



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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Report Date: October 16, 2017

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PEBC Report Citation (Vancouver Style): Fraser G, Varela NP, Dudebout J, Greenspoon J, Hicks L, Laperriere N, Prica A, Kouroukis T, and the Primary Central Nervous System Lymphoma Guideline Development Group. Management of primary central nervous system diffuse large B-cell lymphoma (PCNS DLBCL). Toronto (ON): Cancer Care Ontario; 2017 September 26. Program in Evidence-Based Care Guideline No.: SCT-8.

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

Recommendations

This summary is a quick reference guide and provides the guideline recommendations only. For key evidence associated with each recommendation, see [the full report](#).

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 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 of clinical trials.

Recommendation 4

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

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. A patient-centred, multi-disciplinary approach should be utilized prior to initiating WBRT.

Recommendation 6

WBRT should not be routinely administered in patients who have achieved a complete remission (CR) 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 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. 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.
- 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

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 Statements 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 risks 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.

