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PROGNOSTIC FACTORS INFLUENCING TREATMENT RESPONSE IN PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA

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Abstract

Aims: The aim of this study was to determine the clinicopathological findings of patients with primary central nervous system lymphoma (PCNSL) as real-life data, examine their treatment approaches, and define the prognostic factors.

Methods: Eighty-four patients who presented with a diagnosis of PCNSL between January 2008 and July 2021 were included in this study. The treatments received by the patients and their survival outcomes were retrospectively analyzed.

Results: The median age at diagnosis was 55 (18-80 years). The median progression-free survival (PFS) was 16.8 months (12.421.2 months), while the median overall survival (OS) was 18 months (13.7-22.4 months) in all patients. The most commonly used chemotherapy was high-dose methotrexate based regimens, which were preferred in 68 (81%) patients. Objective response rate and disease control rate were 75% and 83.3%, respectively. Consolidation therapy was an independent prognostic factor for PFS (HR: 0.32, 95% CI, 0.18-0.55, p<0.001). There were 42 (50%) patients who had been treated by consolidation therapy. Patients who received consolidation therapy were observed to have a 67% reduction in mortality compared to those who did not (HR: 0.33, 95% CI, 0.19-0.57, p<0.001). Also, high risk in Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic model was found to be associated with a 2-fold increase in mortality compared to the good risk group (HR: 2.04, 95% CI, 1.02-3.56, p=0.022). Toxicity of any grade was observed in 78 (92.9%) patients. There were 3 (3.6%) patients who died due to treatment toxicity.

Conclusion: Consolidation therapy was found to be an independent predictive factor for both OS and PFS in PCNSL. In addition, high risk class according to MSKCC prognostic model was found to be associated with increased mortality.

Keywords: Primary central nervous system lymphoma, treatment, chemotherapy, radiotherapy, prognosis

INTRODUCTION

Primary central nervous system lymphomas (PCNSL) is a type of lymphoma confined to the brain, spinal cord, cerebrospinal fluid, and vitreoretinal space, without evidence of systemic involvement.[1] It constitutes 4% to 6% of all extranodal lymphomas and makes up 4% of newly diagnosed malignant brain cancers.[2] The median age at diagnosis 65 years, even though PCNSL can be encountered at any age. Individuals who are

immunocompromised, such as those with HIV/AIDS or those who have undergone organ transplants, are at a higher risk for Epstein-Barr virus-related
PCNSL.[1]
The predominant histopathologic subtype of PCNSL is diffuse large B-cell lymphoma (DLBCL), occurring in over 90% of cases. The primary signs and symptoms vary based on the tumor's neuroanatomic location. Most patients present with cognitive, motor, or constitutional symptoms.[3] PCNSL most commonly occurs as a single supra-tentorial brain lesion. It is most commonly located in the frontoparietal lobe, but can also be found in the temporal lobe, the basal ganglia and the corpus callosum, in order of prevalence.[4]
Unlike other brain tumors, PCNSL are highly responsive to chemotherapy and radiotherapy, yet have a high recurrence rate. In general, the prognosis for patients with PCNSL is poor, with an approximate 5-year survival rate of 28%. Although there is still no standard treatment option for firstline treatment, high-dose methotrexate-based (HD-MTX) chemotherapy regimens are generally recommended.[5]
This study aimed to evaluate the demographic and clinical characteristics, as well as the laboratory findings of patients diagnosed with PCNSL using real-life data, analyze treatment strategies, and identify prognostic factors.

METHODS

Ethics

The study was conducted with the permission of the Adıyaman University Non-interventional Clinical Researches
Ethics Committee (Date: 20.04.2022, Decision No: 2022/428). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Population

This research included 84 individuals diagnosed with PCNSL at three oncology centers located in Turkiye, spanning from January 2008 to July 2021. Eligible participants were adults aged 18 and above, with a confirmed diagnosis based on either histological or cytological evidence. Exclusion criteria encompassed patients who were HIV positive, had a history of immunosuppressive disorders, exhibited clinical or laboratory signs of systemic lymphoma, or had previously used steroids. The study gathered extensive laboratory, clinical, and pathological data, including performance status (assessed by the Eastern Cooperative Oncology Group, ECOG), age, gender, tumor location, various treatment strategies, progression-free survival (PFS), overall survival (OS), and any reported adverse effects. Diagnostic imaging for staging was performed using either computed tomography (CT) or positron emission tomography (PET)-CT. To predict patients outcomes, the Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic scoring system was applied, which evaluates two key factors: age and the Karnofsky Performance Status scale. Based on this, patients were classified into three risk categories: good risk (age <50 years), medium risk (age ≥50 years with a Karnofsky score ≥70), and high risk (age ≥50 years with a Karnofsky score <70).[6]

Treatment Protocol

The treatment protocol consisted of an initial phase of chemotherapy, followed by consolidation with either radiotherapy or stem cell transplantation. Whole brain radiotherapy (WBRT) was administered at a dose of 40 Gy, while HD-MTX was used at a dosage of ≥3 g/m^2. To evaluate safety and adverse effects, toxicity levels were measured according to the National Cancer Institute's Common
Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Response Assessment

Post-treatment response was systematically evaluated through magnetic resonance imaging (MRI), focusing on tumor characteristics such as location, quantity, and size, as well as changes in these parameters following therapy. A complete response (CR) was classified by the full resolution of lymphoma, whereas a partial response (PR) was identified by a reduction of at least 50% in tumor size. Progressive disease (PD) was diagnosed when tumor size increased by more than 25%, or new lesions appeared, while stable disease (SD) was noted when tumor size decreased by less than 50%, but no progression was observed.[7] The objective response rate (ORR) was calculated by combining CR and PR rates, whereas the disease control rate (DCR) included CR, PR, and SD.

Statistical Analysis

Data analysis was performed using SPSS version 24.0 (IBM Corporation, Armonk, New York, USA). Chi-square tests (either Pearson's or Fisher's exact) were used to compare categorical variables. Survival data, including OS and PFS, were evaluated using the Kaplan-Meier method. OS was calculated from the diagnosis date to either death or the last known follow-up. PFS was calculated from the diagnosis date to the first occurrence of disease progression, death, or the most recent follow-up, whichever came first. The log-rank test was applied to assess survival differences. Additionally, multivariate analysis was carried out using backward stepwise selection and Cox regression to identify independent survival predictors. In the present study, a confidence interval of 95% was established, and a two-tailed significance p value of 0.05 was accepted.

RESULTS

Demographic and Clinical Data

The median age at diagnosis was 55 years (18–80), and 46 patients (54.8%) were male. ECOG PS was ≥2 in 37 (44%) patients and 29 (34.5%) patients had comorbidities. The most common comorbidity was hypertension, seen in 65.5% (19/29) of patients, followed by diabetes mellitus with 55.2% (16/29). The most frequently observed histological subtype was DLBCL, found in 75 patients (89.3%). According to the MSKCC prognostic model, 26 (31%) patients had highrisk disease (class 3). There were 17 (20.2%) patients with hemoglobin <12 g/dl and 30 (35.7%) patients had low albumin levels (≤3.5 g/dl). Forty-three (51.2%) patients had a history of surgery, and gross total resection had been performed in 26 (60.5%) of these patients. Sixty-eight (81%) patients had been treated by HD-MTX-based chemotherapy. Lumbar puncture had been done in 30 (35.7%) patients, CSF cytology was positive in 10 (33.3%) of these patients. Intrathecal treatment was administered to 10 (11.9%) patients. The other significant characteristics of the patients are outlined in **Table 1**.

The most common localization of lymphomas was frontal lobe (n=20, 23.8%). Deep localization was detected in 20 (23.8%) patients. Headache (n=53, 63.1%) and focal neurologic deficit (n=50, 59.9%) were the most common presenting symptoms. B symptoms were observed in 11 patients (13.1%). Tumor localization and symptoms have been summarized in

Table 2. **Treatment**

Radiation therapy was the initial therapy in 10 (11.9%) patients. Rituximab was used in 26 (31%) patients. Forty (47.6%) patients received HD-MTX alone, while HDMTX+rituximab regimen, being the second most frequent treatment, was administered to 10 (11.9%) patients. The

Table 1. Baseline demographic and clinical characteristics				
Characteristics	Median	Range	No	%
Age (years)	55	18-80		
Age >60 years			27/84	32.1
Male sex			46/84	54.8
Comorbidity			29/84	34.5
Histopathological subtypes				
Diffuse large B-cell lymphoma			75/84	89.3
Other B-cell lymphomas			6/84	7.1
T-cell lymphomas			1/84	1.2
Unclassified			2/84	2.4
MSKCC prognostic score				
Good risk			29/84	34.5
Intermediate risk			29/84	34.5
High risk			26/84	31.0
Treatments				
Surgery			43/84	51.2
Gross total resections			26/43	60.5
HD-MTX-based chemotherapy			68/84	81.0
Rituximab			26/84	31.0
Lumbar puncture			10/30	33.3
Intrathecal therapy			10/84	11.9
Laboratory findings				
LDH level ≥248 U/L			50/84	59.5
Lymphocyte count <1 x109 /L			14/84	16.7
Hemoglobin level <12 g/dl			17/84	20.2
Platelet count <150 x109 /L			5/84	6.0
Serum albumin level ≤3.5 g/dl			30/84	35.7
β2 microglobulin level ≥2.2 mg/L			11/57	19.3
Lymphocyte count (x109 /L)	1.6	0.3-8.8		
Hemoglobin level (g/dL)	13.45	8.7-17.9		
Platelet count (x109 /L)	254.50	121-631		
Serum albumin level (g/dl)	3.90	2.10-5.01		

β2 microglobulin level (mg/L)	1.57	0.73-5.78

ECOG PS: Eastern Cooperative Oncology Group Performance Status, HD-MTX: High dose methotrexate, LDH: Lactate dehydrogenase, MSKCC: Memorial Sloan-Kettering Cancer Center

Table 2. Tumor location and presentation of the symptoms	
n=84 (%)	
Tumor location	
Frontal	20 (23.8)
Parietal	11 (13.1)
Temporal	9 (10.7)
Occipital	4 (4.8)
Multifocal	16 (19)
Cerebellum	9 (10.7)
Basal ganglia and thalamus	6 (7.2)
Corpus callosum	4 (4.8)
Brainstem	1 (1.2)
Leptomeningeal	3 (3.6)
Ocular involvement	1 (1.2)
Deep lesionsa	20 (23.8)
Symptoms	
B symptoms	11 (13.1)
Headache	53 (63.1)
Focal neurological deficit	50 (59.9)
Ataxia	43 (51.2)
Decreased consciousness	37 (44)
Nausea/vomiting	25 (29.8)
Seizures	24 (28.6)
Visual symptoms	20 (23.8)

a Deep brain involvement:corpus callosum, basal ganglia, periventricular region, brainstem, and/or cerebellum

Table 3. Treatment options and response to first-line therapy

Initial treatment regimen n=84 (%)
WBRT 10 (11.9)
HD-MTX 40 (47.6)
HD-MTX+rituximab 10 (11.9)
HD-MTX+Ara-C+rituximab 5 (6.0)
HD-MTX+TMZ+rituximab 5 (6.0)
HD-MTX+IFOS 4 (4.8)
R-CHOP 4 (4.8)
HD-MTX+Ara-C 3 (3.6)
Ara-C 1 (1.2)
HD-MTX+Ara-C+rituximab+thiotepa 1 (1.2)
TMZ+rituximab 1 (1.2)
Consolidation treatment n=42 (%)
WBRT 32 (76.2)
HD-CT with ASCT 3 (7.1)
Ara-C 2 (4.8)
HD-MTX+Ara-C 2 (4.8)
R-CHOP 2 (4.8)
HD-MTX 1 (2.4)
Best response n=84 (%)
CR 40 (47.6)
PR 23 (27.4)
SD 7 (8.3)
PD 14 (16.7)
ORR 63 (75.0)
DCR 70 (83.3)
Ara-C: Cytarabine, ASCT: Autologous stem cell transplantation, HD-MTX: High-dose methotrexate, HD-CT: High-dose chemotherapy, IFOS: Ifosfamide, R: Rituximab, TMZ: Temozolomide, WBRT: Whole brain radiotherapy, CR: Complete response, PR: Partial response, SD: Stable disease, PD: Progressive disease, ORR: Overall response rate (CR±PR); DCR: Disease control rate (CR±PR±SD)

median number of induction chemotherapy cycles was 4, ranging from 1 to 13. There were 42 (50%) patients who had been treated by consolidation therapy. The most common consolidation treatment was radiotherapy (in 32 (76.2%) patients). Autologous stem cell transplantation (ASCT) after high-dose chemotherapy was performed in 3 patients (7.1%). The median number of consolidation chemotherapy cycles was 3 (1-6). ORR and DCR were 75% and 83.3%, respectively. ORR was 70% in those receiving HD-MTX only and 76.9% in those receiving rituximab-based treatment. No statistically significant difference was found between the groups regarding the ORR for both treatments (p=0.601 and p=0.785, respectively). Treatment regimens and response rates had been summarized in

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Table 3. Survival and Prognostic Factors

Progression developed in 56 (66.7%) patients, and 29 (34.5%) patients received treatment after progression. Sixty-five (77.4%) patients were deceased at the time of analysis. Median follow-up was 15.8 (2.1-178) months. The median PFS and OS were 16.8 months (12.4-21.2), and 18 months (13.7-22.4). The 2-year PFS and OS rates were 39.3% and 40.8%, respectively. At the same time the 5-year PFS and OS rates were 26% and 25%, respectively.

Univariate analyses revealed that median PFS was 24 months in patients receiving consolidation therapy while 5.7 months in patients who did not receive consolidation (p<0.001). Also, PFS was found to be significantly longer in patients who received rituximab-based treatment regimens than those who did not (24.2 vs 11.9 months, respectively, p=0.020) (**Figure 1**). Patients with high risk according to MSKCC prognostic model had lower OS than patients with low risk patients (8.5 vs. 26.4 months, respectively, p=0.013). OS was found to be shorter in patients with hemoglobin <12 g/dl and albumin levels below 3.5 g/dl compared to those with higher levels (p=0.051 and p=0.040, respectively). OS was also significantly longer in patients who received consolidation therapy with 24 months, whereas it was 8.5 months in those who did not (p<0.001). In addition, patients who received rituximabbased therapy were found have longer OS than those who did not (33.3 vs. 15.3 months, respectively, p=0.037) (**Figure 2**). **Table 4** provides a summary of the univariate analysis results for PFS and OS.

Multivariate analyses for prognostic factors revealed that consolidation therapy was an independent prognostic factor for PFS (HR: 0.32, 95% CI, 0.18-0.55, p<0.001). Patients who received consolidation therapy were observed to have a 67% reduction in mortality compared to those who did not (HR: 0.33, 95% CI, 0.19-0.57, p<0.001). Also, high risk in MSKCC prognostic model was found to be associated with a

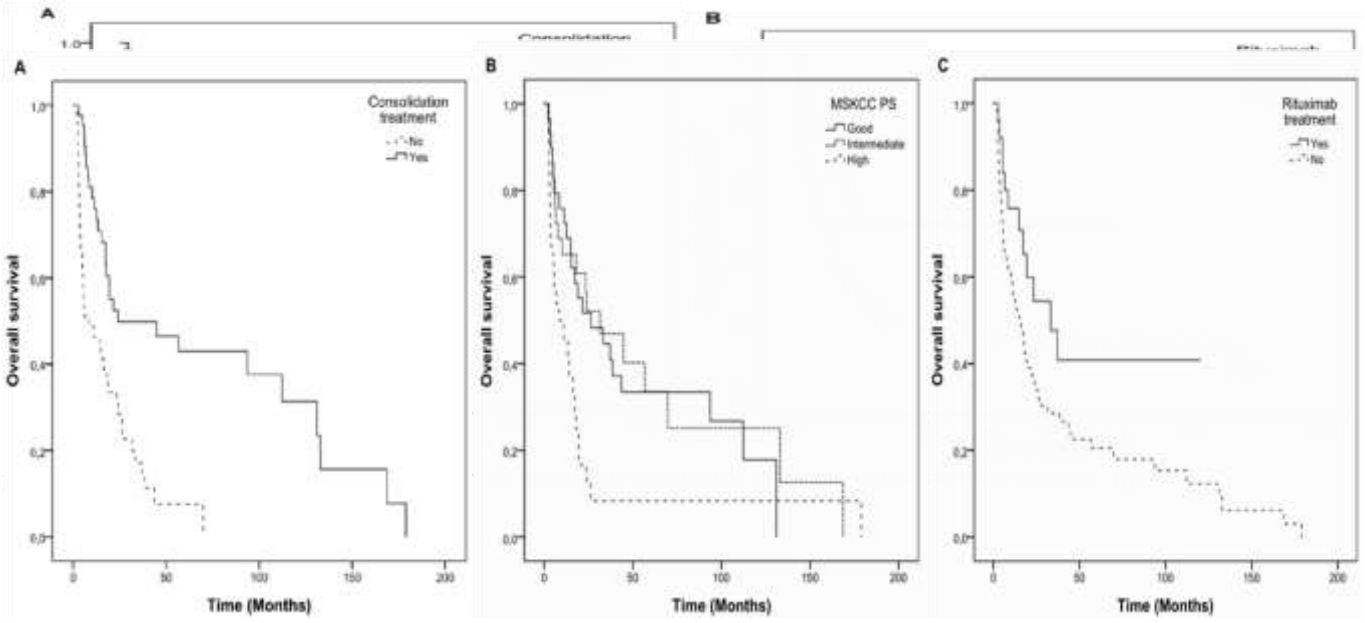

Figure 2. Kaplan–Meier curves of overall survival according to consolidation treatment (**A**), MSKCC prognostic model (**B**), and rituximab treatment (**C**)
MSKCC: Memorial Sloan-Kettering Cancer Center

2-fold increase in mortality compared to the good risk group (HR: 2.04, 95% CI, 1.02-3.56, p=0.022). The results of multivariate analyses for PFS and OS are summarized in **Table 5**.

Toxicity

Toxicity of any grade was observed in 78 (92.9%) patients. Dose reduction was required in 20 (23.8%) patients. A total of 52 patients (61.9%) successfully completed the prescribed treatment regimen. There were 3 (3.6%) patients who had died due to treatment toxicity. The most common grade 1 adverse event was anemia in 30 (35.7%) patients, followed by elevated transaminases in 29 (34.5%) patients. The second most common grade 1 hematological toxicity was thrombocytopenia in 27 (32.1%) patients. Mild nausea and vomiting (grade 1) were experienced by 26 patients, accounting for 31% of the total patient population. The

Table 5. Multivariate analysis of prognostic factors associated with progression-free survival and overall survival

Progression-free surv ival			Overall survival		
Variables (n=84)	HR (95% CI)	p value	HR (95% CI)	p value	
	0.87 (0.48-1.78)				
2.04 (1.02-3.56)	0.015				
0.661					
0.022					
Hemoglobin ≥12 g/dl vs <12 g/dl	0.65 (0.31-1.35)	0.253	0.79 (0.38-1.64)	0.529	
Serum albumin level >3.5 g/dl vs ≤3.5 g/dl	0.83 (0.43-1.60)	0.593	0.73 (0.39-1.35)	0.320	
Initial treatment Others vs HD-MTX-based chemotherapy	0.92 (0.47-1.8)	0.817	0.91 (0.47-1.77)	0.792	
Rituximab Yes vs no	0.54 (0.27-1.05)	0.069	0.59 (0.31-1.12)	0.108	
Consolidation treatment Yes vs no	0.32 (0.18-0.55)	<0.001	0.33 (0.19-0.57)	<0.001	

CI: Confidence interval, HD-MTX: High-dose methotrexate, HR: Hazard ratio, MSKCC: Memorial Sloan-Kettering Cancer Center

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Table 4. Univariate analysis of prognostic factors associated with progression-free survival and overall survival

Variables (n=84)	PFS HR (95% CI)	p value	OS HR (95% CI)	p value
Age >60 years vs ≤60 years	1.37 (0.77-2.44)	0.280	1.45 (0.85-2.46)	0.166
Gender Male vs female	1.11 (0.66-1.87)	0.689	1.42 (0.85-2.35)	0.172
ECOG PS ≥2 vs 0-1	1.21 (0.71-2.07)	0.480	1.61 (0.98-2.63)	0.060
Comorbidity Yes vs no	0.92 (0.53-1.60)	0.776	1.01 (0.60-1.70)	0.961
MSKCC prognosis score 0.445 0.015 Intermediate risk vs good risk 1.01 (0.54-1.87) 0.981 0.97 (0.52-1.80) 0.923 High risk vs good risk 1.47 (0.75-2.87) 0.255 2.14 (1.17-3.93) 0.013				
LDH elevated vs normal	0.98 (0.56-1.70)	0.939	0.92 (0.54-1.55)	0.741
Lymphocyte <1x109/L vs ≥1 x109/L	1.32 (0.62-2.81)	0.467	1.64 (0.83-3.27)	0.153
Hemoglobin ≥12 g/dl vs <12 g/dl	0.57 (0.30-1.08)	0.086	0.54 (0.29-1.00)	0.051
Serum albumin level >3.5 g/dl vs ≤3.5 g/dl	0.65 (0.37-1.12)	0.123	0.58 (0.34-0.97)	0.040
β2 microglobulin ≥2.2 mg/L vs <2.2 mg/L	1.08 (0.44-2.63)	0.864	1.70 (0.76-3.77)	0.193
Surgery Subtotal resections vs gross total resections	0.66 (0.30-1.47)	0.317	0.57 (0.28-1.25) 0.171	
Initial treatment others vs HD-MTX-based chemotherapy	1.6 (0.87-2.94)	0.130	1.67 (0.95-2.96) 0.077	
Rituximab Yes vs no	0.45 (0.24-0.88)	0.020	0.52 (0.28-0.96)	0.037
Consolidation treatment Yes vs no	0.29 (0.17-0.52)	<0.001	0.34 (0.20-0.58)	<0.001
Deep lesions Yes vs no	0.76 (0.41-1.42)	0.392	0.69 (0.39-1.23)	0.211
B symptoms Yes vs no	1.19 (0.58-2.47)	0.621	0.82 (0.36-1.72)	0.592

CI: Confidence interval, ECOG PS: Eastern Cooperative Oncology Group Performance Status, HD-MTX: High-dose methotrexate, HR: Hazard ratio, LDH: Lactate dehydrogenase, MSKCC: Memorial Sloan-Kettering Cancer Center, OS: Overall survival, PFS: Progression-free survival

most common grade 2 toxicity was nausea in 33 (39.3%) patients, followed by anemia in 30 (35.7%) patients, and elevated transaminase levels in 16 (19%) patients. The most common grade 3 toxicity was elevated transaminase levels in 10 (11.9%) patients, followed by anemia (n=8, 9.5%) and thrombocytopenia (n=8, 9.5%). The most frequent grade 4 adverse event was neutropenia, observed in 20 patients (23.8%), while grade 4 febrile neutropenia occurred in 6 patients (7.1%). Thrombocytopenia was the second most common grade 4 toxicity, observed in 14 (16.7%) patients. Data on treatment toxicity are summarized in **Table 6**.

DISCUSSION

In this study, we evaluated the clinicopathological characteristics, treatment regimens and their clinical outcomes, toxicity profile and prognostic factors in PCNSL. The median age at diagnosis was relatively younger compared to the literature and patients were mostly male. Headache and neurological deficits were the most frequently reported presenting symptoms. The most common tumor location was the cerebral hemisphere. Upfront treatment was most commonly initiated with HD-MTX-based chemotherapy Regimens, cranial radiation was the most common consolidation treatment. Consolidation therapy was determined to be an independent factor influencing both

Table 6. Toxicities during treatment

Toxicity	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)
Nausea	26 (31)	33 (39.3)	3 (3.6)	1 (1.2)
Vomiting	26 (31)	8 (9.5)	3 (3.6)	1 (1.2)
Diarrhea	9 (10.7)	4 (4.8)	1 (1.2)	1 (1.2)
Mucositis	15 (17.9)	5 (6.0)	5 (6.0)	4 (4.8)
Neutropenia				
Thrombocytopenia				
Anemia				
Sensory neuropathy				
Nephrotoxicity	11 (13.1)	4 (4.8)	6 (7.1)	0
Elevated transaminases	29 (34.5)	16 (19.0)	10 (11.9)	6 (7.1)
Hyperbilirubinaemia	9 (10.7)	3 (3.6)	2 (2.4)	1 (1.2)
Febrile neutropenia	9 (10.7)	2 (2.4)	3 (3.6)	6 (7.1)
Pneumonitis	1 (1.2)	0	1 (1.2)	0

PFS and OS. In addition, high risk class according to MSKCC prognostic model was found to be associated increased mortality compared to the good prognostic class. The most common grade 1 and 2 side effects were nausea, vomiting, anemia, thrombocytopenia and elevated transaminases, while the most commonly observed grade 3 and 4 side effects, as expected were neutropenia, thrombocytopenia and elevated transaminases.

PCNSL is a type of extranodal non-Hodgkin lymphoma. Its incidence increases with age and varies according to gender.[8] A retrospective series reported that the median age at diagnosis was 58 with male predominance.[9] In our previous analysis lymphoma was found to be 10 years younger than western world.[10] In contrast to systemic lymphomas, B symptoms are less common. About 50% to 70% of patients present with focal neurological deficits. Symptoms of increased intracranial pressure are seen in one third of patients.[1,4] The lesions are often located in the cerebral hemisphere. In our study, male predominance among demographic characteristics, symptoms and lesion locations were consistent with the literature, and the patients were observed to be diagnosed at a relatively younger age with a median age of diagnosis of 55 years.

Treatment of PCNSL consists of combination induction chemotherapy regimens containing HD-MTX and consolidation treatments including radiotherapy and highdose chemotherapy rescued by ASCT.[1,11] Limited drug penetration to central nervous system due to the bloodbrain barrier (BBB), concerns about

radiotherapy-induced neurotoxicity, and short duration of remission despite high response rates challenges the therapeutic decision-making process.[12] In addition, its rare incidence limits the number of randomized studies, and standard treatment is still to be determined. Therefore, issues including the role of surgery, dosing of methotrexate, optimal combinations, addition of rituximab treatment, number of consolidation chemotherapy cycles and salvage treatment approach in relapsed disease remain unclear.

In the past, the role of surgery in PCNSL was limited to biopsy, except for large masses leading to increased intracranial pressure and signs of herniation.[13] since the disease is highly sensitive to chemotherapy and radiation therapy, surgical resection was believed to pose an unnecessary risk. Also, surgical resection was thought to be impractical since 65% of the lesions involved deep brain structures and 44% of the lesions were multifocal. In their 2012 study, Weller et al.[14] suggested a re-evaluation of the position that surgery has no prognostic role. A few subsequent studies reported that surgical resection may have certain benefits for some patients.[15,16] However, there are also contradictory studies reporting that resection has no OS or PFS benefit.[17] In our study, surgical treatment was found not to be improve PFS or OS. The cause of this condition may be due to the different and probably incomplete surgical approach. The role of surgical resection in treatment is still unclear and there is no clear consensus.

Standard chemotherapeutic agents used for the treatment of systemic lymphomas have not proven to be effective enough in PCNSL, possibly due to poor penetration from the BBB.

Methotrexate penetrates the BBB at doses above 1.5 g/m^2 and reaches cytotoxic concentrations in the CSF. Different drugs have been used in combination with HD-MTX to enhance response rates and improve survival. The ORR with MTX as single agent and combination of MTX with cytarabine (ARA-C) was found to be 40% and 69%, respectively.[18] In another study, HD-MTX was compared with rituximab plus HD-MTX and the ORR was reported to be 60% and 89%, respectively. In patients receiving only HD-MTX, PFS was 4 months and OS was 16.3 months.[19] In the combination of temozolomide-MTX and rituximab, the ORR was 66% and the 2-year PFS was 57%.[20] A retrospective analysis reported that the median PFS was 17 months, and the median OS was 37 months in patients receiving HD-MTX-based therapy. Five-year PFS and OS rates were found to be 20% and 35%, respectively.[9] WBRT alone provides an impressive ORR of 90%, however, the responses are not sustained, with a survival of only 12 to 18 months.[21,22] In our study, HD-MTX-based treatment regimen was the most common treatment of choice and the ORR obtained with this regimen was calculated to be 75%. The median PFS was 16.8 months, and the median OS was 18 months across all patients. The two-year PFS rate was 39.3%, while the two-year OS rate was 40.8%. The fiveyear PFS rate was 26%, and the five-year OS rate was 25%. The survival data in the literature is heterogeneous and our results were consistent with the previously reported studies. Separate analysis could not be performed due to the limited number of patients initially treated WBRT and with combination regimens.

Consolidation treatment approaches can differ and are typically customized based on the patient's age, comorbidities, and response to induction therapy. WBRT is the most commonly used consolidation strategy. An appropriate alternative to WBRT is ASCT combined with high-dose chemotherapy (HDC).[23] In

a phase 2 study that implemented WBRT as consolidation after HD-MTX-based induction chemotherapy, radiological response and 3-year OS were shown to be significantly improved in the consolidation arm. However, considerable increases in neurotoxicity have also been reported.[18] In a later phase 3 study, consolidating HD-MTX-based chemotherapy with WBRT improved PFS but this was not reflected in OS.[24] ASCT following more intensive high-dose myeloablative chemotherapy regimens is typically used in younger patients (<70 years) with minimal comorbidities. Recent phase 2 studies involving HDC-ASCT as consolidation therapy have shown higher ORR (>90%) and extended PFS (>74 months).[25-27] However, significant toxicity associated with this regimen should also be kept in mind when considering this treatment approach. Half of the patients in our study population received consolidation therapy, and WBRT was the most common consolidation strategy in concordance with the literature. A comparison could not be made because the number patients receiving non-WBRT treatment regimens was very limited. However, both PFS (24 vs 5.7 months, respectively) and OS (24 vs 8.5 months, respectively) were statistically significantly improved in patients who received consolidation treatment than those who did not ($p<0.001$). In our study, there were many patients who received treatment in different centers and according to previous treatment standards, so the rates of HDC-ASCT as consolidation therapy were low.

The prognostic impact of several factors in PCNSL is controversial. MSKCC prognostic model, the International Extranodal Lymphoma Study Group (IELSG) scoring system, and a new prognostic model using the absolute lymphocyte count use different variables to predict prognosis.[6,28,29] We failed to demonstrate association of PFS and OS with the variables used in IELSG scoring system including age, ECOG PS status, lesion location in deep brain, and lactate dehydrogenase level. This may be related to the small number of our patients. However, in our study, high risk class according to the MSKCC prognostic model was found to be associated with a 2-fold increase in mortality compared to the good prognostic class ($p=0.022$). Consolidation therapy was an independent prognostic factor for both PFS and OS ($p<0.001$ for both).

In a study evaluating the effectiveness of HD-MTX, the most common grade 1 adverse events were elevated transaminases (33%), nephrotoxicity (29.8%), and thrombocytopenia (20.2%), while the most common grade 2 adverse events were anemia (49%), elevated transaminases (23.3%), and nephrotoxicity (20.2%).[30] In another study investigating the contribution of adding WBRT to HD-MTX treatment, the authors reported that the most common grade 3-4 side effects were leukopenia (24%), anemia (14%), thrombocytopenia (11%), and elevated transaminases (19%).[24] Toxicity results in our study are consistent with the literature, and the most common side effects were transaminase elevations and hematological side effects. Nephrotoxicity was observed less frequently compared to the literature.

Limitations

Although our study included patients from more than one centre, the retrospective design and the small number of patients were important limitations of our study. Due to the small number of patients, we could not compare the treatment groups separately in all analyzes. Also, since CSF examination could not be performed in all patients, we were not able to evaluate its prognostic significance. We could not obtain data on other detailed pathological prognostic factors, therefore not able to include them in the analyses. The most common consolidation treatment was WBRT, but we could not thoroughly evaluate neurotoxicity due to the study's retrospective design. Despite its limitations, we think that our study will make a significant contribution to the literature by reflecting real-life data and clinical practice as well as evaluating the

toxicity findings in PCNSL, which has a low incidence and on which there are limited number of phase 3 studies.

CONCLUSION

As a result, in this study in which we evaluated the clinicopathological features of patients with PCNSL, consolidation therapy was found to be an independent predictive factor for both OS and PFS. In addition, high risk class according to MSKCC prognostic model was found to be associated with increased mortality. All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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