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Methods: Patients diagnosed with PCNSL at our institute from August 2010 to May 2015 were evaluated. During the said period, a total of 14 cases were diagnosed with PCNSL.

Results: Deep frontal lobe was the most common site of involvement while diffuse large B-cell lymphoma (DLBCL) was the most common histological pattern. 10 patients were treated with 3.0 g/m² methotrexate (MTX) intravenously concomitant with intraventricular 15 mg MTX and 2 patients were treated with radiotherapy (RT). Two of the patients died due to respiratory failure a short time after the treatment started. The median overall survival (OS) was 8 months (minimum: 1 months, maximum: 15 months) and the median OS was 12.42±13.20 months (min: 1 month, max: 48 months).

Keywords: methotrexate, overall survival, primary central nervous system lymphoma, radiotherapy.

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CHARACTERISTICS AND OUTCOMES OF PATIENTS WITH PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA

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Characteristics and Outcomes of Patients with Primary Central Nervous System Lymphoma

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Conclusion: As stated in the previous studies, MTX-based chemotherapy regimens are still the most effective treatment option in this patient population.

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I. INTRODUCTION

Primary central nervous system lymphoma is a rare type of cancer accounting for less than 3% of all the brain tumors. Majority of the primary central nervous system lymphoma are diffuse giant B cell lymphoma.

The yearly incidence of PCNSL is 0,5 cases per 100 000 people. The incidence is higher in immunocompetent individuals, whereas it seems to be lower in patients with HIV infection. Median age at diagnosis is 60–65 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}

Unlike in systemic lymphomas, long term remission is very in PCNSL. Chemotherapy, radiotherapy, surgery and a combination of these can be used in intracranial lymphomas.¹⁰

While combined chemotherapy and RT produces response rates of up to 80–90% and median

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OS close to 5 years in PCNSL^{11,12,13} neurocognitive toxicity stands as the major limitation of the said combined treatment.¹⁴ Delayed neurotoxicity presenting itself with memory deterioration and personality changes early in the course is followed by gait disturbance and urinary incontinence, all of which are generally permanent.¹⁴

The prognosis and outcome of treatment differ in younger and older patients. Interestingly, when compared those who did not receive radiation, the outcomes are not improved when radiation is added to the treatment regimen of elderly patients. The optimal combination regimen or dose of MTX remains to be elucidated.

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

II. PATIENTS AND METHODS

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

a) Patients

Fourteen patients were diagnosed as PCNSL with histological confirmation. Clinical data for all patients constituting the study cohort were available. All patients had one or more intracranial mass lesions. Histological confirmation of PCNSL was made through brain biopsy or open biopsy. Systemic lymphoma was excluded through staging evaluation by neck, chest,

abdominal, and pelvic computed tomography (CT) and by bone marrow biopsy. Thirteen patients underwent cranial neuroimaging at diagnosis by magnetic resonance imaging (MRI). Only one underwent contrast-enhanced cranial CT due to having hip prosthesis. Fourteen patients underwent lumbar puncture and a complete ophthalmologic evaluation including a slit-lamp examination. Testicular ultrasonography was performed in male patients. There were no laboratory abnormalities before chemotherapy and the laboratory diagnosis of a latent or obvious infection was excluded.

b) Immunohistochemistry

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

c) Treatment protocol

In DLBCL patients, treatment consisted of six cycles of chemotherapy administered at 28-day intervals, consisting of the following: MTX 3.0 g/m² for one day, followed by 15 doses of leucovorin rescue. At diagnosis, 8 patients underwent to Ommaya reservoir implantation and 6 courses of intraventricular MTX (15 mg) at 3-day cycle were administered to the patients. RT has been given in 2 patient. One of these patients had low grade lymphoma and the other had diffuse giant cell lymphoma. DLBCL patients were treated with a chemotherapy.

d) Follow-up

Repeat neuroimaging was conducted by MRI or CT at the completion of 3 chemotherapy cycles and then the completion of 6 chemotherapy cycles and lastly every 3 months. 1.5T clinical scanner was used during MRIs. The deep brain structures defined were basal ganglia, the corpus callosum, brain stem and cerebellum. Peritumoral edema was categorized as < or ≥ 2 cm from the brain tumour as assessed in T2-weighted MR images.

e) Evaluation of response to treatment

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

The International Extranodal Lymphoma Study Group (IELSG) score was used to define the risk group. Using the prognostic scoring system of the IELSG, the

patients were categorized into three risk groups as low, intermediate, and high. Age, ECOG performance status grade, lactate dehydrogenase (LDH) serum level, protein concentration in CSF, and involvement of deep brain structures were the variables included.

f) Statistical methods

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

g) Ethics statement

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

III. RESULTS

a) Patients and treatment

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

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

The obtained samples did not reveal any CFD involvement. 9 patients had a high level of LDH. β₂-microglobulin was high in 10 patients. Characteristics of the patients are summarized in Table 1. A total of 10 patients received HD-MTX with a concomitant intravascular chemotherapy as an initial treatment. 5 of them received 6 cycles of HD-MTX, 1 patient was stable after 3 cycles of HD-MTX, so RT was administered as a salvage regimen. After 3 cycles of HD-MTX, the disease became progressive in 1 patient and the patient died due to respiratory failure. 3 of the patients died due to sepsis after the second cycle of HD-MTX. In 2 patients, RT was planned to cranium in a fraction of 20 at a dose of 36 Gy in total.

b) Response to treatment

Of the remaining 4 patients, 1 was regarded as having a progressive disease and died due to respiratory failure. The rest 3 patients died due to sepsis after the second cycle of HD-MTX (these patients were included in the progressive disease group). RT treatment was administered as the initial treatment in 2 patients. One of these patients had low grade B cell lymphoma and died due to comorbid diseases on the 16th day of the treatment. The patients receiving RT had diffuse cell lymphoma that yielded partial remission. 10 patients additionally received 6 cycles of intraventricular chemotherapy. No recurrence was observed in the

study population. Toxicities included pancytopenia, infection, mucositis and neurotoxicity. 3 patients died as a result of sepsis due to severe neutropenia. Outcomes are summarized in Table 2.

c) Toxicity

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

There was neurotoxicity proven by MRI only in one patient, but the patient did not clinically exhibit any neurologic pattern. The details about toxicity are outlined in Table 3.

IV. DISCUSSION

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

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

cerebellar region which is very rare localization. There were multiple lesions in 2 patients.

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

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

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

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

As a result, PCNSL affects mostly the 6th decade and DLBCL is the most commonly encountered pathological type. Although single agent treatment modalities are frequently used in the treatment of newly diagnosed PCNSL, comprehensive randomized studies are needed. However, single agent high dose MTX seems to be causing toxicity less. Due to its neurocognitive toxicity, RT is mostly used in only relapsed/refractory patients.

V. ACKNOWLEDGMENTS

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

REFERENCES RÉFÉRENCES REFERENCIAS

1. Lee CH, Jung KW, Yoo H, Park S, Lee SH. Epidemiology of primary brain and central nervous system tumors in Korea. *J Korean Neurosurg Soc* 2010; 48: 145-52.
2. Abrey LE, Ben-Porat L, Panageas KS, Yahalom J, Berkey B, Curran W, et al. Primary central nervous system lymphoma: the Memorial Sloan-Kettering Cancer Center prognostic model. *J Clin Oncol* 2006; 24: 5711-5.
3. Ferreri AJ, Blay JY, Reni M, Pasini F, Spina M, Ambrosetti A, et al. Prognostic scoring system for primary CNS lymphomas: the International Extranodal Lymphoma Study Group experience. *J Clin Oncol* 2003; 21: 266-72.
4. Bessell EM, Hoang-Xuan K, Ferreri AJ, Reni M. Primary central nervous system lymphoma: biological aspects and controversies in management. *Eur J Cancer* 2007; 43: 1141-52.
5. Ekenel M, Deangelis LM. Treatment of primary central nervous system lymphoma. *Curr Treat Options Neurol* 2007; 9: 271-82.
6. Gerstner E, Batchelor T. Primary CNS lymphoma. *Expert Rev Anticancer Ther* 2007; 7: 689-700.
7. Jahnke K, Thiel E. Treatment options for central nervous system lymphomas in immunocompetent patients. *Expert Rev Neurother* 2009; 9: 1497-509.
8. Morris PG, Abrey LE. Therapeutic challenges in primary CNS lymphoma. *Lancet Neurol* 2009; 8: 581-92.
9. Kadan-Lottick NS, Skluzacek MC, Gurney JG. Decreasing incidence rates of primary central nervous system lymphoma. *Cancer* 2002; 95: 193-202.
10. Dubuisson A, Kaschten B, Lénelle J, Martin D, Robe P, Fassotte MF, et al. Primary central nervous system lymphoma report of 32 cases and review of the literature. *Clinical Neurology and Neurosurgery* 2004; 107: 55-63.
11. Shah GD, Yahalom J, Correa DD, Lai RK, Raizer JJ, Schiff D, et al. Combined immunochemotherapy with reduced whole-brain radiotherapy for newly diagnosed primary CNS lymphoma. *J Clin Oncol* 2007; 25: 4730-5.
12. Gavrilovic IT, Hormigo A, Yahalom J, DeAngelis LM, Abrey LE Long-term follow-up of high-dose methotrexate-based therapy with and without whole brain irradiation for newly diagnosed primary CNS lymphoma. *J Clin Oncol* 2006; 24: 4570-4.
13. Omuro AM, DeAngelis LM, Yahalom J, Abrey LE. Chemoradiotherapy for primary CNS lymphoma: an intent-to-treat analysis with complete follow-up. *Neurology* 2005; 64: 69-74.
14. Abrey LE, Yahalom J, DeAngelis LM. Treatment for primary CNS lymphoma: the next step. *J Clin Oncol* 2000; 18: 3144-50.
15. Correa DD, DeAngelis LM, Shi W, Thaler H, Glass A, Abrey LE Cognitive functions in survivors of primary central nervous system lymphoma. *Neurology* 2004; 62: 548-55.
16. Crossen JR, Garwood D, Glatstein E, Neuwelt EA Neurobehavioral sequelae of cranial irradiation in adults: a review of radiation-induced encephalopathy. *J Clin Oncol* 1994; 12: 627-42.
17. Deangelis LM, Iwamoto FM. An update on therapy of primary central nervous system lymphoma. *Hematol Oncol Clin North Am* 2006; 20: 1267-85.
18. Bataille B, Delwail V, Menet E, Vandermarcq P, Ingrand P, Wager M, et al. Primary intracerebral malignant lymphoma: A report of 248 cases. *J Neurosurg* 2000; 92: 261-6.
19. Basso U, Brandes AA. Diagnostic advances and new trends for the treatment of primary central nervous system lymphoma. *Eur J Cancer* 2002; 38: 1298-312.
20. Jaiswal AK, Mahapatra AK, Sharma MC. Primary central nervous system lymphoma presenting as bilateral cerebellopontine angle lesions: a rare case report. *Journal of clinical neuroscience* 2004; 11: 328-31.
21. Sarkar C, Sharma MC, Deb P, Singh R, Santosh V, Shankar SK. Primary central nervous system lymphoma: A hospital based study of incidence and Clinicopathological feature from India (1980 -2003). *J Neurooncol* 2005; 71: 199-204.
22. Ferreri AJ, Guerra E, Regazzi M, Pasini F, Ambrosetti A, Pivnik A et al. Area under the curve of methotrexate and creatinine clearance are outcome-determining factors in primary CNS lymphomas. *Br J Cancer* 2004; 90: 353-8.
23. Hoang-Xuan K, Taillandier L, Chinot O, Soubeyran P, Bogdhan U, Hildebrand J, et al. Chemotherapy alone as initial treatment for primary CNS lymphoma in patients older than 60 years: a multicenter phase II study (26952) of the European Organization for Research and Treatment of Cancer Brain Tumor Group. *J Clin Oncol* 2003; 21: 2726-31.
24. Plotkin SR, Batchelor TT. Primary nervous-system lymphoma. *Lancet Oncol* 2001; 2: 354-65.
25. Blay JY, Conroy T, Chevreau C, Thyss A, Quesnel N, Eghbali H, et al. High-dose methotrexate for the treatment of primary cerebral lymphomas: analysis of survival and late neurologic toxicity in a retrospective series. *J Clin Oncol* 1998; 16: 864-71.

FIGURES LEGENDS

Table 1: Patient characteristics

	Total (n=14)	HD-MTX (n=10)	Nontreatment (n=2)	Radiotherapy (n=2)
Age				
Median (years)	62	56.4	58	68
Range (years)	42-80	42-80	58	61-75
Gender				
Female	5	3	1	1
Male	9	7	1	1
Lesions				
Single	12	9	1	2
Multiple	2	1	1	-
Surgical procedure				
Stereotactic biopsy	3	3	-	-
Open biopsy	1	1	-	-
Tumor resection	3	1	1	1
Pathology				
DBLCL	13	10	2	1
Other	1	-	-	1
LDH				
Elevated	9	6	1	2
Normal	5	4	1	-
B-2 Microglobulin				
Elevated	10	7	2	1
Normal	4	4	-	-
CSF cytology				
Negative	10	10	-	-
Positive	-	-	-	-
Not performed	4	-	2	2
IELSG score:				
0-1	2	2	-	-
2-3	5	3	2	-
4-5	7	5	-	2

* HD-MTX, high-dose methotrexate; IELSG, international extra-nodal lymphoma study group; CSF, cerebrospinal fluid.

Table 2: Outcome of HD-MTX-based chemotherapy and radiotherapy in PCNSL

	HD-MTX (n=10)	Radiotherapy (n=2)	Tedavisiz (n=2)
Complete Remission	5/10 (50%)	0/2 (0%)	0/2
Partial Remission	-	1/2 (50%)	*Not evaluated
Progressive Disease	***3/10 (%20)	**Not evaluated	*Not evaluated
Stable Disease	2/10 (%25)	**Not evaluated	*Not evaluated

* The patient has died at the 16th day of radiation therapy.

** 2 patients died due to respiratory failure after the diagnosis.

*** 2 patients died due to sepsis after the 2nd cycle of HD-MTX treatment.

Table 3: Toxicity of HD-MTX-based chemotherapy and radiotherapy in PCNSL

	HD-MTX (n=10)	Radiotherapy (n=2)
Anemia (grade 3/4)	5 (50%)	0
Thrombocytopenia (grade 3/4)	5 (50%)	0
Neutropenia (grade 3/4)	5 (50%)	0
Renal toxicity (grade 3/4)	1	0
Liver toxicity (grade 3/4)	1	0
Infections (grade 3/4)	3(33%)	0
Mucositis	2 (20%)	1 (50%)
Neurotoxicity	1 (10%)	0
Toxic Death	3	0

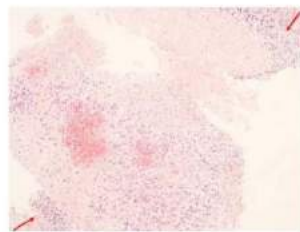


Figure 1: Cerebellar tissue (red arrows) and large scattered atypical lymphocytes (H&E,x100). The tumour cells have round vesicular nucleus with multiple nuclei. The cells have scanty cytoplasm. There are characteristic lymphocytic infiltrates around vessels. [Immunohistochemically, LCA and CD20 positive; CD5, CD15, CD30, CD56, ER, PR, Chromogranin A, Synaptophysin, GFAP, CK7, GCDFP-15 and TTF-1 negative]