapy with MTX and AraC	Grade 3 or 4 Toxicities • Neutropenia: 19% • Thrombocytopenia: 8% • Anemia: 8% • Hepatitis: 16% • Renal: 4%
Fritsch et al., 2011 [8]	28	75 [65-83]	Open-label monocentric pilot study	RTX, MTX, Folinic rescue, PCV, CCNU	Deaths (treatment-related): 7% 1 pulmonary embolism and 1 pneumonia

Jahnke et al., 2005 [9]	154	>70	Phase IV multicenter trial	HD-MTX followed by leucovorin rescue (MTX was renally dose adjusted using CrCl of 100 ml/min or greater as patients that would get 100% dose)	Grade 3 or 4 Toxicities (WHO criteria)[29] • Neutropenia: 10% • Thrombocytopenia: 19% • Anemia: 19% • Leukopenia: 5% • Infection: 14% • Creatinine: 5% • Transaminitis: 10% • Bilirubin: 5% • Mucositis: 0%
		>60			---------- • Neutropenia: 6% • Thrombocytopenia: 11% • Anemia: 15% • Leukopenia: 15% • Infection: 13% • Creatinine: 7% • Transaminitis: 16% • Bilirubin: 2% • Mucositis: 5%

Abbreviations: AraC (cytarabine); CCNU (lomustine); COP (cyclophosphamide, vincristine, methotrexate plus hydrocortisone, methylprednisolone); CYM (methotrexate, methotrexate plus hydrocortisone, cytosine arabinoside, cytosine arabinoside plus hydrocortisone); EORTC (European Organization for Research and Treatment of Cancer); GELA (Groupe d'Etude des Lymphomes de l'Adulte); HD-MP (high-dose methylprednisolone); HD-MTX (high-dose methotrexate); MCOPA (vincristine, methotrexate, doxorubicin, cyclophosphamide, methotrexate plus hydrocortisone, methylprednisolone); MCVP (methotrexate, cyclophosphamide, etoposide, cutosine arabinoside plus hydrocortisone, methylprednisolone); MP (methylprednisolone); PCV (procarbazine); RTX (rituximab)

* Only five studies measured the toxic effect of chemotherapy in elderly patients (older than 60 years)

Appendix 8: Percentages of Toxicities Reported by the International Extranodal Lymphoma Study Group IELSG32 Phase II Trial (Grade ≥3)

Trial	IELSG32 [1]		
Treatment-Related Toxicities	MTX, AraC (%)	MTX, AraC, RTX (%)	MTX, AraC, RTX, THIO (%)
Neutropenia	52	56	67
Thrombocytopenia	71	74	83
Anemia	32	36	47
Febrile neutropenia	21	13	16
Hepatotoxicity	12	12	8
Nephrotoxicity	1	2	2
Cardiotoxicity	0	<1	2
Coagulopathy	1	2	2
Gastrointestinal	<1	3	4
Mucositis	1	2	<1
Acute neurotoxicity	2	2	3
Hyperglycemia	2	0	<1
Sudden death	<1	<1	<1
Deaths due to toxicity	9	4	4

Abbreviations: MTX, AraC (methotrexate, cytarabine); MTX, AraC, RTX (methotrexate, cytarabine, rituximab); MTX, AraC, RTX, THIO (methotrexate, cytarabine, rituximab, thiotepa).

Appendix 9: Neurotoxicity Reported by the Nordic Lymphoma Group NLG Phase II trial

Treatment Phase	Medication before onset of symptoms	Day of onset (# events)	Symptoms (duration)	CNS Lymphoma	DepoCyt suspected
Cycle 1	RTX, HD-MTX (d.1) IFO, DEXA (d.2-5) DepoCyt (d.2)	d.3 (n=6) d.4 (n=2) d.15 (n=1)	Progressive sensory loss of the legs, arachnoiditis suspected (5 d.) Ataxia, somnolence, urinary and bowel incontinence. Cauda equine syndrome and brain dysfunction suspected (unresolved) Headache, nausea, fever, photophobia, stiffness of the back. Arachnoiditis suspected (3 d.) Fever, clinical signs of meningitis. Arachnoiditis suspected (1 d.) Nausea, fever and severe headache. Arachnoiditis suspected (day of recovery not reported) Headache, fever, vomiting, leg pain, arachnoiditis, pleocytosis in the spinal fluid (4 d.) Fever, headache, somnolence, dyspnea. Arachnoiditis and brain dysfunction suspected (4 d.) Photophobia, headache and tremor. Arachnoiditis suspected (d. 3) Fever and headache. Arachnoiditis suspected (4 d.)	Present in all nine patients	Yes
Cycle 4	HD-MTX (d.1) IFO, DEXA (d.2-5) DepoCyt (d.2)	d.7 (n=1)	Headache, nausea, vomiting, not able to eat or drink. ECOG 4. Arachnoiditis suspected (3 d.)	No	Yes
Cycle 4	HD-MTX (d.1) TMZ (d.2-6) DEXA (d.2-5) DepoCyt (d.2)	d.15 (n=1)	Sudden dysfunction and loss of sensibility of the left leg. Not able to stand or walk. Arachnoiditis suspected (2 d.)	Yes	No
Cycle 5	HD-MTX (d.1) TMZ (d.2-6) DEXA (d. 2-5)	d. 3 (n=1)	Sudden dysfunction and loss of sensibility of the left leg. Not able to stand or walk. Cognitive impairment. Arachnoiditis and brain dysfunction suspected (43 d.)	Yes	No
Cycle 1	RTX, HD-MTX (d.1)	d.2 (n=1)	Ataxia and somnolence increasing to coma. Brain dysfunction suspected (73 d.)	Yes	No

	IFO, DEXA (d.2)				
Cycle 1	AraC (d.1-2) DEXA (d.3-7) VDS (d.1)	d.7 (n=1)	Fatigue and confusion. Brain dysfunction suspected (unresolved)	Nor known	No
Maintenance	TMZ (d.1-5)	d.24 (n=1) d.3 (n=1)	Hemiparesis. Brain dysfunction suspected (unresolved) Taste disturbances. Dysfunction of brain or sensory nerves suspected (20 d.)	No	No

Other Reported Toxicities

- Organ Toxicity: 6.1% impaired kidney function, 10.6% deep venous thrombosis
- Neurotoxicity: 16 grade 2-4 events were reported in 15 patients during induction (n=13) or maintenance (n=2) therapy

Appendix 10. Modifications from the 2020 Assessment

Orignal 2017	Modified 2020
Recommendation 5	**Recommendation 5**
Whole brain radiotherapy (WBRT) or comfort-based palliative care are reasonable treatment options for patients who refuse aggressive chemotherapy or who are considered ineligible for HD-MTX-based, or alternative, chemotherapy regimens.	Whole brain radiotherapy (WBRT) or comfort-based palliative care are reasonable treatment options for patients who refuse aggressive chemotherapy or who are considered ineligible for HD-MTX-based, or alternative, chemotherapy regimens.
Qualifying Statements for Recommendation 5	***Qualifying Statements for Recommendation 5***
The clinical benefit of WBRT in this poor-risk population, compared with supportive care, has not been confirmed in prospective comparative clinical trials. WBRT as a single treatment modality is associated with a response rate of approximately 50% and median survival of approximately one year that is offset by a risk of neurotoxicity. A patient-centred, multi-disciplinary approach should be utilized prior to initiating WBRT.	The clinical benefit of WBRT in this poor-risk population, compared with supportive care, has not been confirmed in prospective comparative clinical trials. WBRT as a single treatment modality is associated with a response rate of approximately 50% and median survival of approximately one year that is offset by a risk of neurotoxicity.
Key Evidence for Recommendation 5	***Key Evidence for Recommendation 5***
• There are limited data on which to base a recommendation regarding alternative treatment for patients who are not eligible for HD-MTX-based chemotherapy regimens. • This recommendation was informed by expert opinion of the members of the Working Group.	• There are limited data on which to base a recommendation regarding alternative treatment for patients who are not eligible for HD-MTX-based chemotherapy regimens. • This recommendation was informed by expert opinion of the members of the Working Group.
Interpretation of Evidence for Recommendation 5	***Interpretation of Evidence for Recommendation 5***
Many patients with PCNS lymphoma may refuse aggressive chemotherapy due to toxicity concerns or may not be eligible for HD-MTX-based chemotherapy regimens due to unfavourable prognostic factors for survival (e.g., advanced age, poor performance status, significant comorbidities/organ dysfunction) and the decision to use alternative treatments for these patients must take a patient-centred approach carefully weighing the risks	Many patients with PCNS lymphoma may refuse aggressive chemotherapy due to toxicity concerns or may not be eligible for HD-MTX-based chemotherapy regimens due to unfavourable prognostic factors for survival (e.g., advanced age, poor performance status, significant comorbidities/organ dysfunction) and the decision to use alternative treatments for these patients must take a patient-centred approach carefully weighing the risks versus benefits of available treatment options. It is the

versus benefits of available treatment options. It is the opinion of the members of the Working Group that WBRT or comfort-based palliative care are reasonable alternatives in patients who are considered ineligible and/or refuse HD-MTX-based chemotherapy regimens.	opinion of the members of the Working Group that WBRT or comfort-based palliative care are reasonable alternatives in patients who are considered ineligible and/or refuse HD-MTX-based chemotherapy regimens.
Recommendation 6 Whole brain radiation therapy (WBRT) should not be routinely administered in patients who have achieved a complete remission following first-line chemotherapy. If a decision is made to proceed with WBRT as consolidation therapy, a patient-centred, multi-disciplinary approach is recommended to inform patients of the trade-off in risks and benefits associated with WBRT in this setting, and a dose of 40 to 45 Gy in 1.8 to 2.0 Gy fractions should be used. ***Qualifying Statements for Recommendation 6*** • In patients who achieve a CR following first-line chemotherapy, consolidation with WBRT has not been clearly shown to improve OS when compared with no radiotherapy. The addition of WBRT is associated with an increased risk of neurotoxicity that may have a significant impact on quality of life. The risk of neurotoxicity is particularly high in patients older than 60 years of age. The role of WBRT in patients who have achieved a CR following first-line chemotherapy remains controversial; a patient-centred, multi-disciplinary approach is recommended to inform patients of the trade-off in risks and benefits associated with WBRT consolidation in this setting. For transplant eligible patients, autologous stem cell transplantation (ASCT) is a reasonable alternative consolidation treatment and patients should also be informed of this treatment option (See Recommendation 7) • WBRT is a reasonable consolidation option for patients in partial remission following first line chemotherapy who are not eligible for ASCT.	**Recommendation 6** Whole brain radiation therapy (WBRT) should not be routinely administered in patients who have achieved a complete remission following first-line HD-MTX-based chemotherapy. ***Qualifying Statements for Recommendation 6*** • For transplant eligible patients, autologous stem cell transplantation (ASCT) is a reasonable alternative consolidation treatment and patients should also be informed of this treatment option (See Recommendation 7) • In patients who achieve a CR following first-line chemotherapy, consolidation with WBRT has not been clearly shown to improve OS when compared with no radiotherapy. The addition of WBRT is associated with an increased risk of neurotoxicity that may have a significant impact on quality of life. The risk of neurotoxicity is particularly high in patients older than 60 years of age. The role of WBRT in patients who have achieved a CR following first-line chemotherapy remains controversial; a patient-centred, multi-disciplinary approach is recommended to inform patients of the trade-off in risks and benefits associated with WBRT consolidation in this setting. • WBRT is a reasonable consolidation option for patients in partial remission following first line chemotherapy who are not eligible for ASCT. • Reduced-dose WBRT consolidation (23.4 to 30.0 Gy in 1.8 to 2.0 Gy fraction) has not been adequately compared with the standard-dose WBRT (40 to 45 Gy in

- Reduced-dose WBRT consolidation (23.4 to 30.0 Gy in 1.8 to 2.0 Gy fraction) has not been adequately compared with the standard-dose WBRT (40 to 45 Gy in 1.8 to 2.0 Gy fraction) in a prospective randomized trial; thus, the risks and benefits associated with this approach are unclear and cannot be recommended outside a clinical trial.
- Hyperfractionated WBRT consolidation has not been adequately compared with the standard-dose WBRT in a randomized trial, and therefore the optimal dose for hyperfractionated schedules remains unclear and cannot be recommended outside a clinical trial.
- Elderly patients (older than 60 years of age) have an increased risk of neurotoxicity when WBRT is combined with chemotherapy. If a CR is reached in this patient group, WBRT should be avoided.

Key Evidence for Recommendation 6

The recommendation represents the consensus of the Working Group after reviewing the evidence from the 2015 European Association for Neuro-Oncology Guidelines [2], one phase III randomized controlled trial [10], and a single-arm phase II trial .

- The 2015 European Association for Neuro-Oncology acknowledged the greater risks of neurotoxicity associated with WBRT, and concluded that consolidation WBRT after HD-MTX-based chemotherapy remains controversial. It is the opinion of the European task force that although the optimal dose has not yet been defined, it should be chosen on the basis of the response to primary chemotherapy. In patients younger than 60 years of age with progressive or residual disease after primary chemotherapy, a total dose of 40 to 45 Gy with 1.8 to 2.0 Gy dose per fraction was recommended. The decision to deliver WBRT to patients with CR should be discussed with the patient. The authors recommended

1.8 to 2.0 Gy fraction) in a prospective randomized trial; thus, the risks and benefits associated with this approach are unclear and cannot be recommended outside a clinical trial.
- Hyperfractionated WBRT consolidation has not been adequately compared with the standard-dose WBRT in a randomized trial, and therefore the optimal dose for hyperfractionated schedules remains unclear and cannot be recommended outside a clinical trial.
- Elderly patients (older than 60 years of age) have an increased risk of neurotoxicity when WBRT is combined with chemotherapy. If a CR is reached in this patient group, WBRT should be avoided.

Key Evidence for Recommendation 6

The recommendation represents the consensus of the Working Group after reviewing the evidence from the 2015 European Association for Neuro-Oncology Guidelines [2], one phase III randomized controlled trial [10], and a single-arm phase II trial .

- The 2015 European Association for Neuro-Oncology acknowledged the greater risks of neurotoxicity associated with WBRT, and concluded that consolidation WBRT after HD-MTX-based chemotherapy remains controversial. It is the opinion of the European task force that although the optimal dose has not yet been defined, it should be chosen on the basis of the response to primary chemotherapy. In patients younger than 60 years of age with progressive or residual disease after primary chemotherapy, a total dose of 40 to 45 Gy with 1.8 to 2.0 Gy dose per fraction was recommended. The decision to deliver WBRT to patients with CR should be discussed with the patient. The authors recommended that reduced-dose WBRT consolidation should only be investigated in clinical trials.

that reduced-dose WBRT consolidation should only be investigated in clinical trials. • The phase III randomized controlled trial [10] used a non-inferiority design to evaluate the role of WBRT in primary therapy of patients with PCNS lymphoma. Patients were randomly allocated to receive HD-MTX-based chemotherapy alone or followed by WBRT. The statistical proof of non-inferiority regarding survival was not proven because the lower limit of the confidence intervals crossed the a priori defined non-inferiority margin of 0.9. The authors reported comparable survival rates (32.4 versus 36.1 months; HR, 0.98; 95% CI, 0.79 to 1.26; p=0.98) after a follow-up of 81.2 months. Treatment-related neurotoxicity was more common in patients receiving WBRT than in those who did not receive WBRT (49% versus 26%; p=0.054 by clinical assessment, and 71% versus 46%; p=0.04 by neuroradiology assessment). • The single-arm phase II trial [11], a prospective cooperative group study, reported on the use of MTX, rituximab, and temozolomide, followed by hyperfractionated WBRT and subsequent temozolomide for the treatment of patients with PCNS lymphoma. The authors reported significantly improved two-year PFS (63.6% versus 50%; p=0.03) and OS (80.8% versus 64%; p=0.006) when compared with historical controls from the RTOG-9310 trial. • The recommendation for elderly patients represents the consensus of the members of the Working Group ***Interpretation of Evidence for Recommendation 6*** WBRT as consolidation treatment has not been clearly shown to improve overall survival in patients who have achieved a CR following first-line HD-MTX-based chemotherapy regimens. Patients treated with WBRT following standard first-line chemotherapy regimens are at increased risk for developing clinical neurotoxicity including	• The phase III randomized controlled trial [10] used a non-inferiority design to evaluate the role of WBRT in primary therapy of patients with PCNS lymphoma. Patients were randomly allocated to receive HD-MTX-based chemotherapy alone or followed by WBRT. The statistical proof of non-inferiority regarding survival was not proven because the lower limit of the confidence intervals crossed the a priori defined non-inferiority margin of 0.9. The authors reported comparable survival rates (32.4 versus 36.1 months; HR, 0.98; 95% CI, 0.79 to 1.26; p=0.98) after a follow-up of 81.2 months. Treatment-related neurotoxicity was more common in patients receiving WBRT than in those who did not receive WBRT (49% versus 26%; p=0.054 by clinical assessment, and 71% versus 46%; p=0.04 by neuroradiology assessment). • The single-arm phase II trial [11], a prospective cooperative group study, reported on the use of MTX, rituximab, and temozolomide, followed by hyperfractionated WBRT and subsequent temozolomide for the treatment of patients with PCNS lymphoma. The authors reported significantly improved two-year PFS (63.6% versus 50%; p=0.03) and OS (80.8% versus 64%; p=0.006) when compared with historical controls from the RTOG-9310 trial. • The recommendation for elderly patients represents the consensus of the members of the Working Group ***Interpretation of Evidence for Recommendation 6*** WBRT as consolidation treatment has not been clearly shown to improve overall survival in patients who have achieved a CR following first-line HD-MTX-based chemotherapy regimens. **Patients treated with WBRT following standard first-line chemotherapy regimens are at increased risk for developing clinical neurotoxicity including impaired cognition, dementia, ataxia, and incontinence.** It is the opinion of the members of the

impaired cognition, dementia, ataxia, and incontinence. It is the opinion of the members of the Working Group that a patient-centred, multi-disciplinary approach is recommended to inform patients of the trade-off in risks and benefits associated with WBRT consolidation in this setting. Elderly patients (>60 years) are at particularly high risk for neurotoxicity with WBRT consolidation following chemotherapy; therefore, it is the opinion of the Working Group that WBRT should be avoided in this patient group.	Working Group that a patient-centred, multi-disciplinary approach is recommended to inform patients of the trade-off in risks and benefits associated with WBRT consolidation in this setting. Elderly patients (>60 years) are at particularly high risk for neurotoxicity with WBRT consolidation following chemotherapy; therefore, it is the opinion of the Working Group that WBRT should be avoided in this patient group.
Recommendation 7 High-dose thiotepa-based conditioning chemotherapy and ASCT is a reasonable consolidation option for transplant-eligible patients with stable disease or better response following first-line HD-MTX-based chemotherapy for the treatment of PCNS lymphoma. ***Qualifying Statement for Recommendation 7*** ASCT and WBRT are both reasonable options for consolidation post-first-line chemotherapy (see Recommendation 6). In the absence of a survival benefit for ASCT versus WBRT, differences in toxicity and patient preference must be carefully considered. It is the opinion of the members of the Working Group that a patient-centred, multi-disciplinary approach should be implemented to inform patients of the benefits and differential risk associated with ASCT (complications related to myeloablative chemotherapy) and WBRT (neurotoxicity). ***Key Evidence for Recommendation 7*** This recommendation is supported by two randomized phase II trials comparing consolidation chemotherapy with WBRT versus ASCT in patients with PCNS lymphoma [12,13]. Both trials compared sequential HD-MTX and AraC-based chemotherapy plus rituximab followed by	**Recommendation 7** High-dose thiotepa-based conditioning chemotherapy and ASCT should be considered as consolidation therapy for transplant-eligible patients with stable disease or better response following first-line HD-MTX-based chemotherapy for the treatment of PCNS lymphoma. ***Qualifying Statement for Recommendation 7*** Despite an absence of data indicating a survival benefit for ASCT over WBRT, ASCT is preferred because of the significant neurotoxicity of WBRT. The differences in toxicity and patient preference must be carefully considered and a patient-centred, multi-disciplinary approach should be implemented to inform patients of the benefits and differential risk associated with ASCT (complications related to myeloablative chemotherapy) and WBRT (neurotoxicity). ***Key Evidence for Recommendation 7*** This recommendation is supported by two randomized phase II trials comparing consolidation chemotherapy with WBRT versus ASCT in patients with PCNS lymphoma [12,13]. Both trials compared sequential HD-MTX and AraC-based chemotherapy plus rituximab followed by WBRT or high-dose chemotherapy (HD-CT)/ASCT with two-

WBRT or high-dose chemotherapy (HD-CT)/ASCT with two-year PFS as the primary endpoint. The conditioning regimen used by the two groups consisted of a high dose of carmustine and thiotepa [12], and thiotepa, busulfan, and cyclophosphamide [13]. These two trials have been published in abstract form. • The IELSG32 trial reported on an intention-to-treat basis. They reported no statistically significant difference in two-year PFS between WBRT and ASCT (80 ± 5% after WBRT versus 70 ± 6% after ASCT). Multivariable analysis suggested no statistical difference in two-year OS between patients treated with WBRT and those treated with ASCT (85 ± 5% versus 71 ± 6%; p=0.12). Comparison of WBRT with ASCT reported significant impairment of attention/executive functions and non-significant trend to impaired memory in patients treated with WBRT, while improved functions were observed in patients treated with ASCT. Both consolidation therapies were reported to be associated with significant improvement in language and quality of life. Further information surrounding quality of life and neurotoxicity have not been reported, but are expected to be available when results from the second randomization addressing the role of consolidation therapy are fully published. • At a median follow-up of 33 months, the Anocef-Goelams trial reported a two-year PFS for patients in the HD-CT/ASCT arm of 86.8% (95% CI, 76.6 to 98.3) compared with a two-year PFS for patients in the WBRT arm of 63.2% (95% CI, 49.5 to 80.5). Data regarding OS and neuropsychological evaluations have not yet been reported.	year PFS as the primary endpoint. The conditioning regimen used by the two groups consisted of a high dose of carmustine and thiotepa [12], and thiotepa, busulfan, and cyclophosphamide [13]. These two trials have been published in abstract form. • The IELSG32 trial reported on an intention-to-treat basis. They reported no statistically significant difference in two-year PFS between WBRT and ASCT (80 ± 5% after WBRT versus 70 ± 6% after ASCT). Multivariable analysis suggested no statistical difference in two-year OS between patients treated with WBRT and those treated with ASCT (85 ± 5% versus 71 ± 6%; p=0.12). Comparison of WBRT with ASCT reported significant impairment of attention/executive functions and non-significant trend to impaired memory in patients treated with WBRT, while improved functions were observed in patients treated with ASCT. Both consolidation therapies were reported to be associated with significant improvement in language and quality of life. Further information surrounding quality of life and neurotoxicity have not been reported, but are expected to be available when results from the second randomization addressing the role of consolidation therapy are fully published. • At a median follow-up of 33 months, the Anocef-Goelams trial reported a two-year PFS for patients in the HD-CT/ASCT arm of 86.8% (95% CI, 76.6 to 98.3) compared with a two-year PFS for patients in the WBRT arm of 63.2% (95% CI, 49.5 to 80.5). Data regarding OS and neuropsychological evaluations have not yet been reported.
Interpretation of Evidence for Recommendation 7	***Interpretation of Evidence for Recommendation 7***
The evidence considered to inform this recommendation derived from two prospective phase II	The evidence considered to inform this recommendation derived from two prospective phase II trials reported in abstract form with a few limitations. The

trials reported in abstract form with a few limitations. The IELSG32 trial was not powered to detect a difference in OS (the primary endpoint of the second randomization was two-year PFS). Neither study was designed to determine whether ASCT has equivalent or non-inferior efficacy (non-inferiority design) than WBRT as the consolidation treatment for patient with PCNS lymphoma, and therefore definitive conclusions regarding the optimal consolidation therapy cannot yet be drawn. In addition, there are limited data on which to base a recommendation regarding the optimal conditioning regimen as only thiotepa-based regimens have been considered.	IELSG32 trial was not powered to detect a difference in OS (the primary endpoint of the second randomization was two-year PFS). Neither study was designed to determine whether ASCT has equivalent or non-inferior efficacy (non-inferiority design) to WBRT as the consolidation treatment for patient with PCNS lymphoma. As per above, ASCT is preferred because of the severe cognitive impairment and neurotoxicity associated with WBRT.