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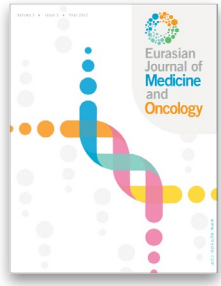

Research Article

Clinical Outcomes and Treatment Patterns of Primary Central Nervous System Lymphoma: Multicenter Retrospective Analysis

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Abstract

Objectives: Primary central nervous system lymphoma (PCNSL) is a rare malignant disease with poor prognosis. Its low incidence leads to challenges in decision-making for treatment. As a matter of fact, there is still no consensus on the appropriate treatment modalities. In this context, the objective of this study is to investigate and comparatively assess the efficacies of several treatment modalities in the treatment of PCNSL.

Methods: Thirty-four patients diagnosed with PCNSL at 5 different hematology centers between 2007 and 2021 were included in the study. Patients' data from all five centers were collected retrospectively. Since ibrutinib is not approved for this indication in Turkey, consent for off-label use of ibrutinib is obtained from each patient. Ethics committee approval was obtained on June 9, 2021 with decision number 2021/18-05.

Results: The median age of the patients was 59 (min.: 22, max.: 78) years. The male-to-female ratio was 1.26/1. Nineteen (55.9%) patients had Eastern Cooperative Oncology Group (ECOG) performance score of ≥2. Fifteen (44.1%) patients had normal lactate dehydrogenase (LDH) levels and only 14.7% of the patients had B symptoms at the time of diagnosis. Magnetic resonance imaging (MRI) revealed a single mass lesion in 14 (41.2%) patients. As an induction therapy, methotrexate-based regimen was administered in 29 (85.3%) patients. Only 14 of the 34 patients received 4 or more cycles of high-dose methotrexate (MTX). About 32.4% of the patients received radiation therapy (RT) during follow-up as a part of induction therapy. Five patients received only RT due to poor performance status. Ibrutinib was administered in 5 patients for refractory disease. It was determined that four or more cycles of MTX treatment increased progression-free survival (PFS) (p=0.031) and overall survival (OS) (p=0.012). Moreover, RT improved PFS (p=0.023). Considering that the complete response achieved by induction therapy influences long-term survival, achievement of the best response to the treatment regimens administered in combination with new agents may prolong survival (PFS: p=0.01, OS: p=0.023).

Conclusion: The findings of this study indicate that the initial response to treatment is crucial. Additionally, it was found that high-dose MTX treatment should be administered for 4 cycles or more in order to achieve the best results. Furthermore, it was determined that ibrutinib monotherapy was well-tolerated in our patients with relapsed/refractory disease, with excellent clinical benefits. In conclusion, a combination therapy consisting of high-dose MTX, ibrutinib, and rituximab appears to be a promising initial treatment approach in appropriate patients.

Keywords: PCNSL, methotrexate, radiotherapy, ibrutinib

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Primary central nervous system lymphoma (PCNSL) is a subtype of extra-nodal non-Hodgkin lymphoma (NHL), in which the involvement is restricted to brain, spinal cord, cranial nerves, leptomeninges, and vitreo-retina.[1,2] It is relatively rare tumor, accounting for about 1% of NHLs and 3–4% of intracranial tumors.[3] More than 95% of PCNSL cases are diffuse large B cell lymphoma (DLBCL), which is listed as a separate entity in the World Health Organization (WHO) Classification of Tumors of Hematopoietic and Lymphoid tissues, 2016 and WHO Classification of Tumors of the Central Nervous System, 2021.[4,5]

The treatment of PCNSL includes variety approaches with chemotherapy and radiotherapy (RT). RT is associated with high-risk of severe neurotoxicity. One of the alternative options to RT is systemic chemotherapy (CT). However, the blood-brain barrier is emerging as a problem that creates a challenge in the use of systemic CT.[6] In this context, high-dose methotrexate (MTX), which can cross the blood-brain barrier, is considered the first-line treatment option in PCNSL. Better survival outcomes were reported with high-dose MTX in combination with rituximab and temozolomide.[7,8] Nevertheless, 20-30% of the patients with PCNSL relapse within 6 months, regardless of whether they received induction therapy with high-dose MTX. Therefore, consolidation therapy is becoming increasingly important.[9]

The low incidence of PCNSL makes it difficult to conduct large, prospective, and randomized studies, leading to inability to establish the optimal treatment to date. In this context, the objective of this study is to fill the gap at this point by comparatively evaluating the treatment trends currently used in daily clinical practice, as well as addressing the treatments that would best fit the patients with relapsed/refractory disease and helping establish a standardized treatment approach for PCNSL.

Methods

This was a multi-center and retrospective study which included patients with PCNSL from five different hematology centers between 2007 and 2021. The diagnosis of PCNSL was made according to the International Classification of Diseases (ICD). All patients underwent positron emission tomography or full body computed tomography (CT) scan and bone marrow biopsy to exclude systemic lymphoma. Human Immunodeficiency Virus (HIV)-related cases were also excluded. Additionally, since ibrutinib is not approved for this indication in Turkey, a separate consent for off-label use of ibrutinib was obtained from each patient. The study consisted of 34 patients who met the study inclusion criteria. The study protocol was approved by the local ethics committee, with the decision date 09.06.2021 and number 2021/18-05. The research material comprised patients' demographic characteristics, symptoms at the time of admission, age at diagnosis, results of the imaging studies, ECOG (Eastern Cooperative Oncology Group) performance scores, central nervous system (CSF) involvement, laboratory results, treatments, final hospital visit, information regarding disease progression and mortality.

Results

The clinical and demographic characteristics of the patients are shown in Table 1. Accordingly, 19 (52.75%) patients were male, and the male/female ratio was 1.26. The median age of the patients was 59 (min:22-max:78) years. ECOG performance scores at the time of diagnosis were ≥2 and <2 in 44.1% and 55.9% of the patients, respectively. Twenty (58.8%) patients had multiple lesions. Most of the patients did not have B symptoms. About 55.9% (n=19) of the patients were examined for CSF involvement, and CSF involvement was detected in 16% (n=3) of the patients who underwent CSF examination (Table 1). In all patients, diagnosis of PCNSL was made by biopsy; histologically, all patients had diffuse large B-cell lymphoma.

Table 1. Clinical and Demographic Characteristics of the Patients

Median age; years (min., max.)	59 (22–78)
Age	
<65	24 (70.6)
≥65	10 (29.4)
Gender	
Male	19 (55.9)
Female	15 (44.1)
ECOG score	
<2	15 (44.1)
≥2	19 (55.9)
Exitus	16 (47.1)
B symptoms	
Positive	5 (14.7)
Negative	29 (85.3)
CSF involvement	
(+)	3 (8.8)
(-)	16 (47.1)
NA	15 (44.1)
Type of lesion	
Unifocal	14 (41.2)
Multifocal	20 (58.8)
Site of involvement	
Cerebral	34 (100)
Other	0

n: number; min.: minimum; max.: maximum; ECOG: Eastern Cooperative Oncology Group; CSF: central nervous system; NA: not applicable.

The laboratory findings of all patients at the time of admission are shown in Table 2. Accordingly, 47.1% (n=16) of the patients had elevated (above the upper limit) lactate dehydrogenase (LDH) levels. The data for LDH levels in 8.8% of the patients(n=3) were missing. About 38.2% (n=13) of the patients had low (<3.5 g/dL) albumin levels.

The treatments are shown in Table 3. Accordingly, 85.2% (n=29) of patients received MTX-based regimens, whereas the remaining 5 patients received RT alone. As the initial treatment, of the 29 patients who received MTX-based treatments; 11 patients received high-dose MTX in combination with RT, 9 patients received high-dose MTX in combination with rituximab, 8 patients received high-dose MTX alone, and 1 patient received MATRix (methotrexate, cytarabine, thiotepa and rituximab) protocol. Fourteen patients received 4 or more cycles of high-dose MTX. The dose of MTX was 5 g/m^2 in 21 patients, 3.5 g/m^2 in 7 patients and 8 gr/m^2 in 1 patient. RT was used both alone and in combination, at a treatment dose of 36Gy/20Fr. The dose of RT was similar in patients treated with RT alone or in combination with MTX. After the initial treatment, complete response (CR) was achieved in 18 patients and partial response (PR) in 6 patients. The remaining 10 patients were considered to have a refractory disease. Four patients underwent autologous stem cell transplantation (ASCT) as a consolidation treatment.

Table 2. Laboratory findings at admission

Parameter	Median value	Range (min., max.)	n
Hemoglobin (g/dL)	12.8	(6.4–15.8)	34
WBC (x10^3)	7.8	(2.6–18.4)	34
Plt (uL)	246	(61–430)	34
Sedimentation rate (mm/hrs)	21.5	(3–95)	32
AST (U/L)	19	(10–73)	34
Creatinine (mg/dL)	0.8	(0.5–1.1)	34
LDH (U/L)	229	(133–852)	31
LDH (n, %)			
(≥220 U/L)	16(47.1)		31
(<220 U/L)	15(44.1)		
NA	3(8.8)		
CRP (mg/L)	4.5	(0.1–79)	32
Albumin (g/dL)	3.6	(2.4–4.2)	33
Albumin (n, %)			
(<3.5 g/dL)	13 (38.2)		34
(≥3.5 g/dL)	20 (58.8)		
NA	1 (2.9)		

min.: minimum; max.: maximum; n: number; WBC: white blood cell count; Plt: platelet (thrombocyte) count; AST: aspartate aminotransferase; LDH: lactate dehydrogenase; NA: not applicable; CRP: C-reactive protein.

Clinical parameters were evaluated in univariate analysis in order to assess their effects on progression-free survival (PFS) and overall survival (OS). It was determined that achieving CR after the first treatment (PFS, p=0.001; OS, p=0.023) and receiving 4 or more cycles of high-dose MTX (PFS, p=0.031; OS, p=0.012) were associated with longer survival. Receiving combination therapy consisting of high-dose MTX and radiotherapy was found to be associated with longer PFS (p= 0.023), but not with longer OS. Univariate analysis did not reveal any significant correlation between survival and other parameters including age, gender, ECOG score >2, B symptoms, number of lesions, cerebrospinal fluid involvement, and LDH or albumin levels (Table 4).

Table 3. Treatments

	n	%
Initial treatment	34	100
MTX-based	29	85.3
High-dose MTX	8	23.5
MTX + RT	11	32.4
R-MTX	9	26.5
MATRix	1	2.9
RT alone	5	14.7
Radiotherapy		
Yes	16	47.05
No	18	52.95
Rituximab		
Yes	10	29.4
No	24	70.6
High dose MTX ≥4 cycles		
Yes	14	41.2
No	20	58.8
Dose of MTX		
3.5 g/m^2	7	20.6
5 g/m^2	21	61.8
8 g/m^2	1	2.9
Total	29	85.3
Response		
CR	18	52.9
PR	6	17.6
RD	10	29.5
ASCT		
Yes	4	11.7
No	30	88.3
Total	34	100

n: number; MTX: methotrexate; HD: high-dose; RT: radiotherapy; R: rituximab; MATRix: methotrexate, cytarabine, thiotepa and rituximab; CR: complete response; PR: partial response; RD: refractory disease; ASCT: autologous stem cell transplant.

Table 4. Results of the Univariate Analysis (Kaplan–Meier Method and Long-Rank Test)

Parameter	Median Survival (months)			
	PFS (95% CI)	p	OS (95% CI)	p
Age (years)		0.816		0.334
<65	10.0 (7.0–12.9)		38.0 (0–81.2)	
≥65	19.0 (9.2–28.7)		NA	
Gender		0.266	0.842	
Male	20.0 (3.2–36.7)		38.0 (6.3–69.6)	
Female	10.0 (6.2–13.7)		49.0 (0.0–98.3)	
ECOG PS		0.890		0.701
≤2	11.0 (0.0–50.6)		39.0 (0.5–77.4)	
>2	12.0 (6.6–17.3)		NA	
B symptoms		0.434		0.485
Yes	11.0 (8.8–13.1)		38.0 (0.0–76.9)	
No	12.0 (1.7–22.2)		39.0 (0.0–88.8)	
CSF involvement		0.254		0.465
Yes	11.0 (0.0–25.4)		38.0	
No	13.0 (8.0–17.9)		NA	
NA	10.0 (0.0–22.3)		39.0 (2.7–75.5)	
Number of lesions		0.903		0.302
1	13.0 (0.0–27.0)		NA	
≥2	11.0 (5.3–16.6)		38.0 (0.0–90.1)	
LDH level		0.887		0.699
<220	10.0 (5.7–14.2)		NA	
≥220	13.0 (2.9–23.0)		39.0 (36.3–41.6)	
Albumin level		0.216		0.240
<3.5	10.0 (8.3–11.6)		15.0 (0.0–45.7)	
≥3.5	19.0 (7.8–30.1)		NA	
RT	0.023			0.129
Yes	39.0 (4.7–73.2)		49.0	
No	10.0 (7.5–12.4)		12.0 (0.0–24.7)	
Rituximab		0.080		0.244
Yes	10.0 (2.1–17.9)		38.0	
No	19.0 (5.8–32.1)		49.0 (0.0–98.5)	
Cycle of high-dose MTX		0.031		0.012
<4 cycles	8.0 (2.9–13.0)		8.0 (0.4–15.5)	
≥4 cycles	19.0 (4.3–33.6)		49.0 (34.9–63.0)	
Response		0.001		0.023
CR	49.0 (0.0–104.1)		49.0	
PR	9.0 (5.0–12.9)		10.0 (4.1–15.8)	
RD	4.0 (0.0–8.2)		6.0 (0.3–11.7)	
ASCT		0.813		0.823
Yes	10 (0–36.7)		49.0	
No	12.0 (7.1–16.8)		38.0 (8.4–67.5)	

PFS: progression-free survival; OS: overall survival; p: probability; CI: confidence interval; NA: not applicable; ECOG: Eastern Cooperative Oncology Group; CSF: central nervous system; LDH: lactate dehydrogenase; RT: radiotherapy; CR: complete response; PR: partial response; RD: refractory disease; ASCT: autologous stem cell transplantation.

Multivariate analysis was performed using the Cox proportional-hazards model to further evaluate the independent prognostic factors including gender, ECOG score, number of lesions, radiotherapy treatment, treatment response and use of 4 or more cycles of MTX. The initial response to treatment (PFS: p=0.01, OS: p=0.00), and receiving 4 or more cycles of

high-dose MTX (PFS: p=0.04, OS: p=0.04) were found to be significantly correlated with PFS and OS (Table 5).

Survival Analysis of Patients with Relapsed/Refractory PCNSL

Twenty-three patients with PCNSL had refractory disease who progressed or relapsed after first-line treatment. Of these patients, 13 were female and 16 were under 65 years old. Six of these patients received high-dose MTX alone, 6 received high-dose MTX in combination with Rituximab, 7 received MTX in combination with RT, 3 received RT alone, and 1 received MATRix protocol, as first-line treatment. Subsequently, 4 of these patients underwent ASCT, 1 patient continued high-dose MTX, 1 patient received ifosfamide+etoposide, 5 patients received ibrutinib alone, and 12 patients were treated with palliative care. Because ibrutinib is not licensed in Turkey for this indication, approval for the off-label use of ibrutinib in our patients was obtained from the Ministry of Health, Republic of Turkey. Ibrutinib was administered at a dose of 560 mg per day. The first-line treatment of the patients who received ibrutinib in the second-line was high-dose MTX+Rituximab in 2 patients, MATRix protocol in 1 patient, MTX+RT in 1 patient, and RT alone in an elderly patient. Of the 5 patients who received ibrutinib in the second-line, 2 elderly patients with life-threatening condition died under ibrutinib treatment, whereas the other 3 patients survived for a median follow-up duration of 14 months. One of the patients who received ibrutinib treatment developed mild but temporary neutropenia, without any aspergillus infection.

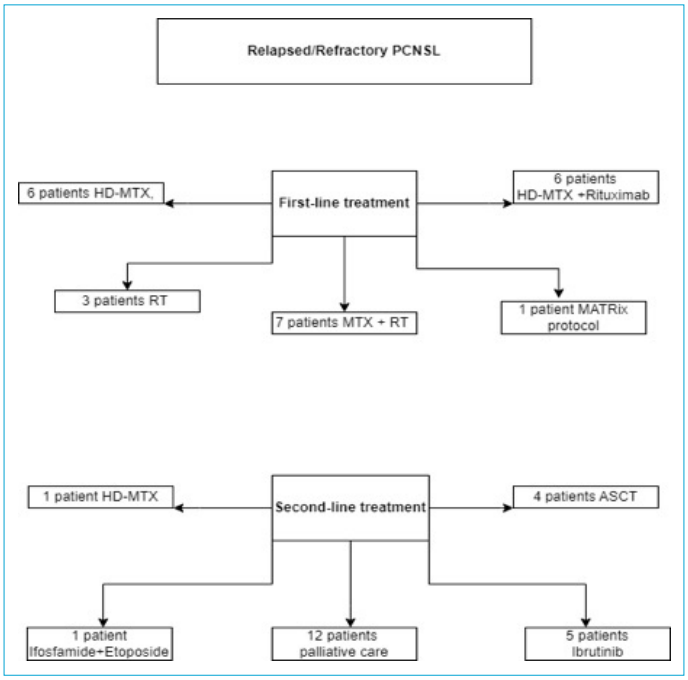

Figure 1. Treatments given in Relapsed/Refractory PCNSL patients.

Table 6. Demographics and Treatment Modalities of Patients with Relapsed/Refractory

Characteristic	n=23	(%)
Age (years)		
≤65	16	69.5
>65	7	30.5
Sex		
Male	10	43.5
Female	13	56.5
First-line treatment		
High-dose MTX	6	26
RT alone	3	13
High-dose MTX + RT	7	30.5
High-dose MTX + Rituximab	6	26
MATRix	1	4.5
Consolidation/maintenance treatment		
ASTC	4	17.4
Ibrutinib	5	21.7
High-dose MTX	1	4.4
Ifosfamid+Etoposit	1	4.4
Palliative Care	12	52.1

Table 5. Results of the Multivariate Analysis

Covariates	PFS		OS	
	HR (95% CI)	p	HR (95% CI)	p
Male vs. female	1.46 (0.45–4.78)	0.52	1.54 (0.48–4.90)	0.46
ECOG PS (≤2 vs. >2)	0.3 (0.07–1.17)	0.08	0.33 (0.08–1.29)	0.11
Multiple lesions	2.96 (0.81–10.83)	0.10	2.64 (0.73–9.50)	0.13
Radiotherapy	0.59 (0.14–2.48)	0.47	0.47 (0.1–2.08)	0.32
High-dose MTX ≥4 cycles	0.28 (0.08–0.96)	0.04	0.3 (0.09–0.98)	0.04
Response	9.12 (1.6–51.8)	0.01	10.6 (1.79–63.06)	0.00

PFS: progression-free survival; OS: overall survival; HR: hazards ratio; CI: confidence interval; p: probability; ECOG: Eastern Cooperative Oncology Group.

Discussion

The findings of this study revealed that the mortality and morbidity rates of patients with PCNSL were very high, regardless of the hematology centers where the patients were diagnosed and treated. It was observed that each hematology center applied a different treatment approach. This finding was attributed to the fact that there is no standard treatment approach in PCNSL due its very low incidence. The treatment approach used in the treatment of PCNSL generally consists of induction and consolidation therapy. However, given the high recurrence rates, maintenance therapy is also critical, as demonstrated in this study. High-dose MTX is the most important building block in the treatment of PCNSL. As a matter of fact, high-dose MTX alone may also be used to treat PCNSL. However, more recently, the use of high-dose MTX in combination with other methods has been shown to produce better results.[10]

Rituximab, the anti-CD20 antibody, has been used as a part of combination therapy in the treatment of patients with PCNSL. Houillier et al. reported that the addition of rituximab to the combination therapy including MTX, procarbazine, vincristine, and cytarabine resulted in an improvement in the overall treatment response rate. In comparison, in this study, rituximab was added to the high-dose MTX therapy in 9 of the 34 patients. One patient received rituximab as part of the MATRIx protocol. Of these 9 patients, six presented with refractory disease or recurrence within 1 year. The patient who received rituximab as part of the MATRIx protocol also became resistant to this treatment. As a result, it was determined that the addition of rituximab to the treatment of PCNSL did not improve PFS (p=0.08) or OS (p=0.244). The low number of patients using rituximab in our study was also effective in this result. There appears to be no significant treatment-related toxicity and rituximab is generally well-tolerated. For these reasons, despite the lack of definitive evidence, many patients with PCNSL are treated with rituximab. However, there is still no consensus on the overall benefit of the addition of rituximab to the combination regimens containing MTX.[8,11,12]

Addition of WBRT to the PCNSL treatment increases the risk of neurotoxicity. Comparisons according to treatment type revealed more pronounced cognitive impairment, particularly in the memory and attention/executive domains, among patients treated with WBRT±CT.[13] In the G-PCNSL-SG1 trial, a randomized study, patients who achieved complete remission after high-dose MTX were administered WBRT (45 Gy in 30 fractions) as a consolidation therapy. Consequentially, it was found that WBRT significantly improved the PFS, but not the OS.[14] In comparison, in this study, RT was administered to a total of 16 patients. Five of these patients received RT alone, whereas the remaining 11 patients received RT in combination with high-dose MTX. Similar to the results reported in the G-PCNSL-SG1 trial, it was determined that radiotherapy significantly improved the PFS (p=0.023), but not the OS (p=0.129). This finding was interpreted as that RT is beneficial when used in the right patient; however, it increases morbidity in general.

ASCT is commonly used as a consolidation therapy for treating PCNSL in selected patients.[15-17] In a phase II study, Omuro et al. reported significant improvements in PFS and OS after the administration of consolidation therapy with stem cell-assisted high-dose CT following 5–7 cycles of R-MPV (rituximab, methotrexate, procarbazine and vincristine).[18] In comparison, in this study, only 4 of the 34 patients underwent ASCT. The reason for the relatively low number of patients who underwent ASCT was not associated with the age of the patients (median age: 59 years) but related to their comorbidities and poor conditions at the time of admission. The results of the multivariate analysis did not indicate any benefit of ASCT on PFS (p=0.813) or OS (p=0.823). This finding was attributed to the low number of patients who underwent ASCT.

In this study, the survival statistics of the patients who received 4 cycles or more of high-dose MTX therapy were significantly better than that of other patients (median PFS: 19 months vs. 8 months, p=0.031; median OS: 49 months vs. 8 months, p=0.012). In a retrospective study by Mao et al. including 91 patients, significant improvements were recorded in both PFS and OS in 61 patients who received 4 or more cycles of high-dose MTX therapy (p=0.00 for both cases). Thus, taken together with the respective findings reported in the literature, the findings of this study suggest that the high-dose MTX treatment should be administered for at least 4 cycles, if feasible.[19]

Of the 34 patients included in this study, 23 had either refractory or relapsed disease. In general, different PCNSL treatments were administered to the patients with relapsed/refractory disease in the hematology centers included in this study. Accordingly, palliative care was preferred in more than half (52%) of the patients with relapsed/refractory PCNSL, while ibrutinib therapy was administered as a continuous treatment in 5 patients. Of the 5 cases, 2 elderly patients with life-threatening condition died under ibrutinib. The remaining 3 patients were followed up in stable condition under ibrutinib monotherapy for 21 months, 14 months, and 5 months, respectively. It was observed that the patients, who received ibrutinib therapy, tolerated the therapeutic 560 mg ibrutinib dose very well. Fungal infection was not observed in any of the cases. Mild neutropenia was observed in only 1 pa-

tient. Similarly, Soussain et al. also reported that 560 mg ibrutinib provided therapeutical efficacy in patients with relapsed/refractory PCNSL. They reported an overall response rate of 52% following the use of ibrutinib during two periods of 28 days each. They reported the PFS and OS in patients with relapsed/refractory PCNSL who received ibrutinib therapy as 4.8 months and 19.2 months, respectively. Pulmonary aspergillosis developed in 2 (4%) patients. There was no fatal bleeding. They concluded that ibrutinib demonstrated clinical efficacy in the brain, CSF, and intraocular compartment and was well-tolerated by patients with relapsed/refractory PCNSL.[20]

Multivariate analysis revealed that receiving 4 or more high-dose MTX cycles and response to first-line therapy were most important determinants of survival. Of the 34 patients included in this study, CR was achieved in 18 patients, PR was achieved in 6 patients but there was no response to treatment in 10 patients. Both PFS (p=0.001) and OS (p=0.023) were found to be significantly higher in patients with CR. Accordingly, it was concluded that the choice of first-line treatment is of critical importance since the achieving CR with first-line treatment provides the most favorable prognostic effect on survival. RT improved PFS outcomes, as well (p=0.023). Four or more cycles of high-dose MTX therapy improved both PFS and OS (p=0.031 and p=0.012, respectively). Ibrutinib was well-tolerated in relapsed/refractory patients. The use of ibrutinib monotherapy as the first-line therapy has provided clear benefits. The combination therapies with acceptable toxicity profiles in particular come to the forefront in the treatment of patients with relapsed/refractory PCNSL.

In conclusion, taken together with the relevant findings reported in the literature, the findings of this study suggest that the concomitant use of ibrutinib with high-dose MTX and rituximab is well-tolerated and likely to result in high rate of CR, leading to significant improvements in both mortality and morbidity associated with PCNSL.

Disclosures

Ethics Committee Approval: Approval was obtained from the ethics committee of Dokuz Eylül University, Faculty of Medicine, with the decision dated 09.06.2021 and numbered 2021/18-05.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – S.G., I.A.; Design – S.G., I.A.; Supervision – I.A.; Materials – S.G., B.Y., E.E.Y., A.F.K.; Data collection &/or processing – S.G., M.G., E.K., H.D.K., T.C., B.B.A., O.G.S., S.Y.K.; Analysis and/or interpretation – S.G., I.A.; Literature search – S.G., I.A.; Writing – S.G., I.A.; Critical review – S.G., I.A., G.H.O., F.D., B.U., M.A.O.

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