

# Primary central nervous system lymphoma in immunocompetent patients: A regional cancer center experience

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## Abstract

**Background:** Primary central nervous system lymphoma (PCNSL) is a rare form of aggressive extranodal non-Hodgkin's lymphoma which occurs in both immunocompromised and immunocompetent patients. It has an overall poor prognosis in spite of a multimodality treatment approach including chemotherapy and radiotherapy. This study attempts to further delineate the clinicopathological, immunohistochemical, and radiological profile of PCNSL at Kidwai Memorial Institute of Oncology, Karnataka, India. **Materials and Methods:** All the pathologically confirmed PCNSL cases between January 2010 and June 2016, at our center, were analyzed retrospectively. The influence of potential prognostic parameters on overall survival (OS) was investigated by log-rank test and Cox regression analysis. **Results:** Of the 26 PCNSL patients, 17 (65.3%) were males. Median age at diagnosis was 42.5 years. None of the patients had HIV or Epstein-Barr virus positivity and only four patients (15.4%) had B-symptoms. The most common location in the brain was cerebral hemispheres in 15 patients (57%) and 10 patients (38.5%) had multiple intracranial lesions. Histologically, all were diffuse large B-cell lymphomas, except one case of anaplastic large cell lymphoma. Immunohistochemically, 18 patients (69%) had MUM 1 positivity and 20 cases (77%) belonged to nongerminal center subtype. DeAngelis protocol was followed in 24 patients (92%), and among this cohort, Memorial Sloan Kettering Cancer Center Class 1 ( $n = 17$ ) and Class 2 ( $n = 7$ ) patients had a median OS of 25 months and 11 months, respectively. **Conclusion:** None of the potential prognostic factors had a statistically significant influence on OS in our patients. High-dose methotrexate combined with radiation is an effective therapeutic approach. However, further prospective studies with a large number of patients are needed to identify more effective primary chemotherapy regimens to further improve the treatment outcome.

**Key words:** Chemotherapy, high-dose methotrexate, primary central nervous system lymphoma, radiotherapy

## Introduction

Primary central nervous system lymphoma (PCNSL) represents a rare subtype of aggressive extranodal non-Hodgkin lymphoma (NHL) restricted to the craniospinal axis (brain parenchyma, spinal cord, eyes, cranial nerves, and/or meninges), without evidence of a systemic lymphoma at the time of diagnosis.<sup>[1]</sup> Ocular involvement can occur in 10–15% of cases and leptomeningeal disease is documented in 20–30% of patients.<sup>[2]</sup> It represents 0.8–6.6% of all primary CNS tumors and about 5% of all extranodal NHLs.<sup>[3]</sup> The majority (>90%) of PCNSLs are of diffuse large B-cell lymphoma (DLBCL) histology, with Burkitt's lymphoma, indolent B-cell lymphomas, and T-cell histologies rarely reported.<sup>[4,5]</sup> The only known risk factor for PCNSL development is congenital or acquired immunodeficiency. In the recent era of highly active antiretroviral therapy (HAART), a dramatic reduction in the incidence of immunodeficiency-associated PCNSL has occurred, correlating with a decline in the proportion of HIV-infected individuals with CD4+ cell counts <50/mm<sup>3</sup>.<sup>[6]</sup> The fact that unlike the western countries, the association of PCNSL with HIV/AIDS in India is very low in spite of substantial prevalence of HIV/AIDS cases, suggests that there is geographic variation in the risk factors.<sup>[7]</sup> Historically, PCNSL has been considered to be associated with a significantly worse prognosis than systemic lymphomas of the same histology despite multimodality treatment approach. With high-dose methotrexate-based chemotherapy, with or without whole-brain radiotherapy, a median survival of 51 months has been reported.<sup>[8]</sup> It remains unclear whether the dismal outcome of PCNSL patients compared with patients with systemic DLBCL is attributable to the immunoprivileged CNS location or reflects a specific aggressive intrinsic biologic behavior.

The best treatment strategy for this rare, aggressive extranodal NHL is still controversial. In the present study, we aimed to investigate

the clinical, immunohistochemical, and radiological findings of the PCNSL cases at our center and to evaluate the influence of potential prognostic factors on the overall survival (OS).

## Materials and Methods

### Patient selection, evaluation, and treatment

All consecutive cases diagnosed with PCNSL between January 2010 and June 2016, at the Department of Medical Oncology, Kidwai Memorial Institute of Oncology, Bengaluru, Karnataka, India, were investigated retrospectively. All the patients underwent a detailed history and physical examination including a neurological assessment. The localization and number of the CNS lesions were investigated by magnetic resonance imaging, and the diagnosis of CNS lymphoma was confirmed by microscopic examination and immunohistochemistry of the biopsy specimens (stereotactic or open biopsy). To exclude systemic lymphoma at presentation, all patients underwent iliac crest bone marrow aspiration and biopsy, whole-body contrast-enhanced computed tomography scan, ophthalmoscopic evaluation, and cerebrospinal fluid (CSF) cytology for malignant cells. Ultrasound examination of the testes was performed in male patients. Memorial Sloan Kettering Cancer Center (MSKCC) prognostic score<sup>[9]</sup> was calculated. Patients were treated with either DeAngelis protocol<sup>[10]</sup> or intensive chemo-immunotherapy with methotrexate, temozolomide, and rituximab induction (high-dose MTR), followed by etoposide and cytarabine consolidation (EA).<sup>[11]</sup>

### Statistical analysis

Duration of OS was calculated from the date of diagnosis until death. The strength of the association between OS and different prognostic variables was investigated by Kaplan–Meier OS curve and log-rank test. These variables included age ( $\geq 60$  years vs. <60 years), multifocal involvement, deep site involvement (i.e. the

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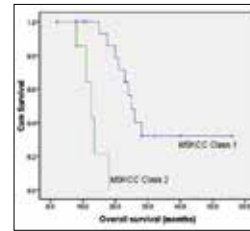
corpus callosum, basal ganglia, periventricular region, brainstem, and cerebellum), CD10 staining, MUM1 staining, subtype (germinal center [GC] vs. non-GC [NGC]), and MSKCC prognostic score. All statistical analyses were performed using SPSS version 17.0 for Windows (SPSS Inc., Chicago, IL, USA).

## Results

Totally, 26 cases of PCNSL were retrospectively reviewed. Median age at diagnosis was 42.5 years (range: 21–62 years), with a male/female ratio of 1.88:1 (17:9). None of the patients had HIV or Epstein-Barr virus (EBV) positivity. B-symptoms were very uncommon in our series, and only four patients (15.4%) had B-symptoms at presentation. The most common presenting symptoms were raised intracranial tension features (headache, vomiting) in 46% ( $n = 12$ ), followed by focal neurological deficits (paresthesia/hemiparesis, cranial nerve palsies, dysarthria) in 30% of patients ( $n = 8$ ). Other presenting symptoms included seizures in 8% ( $n = 2$ ), visual disturbances in 8% ( $n = 2$ ), personality changes in 4% ( $n = 1$ ), and gait disturbances in 4% ( $n = 1$ ) of patients. The median serum lactate dehydrogenase (LDH) was 224 U/L and was elevated in eight patients (30.7%). The most common area of CNS involvement was cerebral hemispheres in 57% ( $n = 15$ ), followed by periventricular regions in 23% ( $n = 6$ ), thalamus in 8% ( $n = 2$ ), cerebellum in 4% ( $n = 1$ ), leptomeninges in 4% ( $n = 1$ ), and corpus callosum in 4% ( $n = 1$ ) of patients. Ten patients (38.5%) had multifocal CNS lesions. As per the MSKCC risk scoring, 19 patients (73%) belonged to Class 1 and the rest were Class 2. The diagnostic procedures employed were stereotactic biopsy in 46% ( $n = 12$ ), surgical decompression in 42% ( $n = 1$ ), and gross total excision in 12% ( $n = 3$ ) of patients. Histologically, all were DLBCL, except one patient who had anaplastic large cell lymphoma (ALCL). Immunohistochemically, 18 patients (69%) had MUM 1 positivity and 20 patients (77%) belonged to NGC subtype. All of the patients with DLBCL histology ( $n = 25$ ) were negative for anaplastic lymphoma kinase (ALK) and had a high Ki-67 index (range: 80–95%; median 90%). The patient with ALCL was positive for ALK and had a Ki-67 index of 70%. All of the cases of NGC subtype were negative for CD10. DeAngelis protocol was followed in 24 patients (92%) and the other 2 patients were treated with MTR regimen, followed by EA. The overall response rate (ORR) was 92% ( $n = 22$ ) after DeAngelis protocol ( $n = 24$ ) and 100% after MTR induction ( $n = 2$ ). The median OS of the patients treated with DeAngelis protocol ( $n = 24$ ) was 20.5 months (range: 8–62 months). Among this cohort, the MSKCC Class 1 patients ( $n = 17$ ) had a median OS of 25 months and MSKCC Class 2 patients ( $n = 7$ ) had a median OS of 11 months [Figure 1]. The 2 patients of the MTR treatment arm had just completed treatment at the time of the last follow-up.

## Discussion

Previously, PCNSL was regarded as the tumor of immunosuppressed individuals. However, after the introduction of HAART, the incidence of PCNSL decreased substantially in these patients. Today, the frequency of PCNSL is much higher in immunocompetent individuals than in immunocompromised ones. However, the exact reason for this rising incidence of PCNSL among the immunocompetent population is still obscure.<sup>[12]</sup> Moreover, whether the disease has a different course in patients without an underlying immune dysfunction is also still unclear. The role of various immunophenotypic markers in predicting survival outcome for this particular patient population is highly debated. Although several implications of EBV, on various types of tumors arising in immunocompromised



**Figure 1: Kaplan–Meier overall survival curve of primary central nervous system lymphoma patients treated with high-dose methotrexate combined with whole-brain radiation therapy (DeAngelis protocol). The Memorial Sloan Kettering Cancer Center Class 1 patients had a significantly better overall survival than Class 2 patients (log-rank  $P < 0.000$ )**

individuals, are well recognized, its etiological role in PCNSL of immunocompetent patients is still unclear. In the present study, none of our patients had EBV positivity.

Unlike individuals with systemic NHL, patients with PCNSL rarely present with B-symptoms. They classically present with focal neurologic or cognitive deficits, sensory-motor symptoms, and symptoms of raised intracranial pressure.<sup>[4,13,14]</sup> New-onset seizures are less common (10–15%).

Several prognostic classifications were proposed for PCNSL to make practical algorithms and determine the best treatment strategy. The International Extranodal Lymphoma Study Group has noted that several factors are associated with a poor prognosis in PCNSL. Age  $>60$  years, Eastern Cooperative Oncology Group performance status  $>1$ , elevated LDH, high CSF protein concentration, and deep brain involvement were independently predictive of poor survival.<sup>[15]</sup> The Nottingham/Barcelona score includes age, performance status, and extent of brain disease.<sup>[16]</sup> A more recent staging system has been developed and validated by the MSKCC Group.<sup>[9]</sup> The group studied multiple factors in over 300 patients and found only two factors, age and performance status, which were predictive of outcome. These factors were able to differentiate patients into three very different prognostic groups: Class 1: Patients  $<50$  years; Class 2: Patients  $\geq 50$  years, Karnofsky performance status (KPS)  $\geq 70$ , and Class 3: Patients  $\geq 50$  years, KPS  $<70$ . Patients with Class I prognosis experienced a median OS of 8.5 years, whereas patients who were Class III had a median OS of only 1.1 years.<sup>[9]</sup>

As per the molecular classification, DLBCL can be categorized into GC and NGC subtypes.<sup>[17]</sup> The NGC subtype has a relatively poor outcome. According to the several published reports, 66–93% of the PCNSL cases belonged to the NGC subgroup.<sup>[4,18,19]</sup> However, none of these studies had demonstrated a statistically significant difference in OS and disease-free survival between these two subtypes. In our series, 77% of the cases were of NGC subtype and there was no significant survival difference between two groups [Table 1].

Results are conflicting regarding the role of Bcl-6 as an independent prognostic variable. Some studies suggested Bcl-6 as a poor prognostic factor,<sup>[18]</sup> some demonstrated its association with a more favorable outcome,<sup>[20]</sup> while others failed to show any impact on survival.<sup>[3,19]</sup> Moreover, there was no significant survival difference between Bcl-2 positive and negative groups also in most of the prior reports.<sup>[3,4]</sup>

Several studies suggested that young age at diagnosis ( $<60$  years) represents a favorable prognosis,<sup>[4,21]</sup> and on the other hand, multifocal involvement and deep site involvement of the brain were proposed to have a negative impact on survival.<sup>[15,20,22]</sup> In our study, we failed to demonstrate an association between these parameters and OS [Table 1]. This may be attributed to the relatively low number of cases enrolled in this study.

High Ki-67 index is a poor prognostic factor in systemic DLBCL, but none of the studies till date showed any significant survival difference between high and low Ki-67 groups.<sup>[18,20]</sup> In our series, the median Ki-67 index (90%) was too high to be divided into high and low subgroups.

The historical mainstay of therapy in PCNSL was previously whole-brain radiation therapy (WBRT) alone.<sup>[23]</sup> Because of the limited long-term efficacy of WBRT alone, there has been considerable interest in combining chemotherapy with WBRT to improve response and survival. CHOP-based chemotherapies have been studied<sup>[24]</sup> but have not offered additional survival benefit to radiation used alone, presumably because of the lack of penetration to the CNS. Subsequent research has centered on the role of systemic methotrexate at doses known to penetrate into the CNS preceding WBRT, which culminated in an RTOG multicenter phase II study of combined modality therapy (CMT) in PCNSL.<sup>[10]</sup> In this study, ORR reached 94% including 58% complete responses, and the median progression-free survival (PFS) was 25 months, with 37 months of median OS. Recently, MSKCC has published long-term follow-up of their experience with CMT.<sup>[8]</sup> Median OS was 51 months for the entire cohort, and for the patients under 60 years, median PFS and OS had not been reached after 115 months of follow-up. In patients  $\geq 60$  years, median OS was only 29 months along with increased neurotoxicity. In an attempt to reduce the toxicity of CMT, the use of chemotherapy alone has been studied. In one multicenter phase II study of high-dose methotrexate (single agent 8 g/m<sup>2</sup>)-based therapy, ORR was 74% but median PFS was only 13 months.<sup>[25]</sup> Final results of the CALGB 50202 trial have been published recently.<sup>[11]</sup> This study has evaluated the efficacy of dose-intensive chemotherapeutic induction (MTR) and consolidation (EA) strategy in 44 newly diagnosed patients with PCNSL. The rate of CR to MTR was 66%. The overall 2-year PFS was 0.57, with a median follow-up of 4.9 years. Patients  $>60$  years of age responded similarly as younger patients. This study showed first time to our knowledge that dose-intensive consolidation for PCNSL is feasible in the multicenter setting and yields rates of PFS and OS at least comparable to those of regimens involving WBRT. However, the optimal methotrexate-based regimen is still unclear in the literature.

## Conclusion

In the current study, we retrospectively investigated the demographic and clinicopathological features of PCNSL cases together with an analysis of potential prognostic factors and their impact on OS. None of the factors had a statistically significant influence on OS. The treatment of PCNSL with high-dose methotrexate combined with WBRT is an effective therapeutic approach. However, further prospective studies with a large patient number are needed to elucidate prognostic factors, as well as optimum treatment regimens including rituximab, particularly in immunocompetent patients with PCNSL.

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Nil.

**Table 1: Multivariate analysis of different prognostic variables**

Prognostic variables	Hazard ratio (95% CI)	P
Age <60 years	0.542 (0.126-1.564)	0.204
Multifocal involvement	0.868 (0.322-2.521)	0.380
Deep site involvement	0.728 (0.272-1.529)	0.265
NGC subtype	1.276 (0.480-2.685)	0.462

CI=Confidence interval, NGC=Nongerminal center

## Conflicts of interest

There are no conflicts of interest.

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