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Original Article

Primary central nervous system lymphoma in immunocompetent individuals: a single center experience

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Abstract: Primary central nervous system lymphoma (PCNSL) is defined as the involvement of brain, leptomeninges, eyes or spinal cord by non-Hodgkin lymphoma. The role of various prognostic markers in predicting adverse outcome is debated. Objectives: To investigate the clinical and immunohistochemical findings of immunocompetent PCNSL cases (39 cases) diagnosed at the study center, and evaluate the influence of potential prognostic factors on overall survival (OS) of patients. Methods: Data regarding patient characteristics, neuroimaging, pathological and immunohistochemical features and follow-up were obtained from patient records. The influence of potential prognostic parameters on OS was investigated by log-rank test and Cox regression analysis. Results: Patients who received combined chemotherapy and radiotherapy had a significantly better OS when compared to chemotherapy alone. Other variables included in this study were not associated with a significant survival advantage. Conclusion: In this study, we failed to demonstrate a relationship between different clinicopathological variables and OS of patients. Prospective studies with large patient series are needed to investigate other potential prognostic factors.

Keywords: Primary central nervous system lymphoma, immunocompetent, PCNSL, prognosis, survival

Introduction

Primary central nervous system lymphoma (PCNSL) is defined as the involvement of brain, leptomeninges, cerebrospinal fluid, eyes or spinal cord by an extranodal non-Hodgkin lymphoma (NHL) without evidence of a systemic lymphoma at the time of diagnosis. It represents 0.8 to 6.6% of all primary CNS tumors [1]. Although the majority of the patients are immunocompetent, immunosuppression for autoimmune diseases and after organ transplantation, acquired immunodeficiency syndrome (AIDS), human immunodeficiency virus infection (HIV), and congenital immunodeficiencies are the major predisposing factors. Approximately 95% of PCNSL are diffuse large B cell lymphoma (DLBCL) and the remaining cases are low grade B cell lymphoma of follicular, lymphoplasmacytic, and mucosa-associated lymphoid tissue types, Burkitt lymphoma or rarely T cell lymphoma [2, 3]. PCNSL-DLBCL was further divided into two subgroups; germinal center and non-germinal center [4]. Prognosis is poor with a median survival of 17 to 45 months in immunocompetent patients, and only 20-30% of cases can be cured successfully. Since the best treatment strategy is still controversial, PCNSL has been the subject of different genomic and retrospective studies in order to establish a validated prognostic classification scheme.

In this study, we aimed to investigate the clinical, immunohistochemical, and neuroimaging findings of immunocompetent PCNSL cases diagnosed at Cerrahpasa Faculty of Medicine, and evaluate the influence of potential prognostic factors on overall survival of patients.

Materials and methods

Patient selection

All consecutive cases diagnosed with PCNSL between 1997 and 2012, at Department of Pathology Cerrahpasa Faculty of Medicine,

were investigated and only the patients who were immunocompetent at the time of diagnosis were enrolled in this study. The diagnosis of CNS lymphoma was confirmed by microscopic examination of biopsy specimens. In order to exclude systemic lymphoma, all cases were consulted to a hematologist after diagnosis. Patients underwent iliac crest bone marrow aspirate and biopsy, and whole body CT scan. Ultrasound examination of testes was performed in male patients, and ophthalmologic examination was performed in most of the cases. In all patients, the localization and number of the lesions were investigated by magnetic resonance imaging (MRI). Data regarding clinical features and follow-up of cases were obtained from patient records and their attendant physicians.

Histology and immunohistochemistry

Tissue specimens were routinely fixed in 10% neutral-buffered formalin and embedded in paraffin. Hematoxylin and eosin stained slides of all cases were reviewed by a neuropathologist and a hematopathologist in order to confirm the diagnosis of lymphoma. All immunohistochemical stains were performed on the Ventana Benchmark automated staining system using 4μm paraffin tissue sections. The primary antibodies used in this study included CD3 (1:200, Novocastra), CD10 (1:100, Novocastra), CD20 (1:500, Cellmarque), bcl-2 (1:80, Novocastra), bcl-6 (1:80, Novocastra), MUM1 (1:100, Novocastra), and ki-67 (1:200, Neomarkers). For CD3, CD10, CD20, bcl-6 and MUM1, the staining was considered positive if more than 30% of the tumor cells were immunoreactive. Nuclear staining was considered positive for bcl-6, MUM1, and ki-67. PCNSL was subclassified into germinal center (GC) and non germinal center (NGC) groups based on the schema proposed by Hans, et al (4). Chromogenic in situ hybridization (CISH) technique for Epstein-Barr virus (EBV)-encoded RNA (EBER) transcript was performed and a strong nuclear staining was considered as EBV positive.

Statistical analysis

Duration of overall survival (OS) was assessed from patient records and calculated from the date of diagnosis until death or last contact. The strength of the association between OS time and single potential prognostic variables was investigated univariately by Kaplan-Meier OS curve and log-rank test. These variables included age (≥ 60 years vs. < 60 years), gender, multifocal involvement, deep site involvement (i.e. the corpus callosum, basal ganglia, periventricular region, brainstem, and cerebellum), bcl-2 positivity, bcl-6 positivity, CD10 expression, MUM1 staining, EBV positivity, subtype (germinal center vs. non-germinal center), and treatment. A Cox proportional hazards model was developed to further investigate the relationship between five prognostic variables, which had been shown to have an impact on survival in different studies, and OS. These included age, multifocal involvement, deep site involvement, bcl-6 positivity and combined therapy. All statistical analyses were performed using SPSS version 17.0 for Windows (SPSS Inc, Chicago, IL).

Results

Patient characteristics

Clinicopathologic features of 39 cases are summarized in **Table 1**. Mean age at diagnosis was 51.87 years (range; 21 to 85 years) with a male/female ratio of 1.17/1 (21:18). The majority of the cases presented with headache (n=12), paresthesias/hemiparesis (n=9), seizures (n=6), and signs of raised intracranial pressure (n=5). Other manifestations of the disease included visual disturbances (n=3), personality changes (n=2), delirium (n=2), dysarthria (n=2), incoordination (n=2), weight loss (n=2), gait disturbances (n=1), vertigo (n=1), syncope (n=1), urinary incontinence (n=1), and nerve palsies (n=1). All of the patients underwent a diagnostic biopsy procedure and 19 patients had total removal of their mass, 18 had stereotactic, and 2 had incisional biopsy. The procedure did not affect the neurological performance status and therapeutic outcome of cases. None of the patients had HIV positivity or a history of immunosuppressive therapy.

Neuroimaging studies

Cranial magnetic resonance imaging was performed in all cases. Parietal lobe was the most commonly involved site as observed in 28.2% of cases (11/39), followed by temporal lobe in 20.5% (8/39), frontal lobe in 17.9% (7/39), and cerebellum in 10.3% (4/39). Other sites of

Table 1. Characteristics of Primary Central Nervous System Lymphoma Patients

Case nu.	Age/sex	Localization	Presentation	Bcl-2	CD10	Bcl-6	MUM-1	Ki-67 (%)	EBV	GC status	Treatment	Follow-up
1	46/M	Supratentorial	NA	–	+	+	–	90	–	GC	CT+RT	12 mo, DOD
2	54/F	L, thalamus	Seizures, syncope	+	–	–	+	95	–	NGC	CT+RT	31 mo, Alive
3	37/F	R, periventricular	Headache	+	–	–	+	100	–	NGC	CT+RT	60 mo, Alive
4	54/M	R, cerebellum	NA	–	–	–	+	95	–	NGC	CT	2 mo, DOD
5	56/M	L, occipital	Paresthesia	–	+	+	–	100	–	GC	CT+RT	24 mo, DOD
6	53/F	Brainstem, cerebellum	Headache, incoordination	+	–	+	+	80	–	NGC	CT	14 mo, DOD
7	63/F	L, parietal	Headache, incoordination	–	+	+	–	95	–	GC	CT+RT	19 mo, DOD
8	54/M	L, parietal	Visual disturbances	+	–	+	+	95	+	NGC	CT+RT	6 mo, DOD
9	48/M	R, parietal	Seizures	–	–	–	+	100	–	NGC	CT	11 mo, DOD
10	53/M	R, frontal	Raised ICP	–	–	–	–	95	–	NGC	CT	5 mo, DOD
11	75/F	R, frontal	Personality changes, delirium	–	–	–	+	95	–	NGC	NA	NA
12	26/M	L, frontal	Headache, seizures	–	+	+	–	95	–	GC	CT+RT	37 mo, DOD
13	65/M	R, cerebellum	Gait disturbance	+	–	–	+	85	–	NGC	CT+RT	NA
14	70/M	L, ventricular trigone	Headache, seizures	+	–	–	+	95	–	NGC	CT+RT	14 mo, DOD
15	63/M	R, cingulate gyrus	Disorientation, urinary incont.	–	–	–	–	100	–	NGC	CT+RT	73 mo, Alive
16	53/F	R, temporal	Raised ICP	–	–	+	+	100	–	NGC	CT+RT	22 mo, DOD
17	21/F	R, periventricular	Raised ICP	–	–	–	–	90	–	NGC	CT+RT	14 mo, DOD
18	49/M	L, parietal	Seizures	–	–	–	+	95	–	NGC	NA	NA
19	48/M	R, parietal	Headache	–	–	+	+	95	–	NGC	CT	9 mo, DOD
20	68/F	Brainstem	Hemiparesis	+	–	–	+	100	–	NGC	CT+RT	61 mo, DOD
21	50/F	L, temporal	Hemiparesis	+	–	–	+	95	–	NGC	CT	6 mo, DOD
22	48/F	Lateral and 4th ventricles	NA	–	–	–	+	100	–	NGC	CT+RT	114 mo, Alive
23	35/M	R, frontal	Raised ICP	–	–	–	+	90	–	NGC	CT+RT	18 mo, DOD
24	41/F	L, temporal	Headache	–	–	–	+	85	–	NGC	CT+RT	43 mo, Alive
25	56/M	L, temporal	Dysarthria, hemiparesis	+	–	–	+	100	–	NGC	CT	17 mo, DOD
26	37/M	R, frontal	Weight loss, headache	–	–	–	+	80	–	NGC	CT+RT	27 mo, Alive
27	40/F	Cerebellum	Vertigo	–	–	+	+	95	–	NGC	CT	14 mo, DOD
28	85/M	L, temporal	Personality changes, delirium	–	+	+	+	100	–	GC	CT	13 mo, DOD
29	48/M	R, temporoparietal	Headache, weight loss	+	–	+	+	95	–	NGC	CT+RT	NA
30	68/F	R, temporal	Dysarthria, paresthesia	+	–	–	+	90	+	NGC	CT+RT	16 mo, DOD
31	61/M	L, parietooccipital	Raised ICP	+	–	–	+	95	–	NGC	CT	4 mo, DOD
32	57/M	L, parietal	Headache, hemiparesis	+	–	–	+	95	–	NGC	CT+RT	24 mo, Alive
33	60/F	R parietal, basal ganglia	Hemiparesis, seizures	+	–	–	+	90	–	NGC	CT+RT	22 mo, Alive
34	36/M	R, parietal	Headache	+	–	+	+	80	–	NGC	CT+RT	20 mo, Alive
35	54/M	L1-L2	Back and leg pain	–	–	–	+	90	–	NGC	CT+RT	26 mo, DOD
36	45/F	L, temporal	NA	+	–	+	+	95	–	NGC	CT+RT	15 mo, Alive
37	50/F	L, frontoparietal	Visual disturbances	–	+	+	–	95	–	GC	CT+RT	12 mo, Alive
38	46/F	L, frontal	Headache, paresthesia	–	–	+	+	90	–	NGC	CT+RT	6 mo, Alive
39	50/F	IIIrd and VIIth nerves, L1	Bell's palsy, diplopia, paraparesis	+	–	+	+	90	–	NGC	None	1 mo, DOD

NA, not available; ICP, intracranial pressure; GC, germinal center subtype; NGC, non-germinal center subtype; CT, chemotherapy; RT, radiotherapy; DOD, dead of disease.

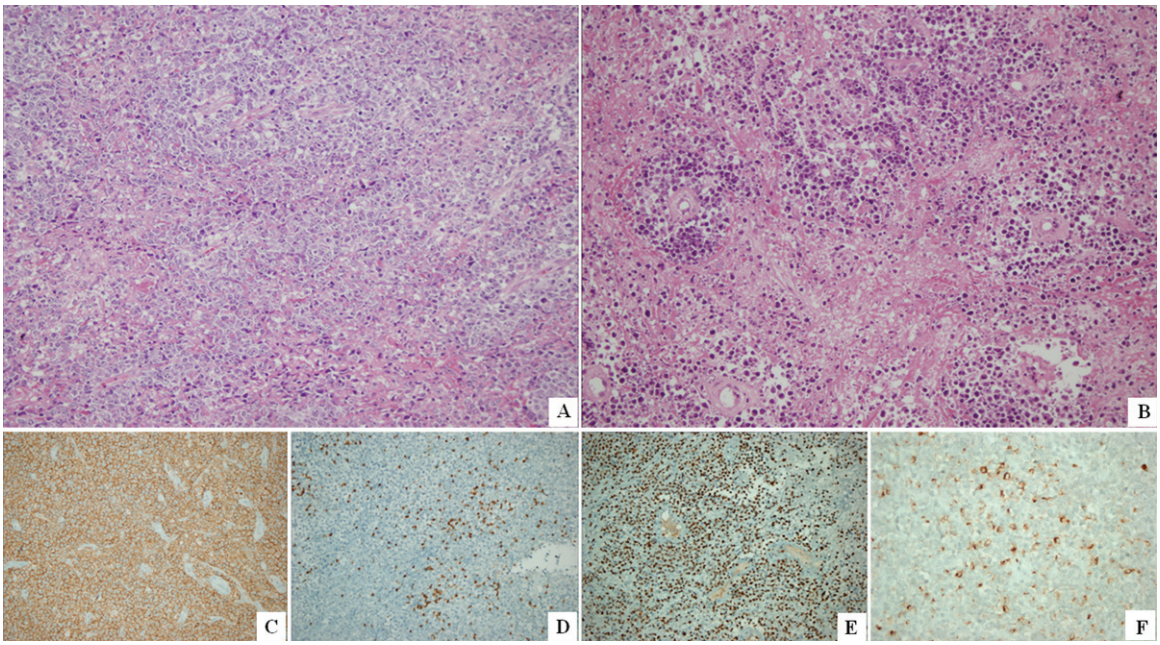

Figure 1. Primary central nervous system lymphoma of immunocompetent patients. Tumor cells had vesicular nuclei and basophilic cytoplasm, infiltrating parenchyma diffusely (A) and demonstrating characteristic perivascular cuffing (B). These cells exhibited positive staining with CD20 (C), while adjacent T cells demonstrated CD3 positivity (D). Ki-67 proliferative index was high (E) and only the cases 8 and 30 showed EBV positivity (F). Magnification x200.

involvement included periventricular region (3/39), occipital lobe (2/39), basal ganglia (2/39), brainstem (2/39), lumbar spinal cord (2/39), cingulate gyrus (1/39), and ventricular trigone (1/39). The lesions showed mild to marked enhancement on imaging, except case 13 which had no enhancement. Multifocal involvement was evident in 23% of the cases (9/39). Scans did not reveal any hemorrhage or cystic changes.

Pathologic features

Of the 39 cases examined, microscopically, tumor cells showed diffuse growth pattern and perivascular accumulation (**Figure 1A** and **1B**). These cells had the appearance of centroblasts with medium to large cells having cleaved or noncleaved vesicular nucleus, two or four nucleoli and scanty amphophilic to basophilic cytoplasm. They were intermingled with reactive small lymphocytes, macrophages and glial cells. Immunohistochemically, all had diffuse, intense staining with CD20 in tumor cells which were negative for CD3 (**Figure 1C** and **1D**). Six cases (15.4%) were of the germinal center subtype. Specifically, all of these cases were positive for CD10, all expressed bcl-6 immunostaining, none of them was positive for bcl-2 and only one case showed MUM1 staining (**Figure 2**). Thirty-three cases (84.6%) belonged to non-germinal center subtype and they were negative for CD10. Thirty of them showed MUM1 staining while 17 cases had bcl-2 expression and 10 cases were bcl-6 positive (**Figure 3**). All of the patients had a high Ki-67 index, ranging from 80 to 100% (mean, 93.5%) (**Figure 1E**). EBV was positive in 2 cases only (5.1%) (**Figure 1F**).

Prognostic factors and survival

Thirty-five cases had sufficient follow-up data for analysis. Median follow-up and survival times were 16 and 18 months, respectively. Univariate analysis was performed for 11 potential prognostic parameters separately, and the log-rank test was used to assess whether the variable had an influence on OS. For different clinical, pathological and treatment variables, median survival times in months and log-rank p values are shown in **Table 2**. Patients who received combined chemotherapy and radiotherapy had a significantly better OS when compared to chemotherapy alone ($p < 0.001$). Other variables did not have an influence on survival of patients.

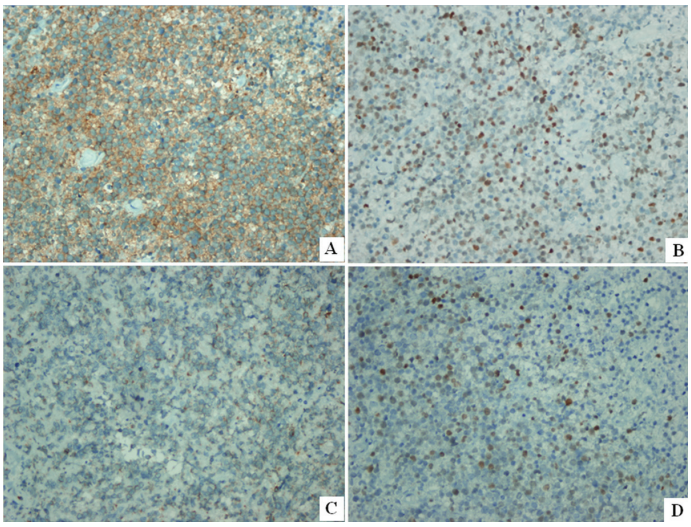

Figure 2. Germinal center subtype, case 28. Tumor cells showed strong CD10 positivity (A), nuclei showed bcl-6 (B) and MUM-1 (D) immunostaining, but bcl-2 expression was not prominent (C). Magnification x400.

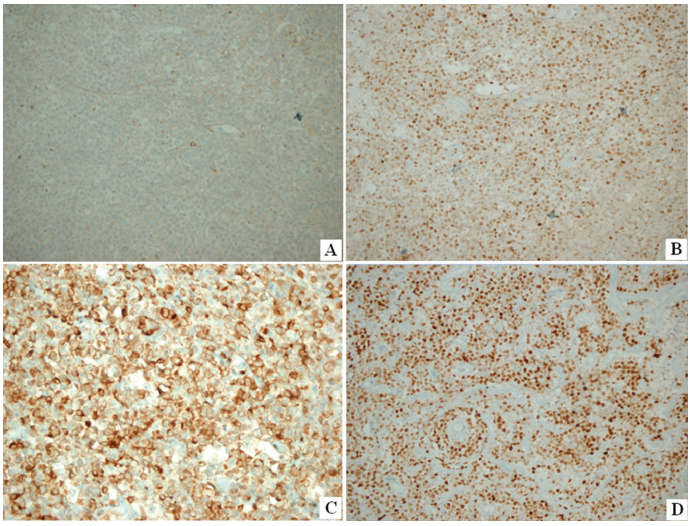

Figure 3. Nongerminal center subtype, case 6. Tumor cells were negative for CD10 (A), but exhibited positivity with bcl-6 (B), bcl-2 (C), and MUM-1 (D). Magnification x200.

On multivariate analysis, Cox proportional-hazard analyses were performed to investigate the association between age, multifocal involvement, deep site involvement, bcl-6 positivity, combined therapy and OS (**Table 3**). Combined chemotherapy plus radiotherapy was found to be an independent factor affecting the OS (HR=0.088, 95% CI=0.028–0.277). Two-year survival rate for patients who received combined therapy was 33% while all patients who received single therapy were dead of disease at 17 months follow-up (**Figure 4**).

Discussion

Previously, PCNSL was regarded as the tumor of immunosuppressed individuals, especially the patients with HIV infection or AIDS, and organ transplant recipients. However, after the introduction of highly active antiretroviral therapy into clinical practice and close monitoring with heightened awareness in these risk groups, the incidence of PCNSL decreased substantially in these patients. Today, the frequency of PCNSL is much higher in immunocompetent individuals than in immunocompromised ones. Whether the disease has a different course in patients without an underlying immune dysregulation is still unclear. The role of various immunophenotypic markers in predicting adverse outcome for this particular group is highly debated.

There are several hypotheses which aim to explain the pathogenesis of PCNSL. Since the central nervous system lacks lymphoid tissue or lymphatic vessels, PCNSL may be caused by the monoclonal proliferation of continuously trafficking T-cells or B-cells in CNS, or the specific tropism of neoplastic T or B lymphocytes for CNS. Malignant transformation of T or B cells after a benign inflammatory process within the CNS may also be the origin of PCNSL. Additionally, neoplastic lymphocytes eradicated by the intact peripheral immune system may escape to the CNS [3].

Patients with PCNSL rarely present with the symptoms associated with other NHLs which include night sweats, fever and weight loss. Headache (30.7%) and paresthesia/paraplegias (23%) were the major presenting symptoms of patients in our study. This may be due to the parietal lobe involvement in the majority of the patients (28.2%). However, most common presenting symptoms varied considerably among

Table 2. Univariate Analysis for Various Clinicopathologic Variables (Log-Rank test)

Prognostic Factor	No (%)	Median survival (months)	*p*-value
Age			
≥ 60 years	8 (22.8)	16	0.940
< 60 years	27 (77.2)	18	
Gender			
Male	18 (51.4)	14	0.170
Female	17 (48.6)	22	
Multifocal involvement			
Yes	9 (25.7)	14	0.503
No	26 (74.3)	19	
Deep-site involvement			
Present	11 (31.4)	19	0.383
Absent	24 (68.6)	18	
Bcl-2			
Positive	15 (42.8)	17	0.835
Negative	20 (58.2)	19	
Bcl-6			
Positive	15 (42.8)	14	0.107
Negative	20 (58.2)	18	
CD10			
Positive	6 (17.1)	19	0.494
Negative	29 (82.9)	17	
MUM1			
Positive	27 (77.1)	17	0.856
Negative	8 (23.9)	19	
EBV			
Positive	2 (5.7)	6	0.131
Negative	33 (94.3)	19	
GC status			
GC phenotype	6 (17.1)	19	0.494
NGC phenotype	29 (82.9)	17	
Treatment			
CTx alone	10 (29.4)	9	0.000
CTx + RTx	24 (70.6)	37	

GC, germinal center; NGC, non-germinal center; CTx, chemotherapy; RTx, radiotherapy.

Table 3. Mulitvariate Cox regression analysis for prognostic factors

Prognostic factor	HR (95% CI)	*p*-value
Age ≥ 60 years	1.376 (0.509–3.715)	0.529
Multifocal involvement	0.566 (0.168–1.916)	0.361
Deep-site involvement	0.464 (0.141–1.523)	0.206
Bcl-6 positivity	1.567 (0.620–3.958)	0.342
Combined therapy	0.088 (0.028–0.277)	0.000

HR, hazard ratio; CI, confidence interval.

different studies including focal neurologic deficits [5], sensory-motor symptoms [2], and symptoms of raised intracranial pressure [6]. Seizures are rarely encountered which might be due to the white matter propensity of PCNSL (15%).

Several prognostic classifications were proposed for PCNSL in order to make practical algorithms, determine the best individualized treatment strategy and improve the outcome. The International Extranodal Lymphoma Study Group prognostic index suggested five independent prognostic variables which include age, performance status, CSF protein concentration, LDH level, and deep site involvement of the brain [7]. The Nottingham/Barcelona score includes age, performance status, and extent of brain disease [8]. The Memorial Sloan-Kettering Cancer Center score proposes age and Karnofsky scores as prognostic factors [9]. Recently, a gene expression study divided DLBCL into three prognostic categories including germinal center (GC), activated-B cell and type 3 subtypes according to differential immunoreactivity for phenotypic markers (i.e. CD 10, bcl-6, MUM-1) [4, 10]. Activated-B cell and type 3 constitute the non-germinal center (NGC) group which has a worse prognosis. When this classification was applied to PCNSL-DLBCL, several studies indicated that 66.7 to 93% of the cases belonged to the NGC group [2, 11, 12]. However, they failed to demonstrate a statistically significant difference in terms of overall and disease free survival between these two subtypes. In our series, 84.6% of the cases had phenotypic features consistent with NGC subtype and there was no significant survival difference between two groups. Therefore, it seems that PCNSL-DLBCL has a different clinical behavior when compared to other extranodal DLBCLs.

Bcl-6 was offered as an independent prognostic variable in PCNSL. However, studies came up with con-

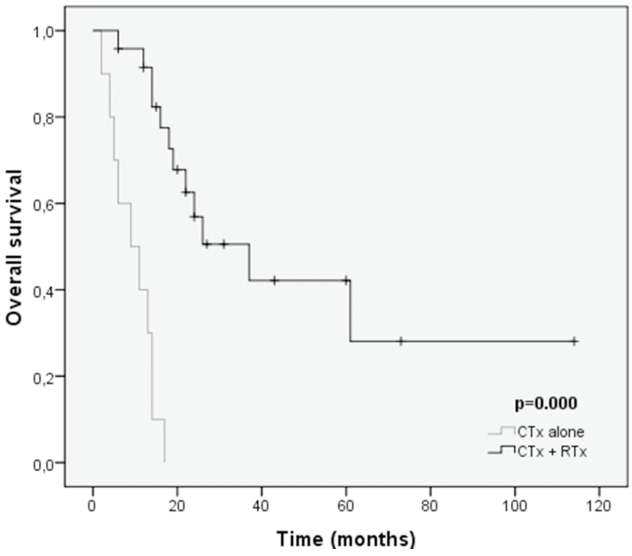

Figure 4. Kaplan-Meier overall survival curve of PCNSL patients treated with chemotherapy alone and combined chemotherapy and radiotherapy. The latter had a significantly better overall survival when compared to cases who received chemotherapy alone ($p < 0.001$).

flicting results: Some suggested bcl-6 as a poor prognostic parameter [11, 13], while others claimed that it was associated with a more favorable outcome [14, 15]. Still others failed to demonstrate a survival difference between positive and negative groups [1, 12]. In univariate log-rank analysis and the Cox regression analysis, we could not show a prognostic difference in these groups, as well. Also, there was no significant survival difference between Bcl-2 positive and negative groups, which was compatible with prior reports [1, 2].

Studies stated that younger age at diagnosis (< 60 years) represents a favorable prognostic factor [2, 16, 17], while deep site or multifocal involvement of the brain was proposed to have a negative influence on survival outcomes [7, 15, 18]. In both univariate and multivariate analyses, we failed to demonstrate an association between these parameters and OS. However, this may be attributed to the relatively lower number of cases enrolled in this study, as well as the censored data.

Being an oncogenic virus, EBV has several implications on various types of tumors arising in immunosuppressed patients, including PCNSL. However, its etiological role in PCNSL of immunocompetent patients remains to be clarified. In the present study, two patients (5.7%) had EBV positivity and they did not show a survival difference when compared to other cases.

Increased proliferative activity by Ki-67 is a poor prognostic parameter in systemic DLBCLs, but several other studies failed to show any significant survival difference between PCNSL patients with high and low proliferative indexes [15]. In our series, mean ki-67 score was too high (93.5%) when compared to other studies in which the proliferative index ranged between 69 to 78% [11].

Treatment is one of the most important prognostic parameters in PCNSL of immunocompetent patients. Patients who received chemotherapy in combination with radiotherapy have a significantly better outcome when compared to cases who received radiotherapy or chemotherapy alone. High-dose methotrexate (HDM) is still the most active drug in the management of PCNSL. Several combinations with HDM were proposed, but optimum regimen has not been defined yet.

In summary, we retrospectively investigated the demographic and clinicopathological features of PCNSL-DLBCL together with a detailed analysis of potential prognostic factors and OS of immunocompetent patients. Combined therapy was superior to chemotherapy alone, but none of the immunophenotypic markers had a statistically significant influence on OS. Prospective studies with large patient series are needed to elucidate prognostic factors, as well as optimum treatment regimens in immunocompetent PCNSL.

Statement of conflict of interest

The authors have no conflict of interest to declare.

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