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# Primary Central Nervous System Lymphoma – Recent Advance on Clinical Research

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## 1. Introduction

A primary central nervous system lymphoma (PCNSL) is an extranodal form of non-Hodgkin's lymphoma arising in the craniospinal axis. For many years, PCNSLs were reported to represent 3–5% of all primary central nervous system (CNS) tumors [1]. However, PCNSL appears to be increasing in incidence [2–4]. PCNSL age-adjusted incidence (0.15 to 0.48, a 3-fold increase) outpaced that of systemic lymphoma (14.1 to 18.5, a 33% increase) for the same registries over the same time periods [2]. The increase is evident in all age groups and in both genders [2]. The tumor manifestation is often diffuse and multifocal, and most frequently affects the supratentorial brain parenchyma. The absence of systemic lymphadenopathies and other extracranial localizations of disease should be confirmed. Most PCNSLs belong to the diffuse large B-cell lymphomas (DLBCLs), but differ from systemic DLBCLs by their less favorable prognosis. The systemic use of high-dose methotrexate (HD-MTX)-based chemotherapy with radiation therapy for newly diagnosed PCNSL has improved the median overall survival (OS) from 20 to 36 months [5–8]. However, more intense efforts are required to improve the outcome of the patients and to identify novel therapeutic strategies. In this article, we will review the recent developments of basic and clinical research on PCNSL.

## 2. Clinical characteristics

PCNSL has been described at all ages, but usually arise in the fifty to sixty years, with a male to female ratio of 1.5 [9]. The symptoms are focal neurological deficits, mental disturbance and increased intracranial pressure. The characteristics of radiographic findings of

PCNSL are homogenous contrast enhancement on MRI with gadolinium at least 15 mm in contact with the subarachnoid space [10], periventricular lesions involving the corpus callosum, basal ganglia, or thalamus. The eye is involved in about 20% of patients [11]. Leptomeningeal involvement is seen in about 18% [12]. The tumor is single in 60% of patients and multiple in the remainder [10]. Diffusion-weighted MRI (DW-MRI) and proton-MR-spectroscopy (1H-MRS) usually reveal a uniformly pathologic pattern of metabolite concentrations [10]. The absence of systemic lymphadenopathies and other extracranial localizations of disease should be confirmed. Corticosteroids can temporarily cause regression of the tumor in 40-85% of patients [13]. Diagnosis requires histologic confirmation. Molecular analysis of the rearrangement of immunoglobulin heavy chain genes by means of polymerase chain reaction (PCR) and Southern blotting may be acceptable [14]. Most PCNSLs belong to diffuse large B cell and phenotypically express pan-B-cell markers such as CD19, CD20, CD22 and CD79a. The majority of PCNSL express BCL-6, a marker of GCB (germinal center B-cell-like) cells, and MUM1, a marker of late GCB cells.

### 3. Treatment

PCNSL is sensitive to radiation therapy, however patients treated with radiotherapy alone had 5-year overall survivals of 3-4%, more than 80% patients relapsed within 10-14 months [15]. Standard radiotherapy for patients consists of 40 Gy to whole brain with an additional boost of 10-20 Gy on the tumor bed [16]. Shibamoto et al. [17] reported the recent improved results of radiation monotherapy, 5-year survival was 25% for patients 63 years old or younger, and 9.8% for those older than 63 years. Since total irradiation dose is an important predictor of delayed neurotoxicity, a decrease in the incidence of this complication should be expected if the total irradiation dose is reduced. Several studies have demonstrated that HD-MTX, with or without other chemotherapeutic agents, yielded high response rates with 33-45 months over all survival. These results are better than the results of radiotherapy alone. HD-MTX is widely recognized as the single most effective chemotherapeutic agent for PCNSL [18-23]. MTX is usually administered at high doses with various schedules. Recently, randomized trials for PCNSLs are reported. Ferreri et al. [6] assessed the effect of adding high-dose cytarabine to methotrexate in patients with newly diagnosed PCNSL in a randomised phase 2 trial. Seventy-nine patients with PCNSLs were randomly divided to receive four courses of either methotrexate 3.5 g/m<sup>2</sup> on day 1 (n=40) or methotrexate 3.5 g/m<sup>2</sup> on day 1 plus cytarabine 2 g/m<sup>2</sup> twice a day on days 2-3 (n=39). Both regimens were administered every 3 weeks and were followed by whole-brain radiotherapy (WBRT). After chemotherapy, seven patients given methotrexate and 18 given methotrexate plus cytarabine achieved a complete remission, with a complete remission rate of 18% and 46% (p=0.006), and a 3-year OS of 32% and 46% (p=0.07) respectively. In patients aged 75 years and younger with PCNSL, the addition of high-dose cytarabine to high-dose methotrexate provides improved outcome with acceptable toxicity compared with high-dose methotrexate alone. Thiel et al. [8] aimed to investigate whether first-line chemotherapy based on high-dose methotrexate was non-inferior to the same chemotherapy regimen followed by WBRT for over-

all survival. Patients received high-dose methotrexate ( $4 \text{ g/m}^2$ ) on day 1 of six 14-day cycles; thereafter, patients received high-dose methotrexate plus ifosfamide ( $1.5 \text{ g/m}^2$ ) on days 3-5 of six 14-day cycles. In those assigned to receive first-line chemotherapy followed by radiotherapy, WBRT was given to a total dose of 45 Gy. 551 patients (median age 63 years) were enrolled and randomised, of whom 318 were treated per protocol. In the per-protocol population, median OS was 32.4 months in patients receiving WBRT ( $n=154$ ), and 37.1 months in those not receiving WBRT ( $n=164$ ), hazard ratio 1.06 ( $p=0.71$ ). Median progression-free survival (PFS) was 18.3 months in patients receiving WBRT, and 11.9 months ( $p=0.14$ ) in those not receiving WBRT. Treatment-related neurotoxicity in patients with sustained complete response was more common in patients receiving WBRT than in those who did not. No significant difference in OS was recorded when WBRT was omitted from first-line chemotherapy in patients with newly diagnosed PCNSL. The PFS benefit afforded by WBRT has to be weighed against the increased risk of neurotoxicity in long-term survivors. The results of this trial may indicate that WBRT can be omitted from first-line treatment of PCNSL.

#### 4. Neurological toxicity

As survival of patients with PCNSL becoming long, the quality of life and mental function is now very important. Neurotoxicity typically is associated with significant cognitive, motor and autonomic dysfunction, and has a negative impact on quality of life. Delayed neurologic toxicity is a serious complication, especially occurring in patients older than 60 years [24]. MTX is a known neurotoxin and has the potential of producing leukoencephalopathy as well as other types of neurotoxicities such as microangiopathy [25]. MTX is a folate antagonist inhibiting nucleic acid and methionine synthesis. Methionine is necessary for CNS myelination. The presence of a risk haplotype defined by polymorphisms influencing methionine metabolism referred a relative risk for CNS white matter changes [26]. MTX in combination with WBRT relates to its potential for causing delayed leukoencephalopathy. Radiation therapy prior to MTX administration increase the risk of leukoencephalopathy. While intrathecal, intravenous MTX and WBRT have the potential for producing leukoencephalopathy independently, when two or three of them are combined the risk will increase [27]. Nguyen et al. [28] reported late treatment-associated neurotoxicity in 15% of patients and was significantly associated with total radiation doses greater than 36 Gy. O'Brien et al. [29] reported 30% of neurotoxicity risk who were treated with MTX ( $1\text{g/m}^2$ ) followed by WBRT. For patients aged >60 years the risk of neurotoxicity at 7 years was 58%. Correa et al. [30] reported the neuropsychological evaluation of 28 patients. These were of sufficient severity to reduce quality of life in half of the patient sample. Patients treated with WBRT+/- chemotherapy revealed more pronounced cognitive impairment, particularly in the memory and attention/executive domain. Extent of white matter disease correlated with attention/executive, memory, and language impairment. PCNSL survivors treated with WBRT+/- chemotherapy displayed more pronounced cognitive dysfunction than patients treated with MTX-based chemotherapy alone. Omuro et al. [31] described delayed neurotoxicity, analyzing 185 PCNSL patients. The 5-year cumulative incidence of neurotoxicity was 24%. Neurotoxicity

presented as a rapidly progressive subcortical dementia characterized by psychomotor slowing, executive and memory dysfunction, behavioral changes, gait ataxia, and incontinence. Imaging findings revealed diffuse white matter disease and cortical-subcortical atrophy. Available autopsy data showed white matter damage with gliosis, thickening of small vessels, and demyelination. Older age, mental status changes at diagnosis, female sex, and radiotherapy predicted neurotoxicity on univariate analysis, but only radiotherapy remained significant in the multivariate setting. They conclude that the core pathophysiological mechanism is the interruption of frontal-subcortical circuits mediated by radiation damage, possibly caused by microvascular alterations, loss of oligodendrocyte progenitors, or oxidative stress. Fliessbach et al. [32] reported the impact of HD-MTX based chemotherapy alone on long term cognition and quality of life in patients with PCNSL. The median follow-up period was 44 months after diagnosis. In long-term follow-up 22 (95%) of 23 patients showed either preserved or improved cognitive functions as compared with pretreatment and immediate posttreatment baseline assessment. Eleven (48%) of 23 patients displayed at least mild cognitive deficits at long-term follow-up not related to therapy. Nineteen (83%) of 23 patients reported a good quality of life (QOL). They conclude that in patients with PCNSL treated with MTX-based chemotherapy alone, no gross cognitive decline has to be expected as a long-term treatment effect. Finally, formal neuropsychological examination guideline in PCNSL clinical trial should be established in the future.

## 5. Molecular biomarker

There are still many individual variations within the diagnostic and prognostic categories, resulting in a need for additional molecular biomarkers, partly because of the inability to recognize these patients prospectively. Although the clinical scoring model using age, Karnofsky Performance Status (KPS), and lactate dehydrogenase (LDH) level has prognostic value for PCNSL [33-35], it has not been used successfully to stratify patients for therapeutic trials. Molecular markers could improve the outcome prediction, discover potential targets for therapeutic intervention, and elucidate mechanisms that result in resistance to chemotherapy. The reason little progress in molecular analyses of PCNSL has been achieved so far is the very tiny sample amounts obtained for genetic analyses. A better understanding of PCNSL biology is crucial to improve its prognosis. However, only a few studies have been reported on gene expression profiles of PCNSLs. Rubenstein et al. [36] compared the gene expression signature of 23 PCNSL patients with that of nine nodal large B-cell lymphoma patients. They showed that individual cases of PCNSL were classified as GCB cell, ABC (activated B-cell-like) cell, or type 3 large B-cell lymphoma based on the cell-of-origin classification described by Alizadeh et al [37]. In addition, PCNSLs were distinguished from nodal B-cell lymphoma by high expression of regulators of the unfolded protein response signaling pathway by c-Myc and Pim-1. The IL-4 signaling pathway is associated with tumorigenesis and adverse prognosis in PCNSL patients [36]. Montesinos-Rongen et al. [38] reported the gene expression profile of 21 PCNSLs. They showed that PCNSLs resembled late GCB cells in their gene expression pattern, and that PCNSLs were distributed among the spectrum of

systemic DLBCLs. Tun et al. [39] reported a gene expression comparison between 13 PCNSLs and 30 non-CNS DLBCLs. PCNSL was characterized by significant expression of multiple extracellular matrix- and adhesion-related pathways. Sung et al. [40] evaluated 12 PCNSL patients by comparative genomic hybridization and 7 out of the 12 patients by expression profiling. They selected eight candidate genes in which expression changes were associated with copy number changes.

Systemic DLBCLs comprise several diseases that differ in responsiveness to chemotherapy [41,42]. The GCB cell-like subgroup expressed genes characteristic of normal GCB cells and were associated with a good outcome, whereas the ABC cell-like subgroup expressed genes characteristic of activated B cells and were associated with a poor outcome. Gene expression analyses of PCNSLs have largely focused on normal lymphocyte development, and the cell-of-origin classification method was investigated so far. Kawaguchi et al. [43] developed a novel scoring system based on molecular markers. Expression profiling was performed on 32 PCNSLs. A gene classifier with 23 genes was developed using the random survival forests model. Based on this, Prognosis Prediction Score using immunohistochemical analysis is also developed and validated in another data set. Among the genes, BRCA1 protein expression was most strongly associated with patient survival. They have identified gene expression signatures that can accurately predict survival in patients with PCNSL.

## 6. Conclusion

Much more aggressive therapies, such as high-dose chemotherapy with stem cell implantation [44] or molecular targeted therapies that specifically target disabled pathways, might be tailored in those patients with a poor prognosis. In this regard, molecular biomarkers might not only predict the likelihood of short-term survival, but also yield clues on individual genes involved in tumor development, progression, and response to therapy. Moreover, the ability to distinguish PCNSLs will enable appropriate therapies to be tailored to specific tumor subtypes. Class prediction models based on defined molecular profiles allow classification of PCNSLs in a manner that will be better correlated with clinical outcomes. Therefore, identification of these molecular subclasses of PCNSLs could greatly facilitate prognosis prediction and ability to develop effective treatment protocols.

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