

# 1 Characteristics and Outcomes of Patients with Primary Central 2 Nervous System Lymphoma

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## 7 **Abstract**

8 Background: The aim of the present retrospective study was to review the clinicopathological  
9 characteristics and outcomes of primary central nervous system lymphoma (PCNSL) cases at  
10 our institute. Methods: Patients diagnosed with PCNSL at our institute from August 2010 to  
11 May 2015 were evaluated. During the said period, a total of 14 cases were diagnosed with  
12 PCNSL. Results: Deep frontal lobe was the most common site of involvement while diffuse  
13 large B-cell lymphoma (DLBCL) was the most common histological pattern. 10 patients were  
14 treated with 3.0 g/m<sup>2</sup> methotrexate (MTX) intravenously concomitant with intraventricular  
15 15 mg MTX and 2 patients were treated with radiotherapy (RT). Two of the patients died due  
16 to respiratory failure a short time after the treatment started. The median overall survival  
17 (OS) was 8 months (minimum: 1 months, maximum: 15 months) and the median OS was  
18 12.42±13.20 months (min: 1 month, max: 48 months).

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20 **Index terms**— methotrexate, overall survival, primary central nervous system lymphoma, radiotherapy.

21 I. Introduction primary central nervous system lymphoma is a rare type of cancer accounting for less than 3% of  
22 all the brain tumors. Majority of the primary central nervous system lymphoma are diffuse giant B cell lymphoma.  
23 The yearly incidence of PCNSL is 0,5 cases per 100 000 people. The incidence is higher in immunocompetent  
24 individuals, whereas it seems to be lower in patients with HIV infection. Median age at diagnosis is 60-65  
25 years 2,3 and median survival is 10-20 months, with a survival rate of less than 20-30% at 5 years. 4,5,6,7,8,9  
26 Unlike in systemic lymphomas, long term remission is very in PCNSL. Chemotherapy, radiotherapy, surgery  
27 and a combination of these can be used in intracranial lymphomas. 10 OS close to 5 years in PCNSL 11,12,13  
28 neurocognitive toxicity stands as the major limitation of the said combined treatment. 14 Delayed neurotoxicity  
29 presenting itself with memory deterioration and personality changes early in the course is followed by gait  
30 disturbance and urinary incontinence, all of which are generally permanent. 14 The prognosis and outcome of  
31 treatment differ in younger and older patients. Interestingly, when compared those who did not receive radiation,  
32 the outcomes are not improved when radiation is added to the treatment regimen of elderly patients. The optimal  
33 combination regimen or dose of MTX remains to be elucidated.

34 Currently, the treatment for PCNSL often involves high-dose MTX (HD-MTX) based chemotherapy with or  
35 without whole brain radiotherapy (WBRT). While both MTX and WBRT may cause CNS damage, there is a  
36 synergistic toxicity when these two modalities are combined. 15,16 The present retrospective study reviews our  
37 experience on patients with diagnosed PCNS at our single centre.

## 38 **1 II. Patients and Methods**

39 The study was conducted on patients histologically diagnosed with PCNSL at our institute from August 2010  
40 to May 2016. The neurological tumour tissue for diagnosis was obtained by stereotactic or craniotomy. The  
41 Haematoxylin and eosin (H&E) stained slides were reviewed and the complete clinical details were obtained  
42 from patient records. Age, sex, radiological findings, immune status, and human immunodeficiency virus (HIV)  
43 serology findings were recorded in each case. The possibility of secondary involvement by a systemic lymphoma

## 10 A) PATIENTS AND TREATMENT

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44 was excluded by obtaining the details pertaining to lymphadenopathy, organomegaly, and bone marrow study.  
45 Cerebrospinal fluid (CSF) findings were recorded whenever available.

### 46 2 a) Patients

47 Fourteen patients were diagnosed as PCNSL with histological confirmation. Clinical data for all patients  
48 constituting the study cohort were available. All patients had one or more intracranial mass lesions. Fourteen  
49 patients underwent lumbar puncture and a complete ophthalmologic evaluation including a slitlamp examination.  
50 Testicular ultrasonography was performed in male patients. There were no laboratory abnormalities before  
51 chemotherapy and the laboratory diagnosis of a latent or obvious infection was excluded.

### 52 3 b) Immunohistochemistry

53 Histological subtype of the tumour with grading of tumour cells on haematoxylin and eosin-stained slides, along  
54 with immunohistochemical details, including typing for leucocyte common antigen (LCA), CD20 (B cell marker)  
55 and CD3 (T cell marker), performed on formalin-fixed, paraffin-embedded tissue samples, were recorded.

### 56 4 c) Treatment protocol

57 In DLBCL patients, treatment consisted of six cycles of chemotherapy administered at 28-day intervals, consisting  
58 of the following: MTX 3.0 g/m<sup>2</sup> for one day, followed by 15 doses of leucovorin rescue. At diagnosis, 8 patients  
59 underwent to Ommaya reservoir implantation and 6 courses of intraventricular MTX (15 mg) at 3-day cycle were  
60 administered to the patients. RT has been given in 2 patient .One of these patients had low grade lymphoma  
61 and the other had diffuse giant cell lymphoma. DLBCL patients were treated with a chemotherapy.

### 62 5 d) Follow-up

63 Repeat neuroimaging was conducted by MRI or CT at the completion of 3 chemotherapy cycles and then the  
64 completion of 6 chemotherapy cycles and lastly every 3 months. 1.5T clinical scanner was used during MRIs. The  
65 deep brain structures defined were basal ganglia, the corpus callosum, brain stem and cerebellum. Peritumoral  
66 edema was categorized as < or ? 2 cm from the brain tumour as assessed in T2weighted MR images.

### 67 6 e) Evaluation of response to treatment

68 The standardized criteria of the National Cancer Institution on the changes in the size of enhanced lesions on T1  
69 weighted MR images were used to define the treatment response. Complete remission (CR) was defined as the  
70 complete disappearance of lymphoma while partial response (PR) as ? 50% decrease in tumour size, progressive  
71 disease (PD) as a ? 25% increase in tumour size or the appearance of any new lesion and stable disease (SD) as  
72 situations that did not meet any of these three previous criteria.

73 The International Extranodal Lymphoma Study Group (IELSG) score was used to define the risk group.  
74 Using the prognostic scoring system of the IELSG, the patients were categorized into three risk groups as low,  
75 intermediate, and high. Age, ECOG performance status grade, lactate dehydrogenase (LDH) serum level, protein  
76 concentration in CSF, and involvement of deep brain structures were the variables included.

### 77 7 f) Statistical methods

78 OS was calculated from the date of histological diagnosis to death or the last date of follow-up. Both median OS  
79 and mean OS was determined.

### 80 8 g) Ethics statement

81 The approval for this study was obtained from the Ethical Committee of Cumhuriyet University Clinic Researches.

## 82 9 III. Results

### 83 10 a) Patients and treatment

84 The study group consisted of 14 patients, including 5 females and 9 males. At least one of the prognostic factors  
85 was poor in all patients. The median age of the patients was 62 years (range; 42-80). 12 patients had single  
86 lesion while the most common site of involvement was the deep frontal region.

87 In 2 patients, MRI showed multiple site of involvement. Cerebellar involvement was very rare (1 patient)  
88 (Figure 1). While 13 of the patients were diagnosed with DLBCL, one of the patients was diagnosed with low  
89 grade lymphoma.

90 The obtained samples did not reveal any CFD involvement. 9 patients had a high level of LDH. ?2microglobulin  
91 was high in 10 patients. Characteristics of the patients are summarized in Table ???. A total of 10 patients received  
92 HD-MTX with a concomitant intravascular chemotherapy as an initial treatment. 5 of them received 6 cycles of  
93 HD-MTX, 1 patient was stable after 3 cycles of HD-MTX, so RT was administered as a salvage regimen. After 3  
94 cycles of HD-MTX, the disease became progressive in 1 patient and the patient died due to respiratory failure. 3

95 of the patients died due to sepsis after the second cycle of HD-MTX. In 2 patients, RT was planned to cranium  
96 in a fraction of 20 at a dose of 36 Gy in total.

## 97 **11 b) Response to treatment**

98 Of the remaining 4 patients, 1 was regarded as having a progressive disease and died due to respiratory failure.  
99 The rest 3 patients died due to sepsis after the second cycle of HD-MTX (these patients were included in the  
100 progressive disease group). RT treatment was administered as the initial treatment in 2 patients. One of these  
101 patients had low grade B cell lymphoma and died due to comorbid diseases on the 16th day of the treatment.  
102 The patients receiving RT had diffuse cell lymphoma that yielded partial remission. ??.

## 103 **12 c) Toxicity**

104 Toxicity included grade 3/4 hematotoxicity (50%), and mucositis (20). Renal toxicity was observed in 1 patient  
105 while liver toxicity was present in 1 patient. These toxicities improved after HD-MTX and the treatment was not  
106 postponed due to toxicity. However, in 5 patients, grade 3/4 hematologic toxicity developed after HD-MTX. These  
107 patients were administered colonystimulating factor and wide spectrum antiotherapy. However, 3 patients died  
108 as a result of sepsis due to infection.

109 There was neurotoxicity proven by MRI only in one patient, but the patient did not clinically exhibit any  
110 neurologic pattern. The details about toxicity are outlined in Table ??.

## 111 **13 IV. DISCUSSION**

112 PCNSL, which is an aggressive lymphoma with poor prognosis, is mostly incurable. 17 This retrospective study  
113 was conducted to evaluate the clinicopathological profiles and outcomes of the patients diagnosed with PCNSL  
114 at our institute. 14 cases were diagnosed with PCNSL between August 2010 and May 2016. In PCNSL, which  
115 is a condition occurring at all ages, the incidence rates reported in the sixth and seventh decades are higher in  
116 immunocompetent patients in the western countries. 18,19 In our study, the average age was 62 years while the  
117 youngest patient was 42 years old and the oldest one was 80 years old. The median age of the patients was 69  
118 years and male-to-female ratio was 9/5. Bataille et al. 18 analysed PCNSL in 248 (121 males and 127 females)  
119 immunocompetent patients where the median age was 61 years. They suggested that this type of lymphoma  
120 occurred more commonly in men than women. 20 In our study, the number of male patients was higher.

121 Intra-cranial lymphomas are diagnosed using both morphological criteria and immunohistochemical studies.  
122 Most primary intra-cranial lymphomas are comprised of non-Hodgkin's B-cells. CSF analysis results in a  
123 cytological diagnosis in fewer than half of patients with B-cell PCNSL. Solitary lesions, which are most commonly  
124 located supra-tentorially, in the white matter of the frontal or parietal lobes or in the subependymal regions can  
125 be revealed by neuro-imaging modalities. Sarkar et al. 21 reported frontal lobe as the most common location  
126 in their study. In our study, 4 of the lesions were located in the parieto-occipital region. Lesions were localized  
127 at the parietal region in 2 patients, temporal region in 2 patients and occipital region in 1 patient. The other 2  
128 lesions were in the frontal lobe, and one of these two lesions was located in cerebellar region which is very rare  
129 localization. There were multiple lesions in 2 patients.

130 The vast majority of PCNSLs are DLBCL. In our study, 13 of the cases were classified as high grade DLBCL,  
131 a predominant histological type as shown in other studies, and 1 was classified as low grade lymphoma. In our  
132 study, none of the tumour cells involved the CSF and all the cases were immunocompetent with no HIV positive  
133 case.

134 Age and performance status are universally accepted as prognostic factors. Ferreri et al. 22 used multivariate  
135 analysis in a large cohort of patients with PCNSL, which is a new understanding in this area. They reported  
136 an independent association between OS and age, performance status, LDH serum concentration, CSF protein  
137 concentration and involvement of deep structures of the brain. A prognostic score, obtained by adding each of  
138 these variables (assigned a score of 0 or 1, if absent or present), was significantly correlated with survival and  
139 made it possible to distinguish low, intermediate and high risk groups. After analysing all of the patients, we  
140 observed that they all were in high risk group.

141 Treatment for intra-cranial lymphoma can include chemotherapy, RT, surgery and a combination of these  
142 treatment modalities. 10 In elderly patients, chemotherapy alone is preferred as it is as effective as and less  
143 neurotoxic than RT or chemoradiotherapy. 23 Introduction of MTX, which is a drug which penetrating the  
144 blood brain barrier effectively, has improved median survival from 10 to 16 months to more than 30 months. 24  
145 In our study, the median OS was  $12.42 \pm 13.20$  months (min: 1 month, max: 48 months).

146 In order to minimize acute and late toxicities in the management of PCNSL, many studies have investigated  
147 the role of single-agent chemotherapy and deferred WBRT. MTX doses greater than 1 g/m<sup>2</sup> are reported to be  
148 necessary for adequate delivery to the CNS. 25 Intraventricular chemotherapy aims to improve CSF drug delivery.  
149 Thus, many studies of PCNSL employed intrathecal/intraventricular chemotherapy. We believe that high dose  
150 MTX as a single dose agent combined with intrathecal/intraventricular chemotherapy is the best treatment  
151 modality in PCNSL management.

152 As a result, PCNSL affects mostly the 6th decade and DLBCL is the most commonly encountered pathological  
153 type. Although single agent treatment modalities are frequently used in the treatment of newly diagnosed PCNSL,

## 14 V. ACKNOWLEDGMENTS

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154 comprehensive randomized studies are needed. However, single agent high dose MTX seems to be causing toxicity  
155 less. Due to its neurocognitive toxicity, RT is mostly used in only relapsed/refractory patients.

## 156 14 V. Acknowledgments

157 The authors declare that there is no conflict of interests regarding the publication of this paper.

158 Figures Legends Table 1

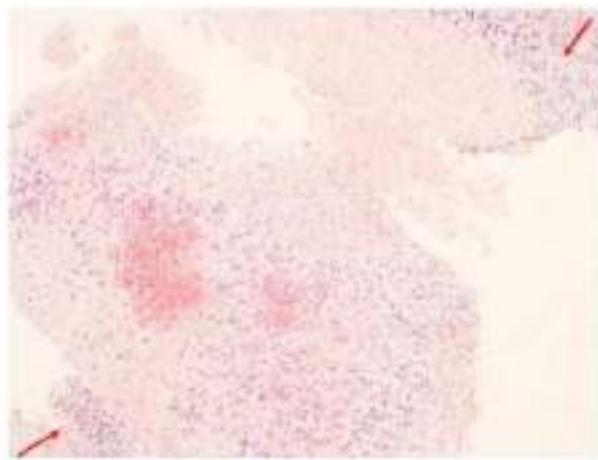


Figure 1: F

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