Balancing relapses versus cognitive impairment in primary central nervous system lymphoma: a single-center experience

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Introduction

Primary central nervous system lymphoma (PCNSL) is a rare subtype of non-Hodgkin lymphoma. The majority of histopathology is diffuse large B-cell lymphoma (DLBCL). The PCNSL involves mainly intracerebral and intraocular areas without evidence of systemic lymphoma. For human immunodeficiency virus (HIV) seronegative patients, the median age of PCNSL patients is 60 years resulting in reduced tolerability to aggressive cancer treatments. The neurological deficit is the most common manifestation. Both patient factors, such as elderly and poor performance status, and disease factors, including aggressive biology and poor blood-brain barrier penetration for chemotherapy, leading to poor prognosis and inferior treatment outcome [1,2].

In this era, treatment outcomes of PCNSL are much improved. The multi-modality regimens, which comprise immunochemotherapy, high-dose chemotherapy followed by autologous stem cell transplantation (ASCT) and/or radiotherapy, are considered as the current effective treatments [3–15]. The high-dose methotrexate (HD-MTX) has become the backbone of standard treatment. In addition, consolidation therapy has been frequently incorporated into the first-line treatment to better clinical outcomes. Whole brain radiotherapy (WBRT) demonstrates its efficacy by improving responses and prolonging duration of remission in many studies. The consolidation treatment with low-dose WBRT is controversial not only due to an awareness of its neurotoxic effects but also due to unknown efficacy [2,3,16–21]. Although the varieties of effective regimens have been established, some expensive targeted therapies are neither available nor reimbursable in limited-resource countries, and elderly patients are not the first candidates for ASCT. These issues strongly influence the decision to choose treatment regimens for most PCNSL patients in limited-resource countries.

One of the major adverse events in PCNSL is the treatment-related cognitive impairment, especially when combined high-dose chemotherapy with WBRT.
Owing to the complexity of neuropsychological test battery [22–24], the screening test was preferred in general clinical practice and hospital without specialist. The Montreal Cognitive Assessment (MoCA) is a global cognitive screening tool which has been validated to detect mild cognitive impairment (MCI) in many populations [25–27].

This study aimed to evaluate the role of low-dose WBRT and treatment outcomes of MTX-based regimens for newly diagnosed PCNSL. In addition, the post-treatment cognitive impairment was serially evaluated during long-term follow up. This is the first report of the MoCA test in this high-risk population.

Materials and methods

The retrospective analytical study recruited newly diagnosed PCNSL (DLBCL) patients who were treated with methotrexate-based regimen at King Chulalongkorn Memorial Hospital from 2011 to May 2016. The diagnosis required the presence of CD20 positive large cells in CNS tissue biopsy without evidence of systemic lymphoma by physical examination, computed tomography of chest and whole abdomen and negative bone marrow biopsy. The patients with positive for HIV antibody tests were excluded. The protocol was approved by the Institutional Review Board of the Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand.

Thirty-seven PCNSL patients received HD-MTX-containing regimens as the first-line treatment. There were 16 patients receiving HD-MTX alone and 21 patients receiving HD-MTX plus ifosfamide regimen (MTX-Ifos). The patients who received MTX-Ifos needed to be younger than 65 years old and had a good performance status. The HD-MTX regimen comprised six cycles of methotrexate 3–4 g/m² every 14 days. The MTX-Ifos comprised six cycles of methotrexate 4 g/m² on day 1 and ifosfamide 1.5 g/m² on day 3–5 every 14 days. The radiotherapy including WBRT was given depending on the response to chemotherapy. In our center, the radiotherapy protocols for PCNSL were 30.6 Gy WBRT for some patients with complete response (CR) and 30–36 Gy WBRT plus a lesional boost up to 45–50 Gy to all partial response (PR) patients (1.8 Gy per fraction).

The PCNSL patients who were still in the first CR were cross-sectionally assessed twice at 2 years apart for the treatment-related cognitive impairment by the trained physician. The Thai version of the Montreal Cognitive Assessment (Thai-MoCA), which had already been validated, was used as a cognitive screening tool. The cut-off score of Thai-MoCA for MCI was 18–24 (total score = 30) yielding 70% sensitivity and 95% specificity. The cut-off score for dementia was less than 18 yielding 80% sensitivity and 95% specificity [26].

The primary endpoint was the progression-free survival (PFS) comparing cases receiving WBRT and cases without WBRT. The secondary endpoints were overall survival (OS), overall response rate (ORR), which consists of CR rate and PR rate, toxicity of chemotherapy and the cognitive impairment screening outcome. The PFS was defined from date of starting chemotherapy to date of progression/relapsed disease or death. The OS was defined from date of starting chemotherapy until death from any causes. The treatment response was evaluated by magnetic resonance imaging according to the international workshop to standardize baseline evaluation and response criteria for PCNSL [28]. Data were analyzed using GraphPad Prism7 software. The Kaplan–Meier analysis, Fisher’s exact test and Mann–Whitney U test were performed as appropriate. The p value <0.05 was considered statistically significant.

Results

Thirty-seven newly diagnosed PCNSL patients comprised 16 patients in the HD-MTX group and 21 patients in the MTX-Ifos group. The median age was 56 (range 16–78) years. The female to male ratio was 1.6:1. According to chemotherapy regimen, the median age and percentage of high Eastern Cooperative Oncology Group (ECOG 2–4) were 57.8 (51–78) years old and 62.5%, respectively, in HD-MTX cohort. The median age and percentage of high ECOG patients of MTX-Ifos group were 52 (16–64) years old and 33.3%. The patients who received HD-MTX were older (p = 0.04). The difference in performance status was not statistically significant (p = 0.18). The other prognostic factors [29], i.e. high lactate dehydrogenase (LDH), deep-structure sites and high cerebrospinal fluid (CSF) protein showed no significant difference between two groups. Rituximab (375 mg/m²) was prescribed to 25% (4/16) and 9.5% (2/21) of HD-MTX and MTX-Ifos patients, respectively, depending on physician preference and patient financial status. The consort diagram of the first-line PCNSL treatment was presented in Figure 1.

The ORR of MTX-Ifos and HD-MTX groups were 66.7% and 50%, respectively (p = 0.34). The CR and PR rates after MTX-Ifos treatment were 47.6% and 19%, respectively, while the CR and PR rates after HD-MTX treatment were 37.5% and 12.5%, respectively. The 37.5% (6/16) of CR patients received WBRT of 30.6 Gy as consolidation therapy. All PR patients were prescribed WBRT of 30–36 Gy plus a lesional boost to 45–50 Gy. The entire group of PR patients achieved CR after received radiotherapy as part of the first-line treatment. The patients who did not respond to MTX-based regimen (21.6%) were changed to another protocol or switched to radiotherapy. The serious adverse events, which leaded to stop treatment
protocols, occurred in 19% and 18.7% of MTX-Ifos and HD-MTX, respectively. The baseline characteristics of patients categorized by the chemotherapy response were shown in Supplementary Table 1. The response and toxicity profiles from these 2 MTX-based regimens were summarized in Table 1. The median OS of CR/PR group was significantly better than those of SD/PD and severe toxicity groups (not reach vs. 14 months vs. 7.5 months, respectively, \( p < 0.0001 \)) (Figure 2).

According to our primary endpoint, the Kaplan–Meier analysis was performed in 22 CR patients. For evaluation of the benefit from low-dose WBRT, the CR patients were categorized into two groups; No-WBRT \( (n = 10) \) and WBRT \( (n = 12) \) groups. The No-WBRT cohort enrolled patients who achieved CR after chemotherapy without receiving WBRT. The WBRT cohort cases were six patients who achieved CR after chemotherapy and underwent WBRT combined with six PR patients who achieved CR after receiving radiotherapy. The patient characteristics were summarized in Table 2. No significant difference in age, prognostic factors and chemotherapy regimen was detected comparing between two groups. The median follow-up time of CR patients was 36 (7–72) months. The No-WBRT group demonstrated the significantly worse PFS than that of WBRT group by the log-rank (Mantel–Cox) test (hazard ratio [HR] 4.75, 95% confidence interval 1.14–19.82; \( p = 0.03 \)). The 3-year PFS comparing between No-WBRT and WBRT were 35% and 78.75%, respectively (Figure 3). The 3-year OS of both groups were similar at 87.5%.

The PFS difference between HD-MTX and MTX-Ifos was not significant using the Kaplan–Meier analysis. Sixty percent (6/10) of patients without WBRT, and 16.7% (2/12) with WBRT had recurrence. The median time to relapse was 22 (3–27) months. Both relapsed patients in the WBRT cohort presented with systemic relapsed DLBCL without CNS disease. All six relapsed patients in No-WBRT group were CNS relapse. The salvage regimens were mostly HD-MTX-based treatment combined with high-dose cytarabine or ifosfamide. Four of six cases and three of six CNS-relapsed patients received rituximab and WBRT, respectively. All relapsed patients achieved CR after salvage therapy.

### Table 1. Treatment response of newly diagnosed PCNSL patients.

| Response | HD-MTX (\( n = 16 \)) (% | MTX-Ifos (\( n = 21 \)) (%) | Total (\( n = 37 \)) (%) |
|----------|--------------------------|-----------------------------|--------------------------|
| CMT response (6 cycles) | | | |
| CR | 6 (37.5) | 10 (47.6) | 16 (43.2) |
| PR | 2 (12.5) | 4 (19) | 6 (16.2) |
| ORR | 8 (50) | 14 (66.7) | 22 (59.5) |
| SD/PD (any cycles) | 5 (31.3) | 3 (14.3) | 8 (21.6) |
| Toxicity* (any cycles) | 3 (18.7) | 4 (19) | 7 (18.9) |
| Post CMT treatment* | (\( n = 8 \)) | (\( n = 14 \)) | (\( n = 22 \)) |
| CR after CMT → no WBRT | 4 | 6 | 10 |
| WBRT in CR patients | 2 | 4 | 6 |
| WBRT + boost in PR | 2 | 4 | 6 |
| Post CMT ± XRT response CR | 8 (50) | 14 (66.7) | 22 (59.5) |

Notes: CMT: chemotherapy; CR: complete response; PR: partial response; ORR: overall response; SD: stable response; PD: progressive disease; XRT: radiotherapy; WBRT: whole brain radiotherapy.

*Patients had intolerable toxicities from CMT and subsequently received only palliative treatments.

*Only CR or PR patients after chemotherapy.
Ten PCNSL patients who continued to be in the first CR were evaluated for cognitive impairment by the MoCA. The median durations from initial chemotherapy to the first MoCA and second MoCA tests were 22.5 (9–49) months and 42 (20–72) months, respectively. Of 10 evaluated, 4 patients demonstrated normal cognitive function, whereas 5 and 1 patients were diagnosed MCI and dementia by the screening test, respectively. All five MCI patients were in WBRT exposed cohort. The median interval between 2 evaluations was 24 (range 21–27) months. The screening results of two patients deteriorated from normal to MCI. However, one patient had a cognitive improvement from MCI to a normal screening test. The results were displayed in Table 3. Except the dementia patient (No. 3), all patients lived independently and could perform their daily-life activities without recognition of their cognitive impairment by themselves or families. The patient No. 3 who never exposed to radiotherapy was dependent due to persistent right hemiparesis and dementia.

**Discussion**

In this study, we presented the treatment outcome of PCNSL in a limited-resource country. The high-dose MTX-based regimens were shown to be effective treatments with manageable toxicities for newly diagnosed PCNSL patients including the elderly. The ORR and CR rates after MTX-based regimens were comparable to previous studies [4–7,17,30–32]. The CR is the primary goal for PCNSL treatment due to significant OS benefit. In our study, 43.2% of patients accomplished CR after chemotherapy alone. Therefore, approximately 50% of the patients needed other treatment modalities to achieve CR. Most Thai patients cannot afford rituximab, temozolomide and thiotepa as well as high-dose chemotherapy followed by stem cell transplantation. Furthermore, procarbazine is currently not available in Thailand. Therefore, the options of salvage treatments were limited.

### Table 2. Baseline characteristics of PCNSL patients in complete remission.

| Prognostic factors | No WBRT (n = 10) (%) | WBRT (n = 12) (%) | p valuea |
|--------------------|----------------------|------------------|----------|
| Age (year)         | 56.5 (48–62)         | 54 (36–69)       | 0.32     |
| ECOG 2-4           | 4/10 (40)            | 4/11 (36)        | >0.99    |
| Elevated LDH       | 3/10 (30)            | 3/11 (27)        | >0.99    |
| Deep structureb    | 6/10 (60)            | 3/12 (25)        | 0.19     |
| High CSF protein   | 5/8                  | 5/7              |          |
| Missing CSF data   | 2                    | 5                |          |
| HD-MTX             | 4/10 (40)            | 4/12 (33.3)      | >0.99    |

Notes: ECOG: Eastern Cooperative Oncology Group; LDH: lactate dehydrogenase; CSF: cerebrospinal fluid.

*aMann–Whitney U test and Fisher’s exact test were performed for continuous data and categorical data, respectively.

*bDeep structure: brain stem, cerebellum, basal ganglion, periventricular and corpus callosum.

### Table 3. The results of the MoCA in PCNSL patients who were continuously in first complete remission (n = 10).

| No | Ageb | CMB | CMT resp | CMT/Boost (Gy) | First MoCAa | First timeb (months) | Second MoCAa | Second timeb (months) |
|----|------|-----|----------|---------------|-------------|-----------------------|--------------|-----------------------|
| 1  | 57   | HD-MTX | CR | No | 25/normal | 49 | 27/normal | 72 |
| 2  | 56   | R-MTX-Ifos | CR | No | 25/normal | 13 | 25/normal | 36 |
| 3  | 61   | MTX-Ifos | CR | No | 9/dementia | 20 |
| 4  | 47   | MTX-Ifos | CR | 30.6 | 23/MCI | 14 | 18/MCI | 38 |
| 5  | 36   | MTX-Ifos | CR | 30.6 | 25/normal | 9 | 23/MCI | 35 |
| 6  | 62   | R-MTX-Ifos | CR | 30.6 | 23/MCI | 9 | 25/normal | 32 |
| 7  | 51   | HD-MTX | PR | 36/43.2 | 27/MCI | 43 | 27/normal | 70 |
| 8  | 56   | MTX-Ifos | PR | 36/30.4 | 25/normal | 29 | 21/MCI | 53 |
| 9  | 42   | MTX-Ifos | PR | 36/30.4 | 21/MCI | 28 | 21/MCI | 52 |
| 10 | 56   | MTX-Ifos | PR | 36/30.4 | 22/MCI | 28 | 20/MCI | 46 |

Notes: No: number; CMT: chemotherapy; CMT resp: response after complete chemotherapy; WBRT: whole brain radiotherapy; MCI: mild cognitive impairment.

*aAge at PCNSL diagnosis.

*bMoCA (The validated Thai version [26]); normal ≥25, 18–24 MCI (sensitivity 70%, specificity 95%), <18 Dementia (sensitivity 80%, specificity 95%).

*Time from start chemotherapy.

*Patient did not have doctor appointment during second MoCA evaluation time and refused to come for extra visit.
The treatment-related cognitive impairment, especially radiotherapy (WBRT), is one of major concerns which lead physicians to omit radiation. The phase III randomized controlled trial showed no significant difference in OS comparing between with and without radiation (45 Gy) [17,18]. Some clinical trials demonstrated efficacy of consolidation therapy with low-dose radiotherapy (23.4 Gy) follow by cytarabine in CR patients with very low cognitive function toxicity [16,33]. Recently, international randomized phase II trial [21] reported no significant difference of PFS and CR rate improvement between WBRT (36 ± 9 Gy) and ASCT as a consolidation therapy after HD-MTX-based chemo-immunotherapy. However, WBRT cohort showed a significant impairment in attention/executive functions compared with ASCT cohort. Our study demonstrated that WBRT significantly prolonged PFS without significant effect on OS. These reflected the efficacy of HD-MTX-based immuno-radiotherapy for salvage PCNSL treatment. Although the recurrence was salvageable, the median time to relapse was only 22 (3–27) months.

Our result supported the existing evidence that WBRT prolongs PFS which need to balance with its toxicity. The risks of neurological deficits including salvage treatment toxicities from relapsed diseases and the risks of cognitive impairment from WBRT should be carefully considered for the role of low-dose WBRT as consolidation therapy, especially CR patients. These lead us to serially evaluate the cognitive impairment and its progression in CR patients using MoCA screening test. With the median interval between two evaluations of 24 months, we detected two cognitive-deteriorated patients and one cognitive-improved patient in WBRT cohort. The median time to second MoCA test was 42 (20–72) months after initial treatment. Our small pilot study presented two normal cognitive functions and one dementia assessed from CR patients who never received WBRT. For WBRT (30.6–36 Gy) exposed patients, two normal and five MCI patients were found. However, without the MoCA screening test, patients and family did not recognize the MCI status by themselves. Owing to the complexity of neuropsychological test battery, the screening test was preferred for clinical practice. Although MoCA is a crude cognitive evaluation, we proposed it as a global screening tool for MCI detection in PCNSL patients after therapy.

**Conclusions**

Our study supported the roles of HD-MTX and MTX-ifos as effective treatments with manageable toxicities for newly diagnosed PCNSL patients, including the elderly patients. In limited-resource countries, subsequent radiotherapy still plays a role in further response improvement. In addition, the role of WBRT consolidation to prevent relapses should be carefully weighed against cognitive impairments, which are mostly mild. However, the long-term post-treatment cognitive adverse effects need further validation in a larger cohort with longer follow up.

**Disclosure statement**

No potential conflict of interest was reported by the authors.

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