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CLINICAL FEATURES AND TREATMENT STRATEGIES OF PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA: A MULTICENTER RETROSPECTIVE STUDY

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ABSTRACT

Aims: Primary central nervous system lymphoma is a rare, highly malignant disease with poor prognosis. The current knowledge about the disease is mostly gathered from prospective clinical trials and the optimal treatment modality is still a matter of debate. In this study it is aimed to acquire more information about the clinical features of the disease and the responses to different treatment modalities.

Methods: The archives in Trakya University Hospital, İnönü University Turgut Özal Medical Center, Pamukkale University Hospital and Erciyes University Hospital researched retrospectively. Demographic, treatment and survival data were retrieved and their statistical analysis was performed. As descriptive statistics number and percentages, arithmetic mean ± standard deviation, median (maximum-minimum) were used. Survival analysis was performed using Kaplan- Meier method.

Results: Median age of patients at diagnosis was 53 (25-76) and out of 28 patients 15 (53.6 %) of them were male. As the symptoms of the disease 18 (66.7%) patients presented headache, 15 (53.8%) presented focal deficit. As initial treatment 26 (92.9%) patients received chemotherapy, while 19 (67.9%) patients were treated with surgical resection and the median overall survival time was 7 months.

Conclusion: Achieving complete remission as response to the initial treatment is associated with an improved overall survival. Other survival analysis to compare the impact of all initial treatment methods on overall survival resulted statistically insignificant.

Keywords: Non-Hodgkin Lymphoma, remission, chemotherapy, radiotherapy

INTRODUCTION

Primary central nervous system lymphoma (PCNSL) is a rare, highly malignant, extranodal form of non- Hodgkin lymphoma (NHL) that invades the brain parenchyma, spinal cord, meninges, cranial nerves and/or the eyes (1). PCNSL accounts for 1.5% to %3 of all brain tumors and compromises approximately 1% of all NHLs (2). The 95% of PCNSLs have a B-cell origin, especially are diffuse large B- cell lymphomas (3). The incidence increases within populations, whose individuals have achieved or congenital immunodeficiency (4). Treatment modalities for PCNSL include intrathecal treatment, surgical resection, chemotherapy and radiotherapy. Surgical therapy other than a diagnostic biopsy is not advised and restricted for patients with ventricular dilatation or impending herniation (3, 4).

Due to poor prognosis with a median survival time of nine months and high malignancy of the disease, PCNSLs optimal treatment modality is still a matter of debate (5,6). Therefore, we carried out a retrospective analysis of patients with PCNSL treated between 2002 and 2015 in Trakya University Hospital, Inönü University Turgut Özal Medical Center, Pamukkale University Hospital and Erciyes University Hospital in order

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to acquire more information about the clinical features of the disease and the responses to different treatment modalities.

MATERIAL AND METHODS

Patients diagnosed with PCNSL and treated between 2002 and 2015 in Trakya University Hospital, İnönü University Turgut Özal Medical Center, Pamukkale University Hospital and Erciyes University Hospital were identified by using the database of the institutions. Patients were included if only the pathology report validated a diagnosis of PCNSL. The data were retrieved from the lab, pathology, diagnostic imaging reports of patients saved in hospitals' database. The following items were recorded: name, age (≤60 vs. >60 years), sex, date of diagnosis, occupation, presence of cancer in family history, presence of immunodeficiency including HIV infection, presence of any transplantation, serum parameters, presenting symptoms, pathology, location of tumor, initial treatment modalities and responses to them, overall survival (OS), progression-free survival (PFS), treatment to recurrence and its response. The recorded serum parameters contained: WBC, HTC, PLT and LDH levels.

As treatment methods only initial treatments were investigated. Recorded data on initial treatment included whether a patient received initial radiotherapy, chemotherapy, surgical resection or a combination of those. The number of cycles, experienced side effects of chemotherapy, the type of chemotherapy drug and the cycle interval were additionally recorded.

Overall survival was defined as the time of diagnosis to the date of death or the date of last contact for patients who lost follow up. PFS was defined as the time of diagnosis to the date of death, recurrence, progression or date of last contact for those censored. PFS could not be used in survival time analysis due to the lack of data and insufficient number of patients. Further endpoints such as: Complete Remission (CR), Partial Remission (PR), Stable Disease (SD) and Progressive Disease (PD) were also recorded.

The statistical analysis was performed by using SPSS 22.0. Number and percentages, arithmetic mean ± standard deviation, median (maximum-minimum) were used as descriptive statistics. To compare the initial treatment methods, survival was estimated by using the Kaplan-Meier method. P value <0.05 was considered significant.

RESULTS

Patient Characteristics and Clinical Course

A total of 28 patients were identified through the database of hospitals. With 420 patients diagnosed with NHL frequency of the disease was found 7% in our research. Median age of patients at diagnosis was 53 (25-76; mean 51,93 ± 13,76), with 9 (32.1%) patients being 60 years or older. The main demographic data of patients and the mean levels of their serum parameters are summarized in Table 1. Out of all patients, 2 (7.4%) of them had immunodeficiency and 7 (25%) of them had cancer in their family history. The most common occupation among the patients was being a housewife. All patients were HIV negative and none of them underwent any transplantation. Pathological types of all lymphomas were diffuse large B-cell lymphoma. The mean serum LDH level was 293,29±188,377 U/L.

Table 1: Patient Characteristics (n=28)

Characteristics	Mean, Percentage, median and number of patients
Male	15 (53.6%)
Age(years)	53 (25-76)
Cancer in family history	7 (25%)
Immunocompromised	2 (7.4%)
Occupation	
Housewife	11 (39.3%)
Retired	5 (17.9%)
Student	1 (3.6%)
Lecture	1 (3.6%)
Farmer	1 (3.6%)
Marble master	1 (3.6%)
Registrar	1 (3.6%)
Petrol station attendant	1 (3.6%)
Serum parameters	
WBC	7631,34 ±3389,8
HCT	49,233 ±49,233
PLT	229920,00±71588,477
LDH	293,29±188,377

The sites of tumor localization are represented in Table 2. All patients had intracranial mass, but only 3 (11.1%) patients had evidence of leptomeningeal involvement. Out of all patients, 3 (11.1 %) of them were diagnosed with multifocal lesions while 24 (88.9%) of them with solitary lesion. The tumor was located in parietooccipital region in 4 (15.4%) of the cases.

Table 2: Location of Tumor (n=28)

Location	Percentage and number of patients
Temporal	2 (7.7%)
Parietooccipital	4 (15.4%)
Frontal	3 (11.5%)
Frontoparietal	2 (7.7%)
Cerebellum	1 (3.8%)
Occipital	1 (3.8%)
Basal ganglia	1 (3.8%)
Lateral ventricles	2 (7.7%)
Thalamus	1 (3.8%)
Quadrigeminal cistern	1 (3.8%)
Corpus callosum + lateral ventricles	1 (3.8%)
Frontal lobe + corpus callosum	1 (3.8%)

The data obtained from medical history reports demonstrated that 18 (66.7%) patients presented headache, 15 (53.8%) presented focal symptoms, 11 (40.7%) disequilibrium, 9 (33.3%) apparent death, 9 (33.3%) peripheral neuropathy and 4 (14.8%) seizure(s).

Treatment and Response

As initial treatment 26 (92.9%) patients received chemotherapy. Out of patients who received chemotherapy most of them (6 patients, 21.4 %) treated with a multidrug therapy protocol including Methotrexate and Cytarabine. Out of all, 5 (17.9 %) of patients received Deangelis based chemotherapy, while 3 (10.7%) of them treated with high dose Methotrexate (HDMTX) therapy. As part of initial treatment, in 6 (21.4%) patients both chemotherapy and radiotherapy were given while 19 (67.9%) patients were treated with surgical resection and 5 (17.9%) patients received a combined therapy containing chemotherapy, radiotherapy and surgical resection. The initial treatment modalities are described in Table 3. The median number of cycles of the chemotherapy drugs is 2 cycles (1-8). Thus, the most preferred interval between cycles was 21 days which was given in 5 (17.9%) patients. 21 (75%) patients experienced side effects caused by chemotherapy drugs. The most common side effects were pancytopenia and mild kidney dysfunction with the same rate of 7.1 %. As the result of first-line treatments 10 (35.7%) patients achieved CR, 7 (25%) patients PR; while 9 (32.1%) patients responded with PD and 1 patient with SD. Tumor recurred in 9 (32.1%) patients.

Table 3: Initial treatments received by patients with PCNSL (n=28)

Treatment method in initial therapy	Percentage, number of patients
High-dose methotrexate	10.7% (3)
Methotrexate-cytarabine	21.4% (6)
Deangelis	17.9% (5)
ABREY KT	7.1% (2)
R-CHOP	7.1% (2)
RTOG	3.6% (1)
Chemotherapy + radiotherapy	21.4% (6)
Surgical resection	67.9% (19)
Surgical resection + radiotherapy	14.3% (4)
Surgical resection + radiotherapy + chemotherapy	17.9% (5)

Survival

As for September 2015, 9 (32.1%) patients survived and were disease-free; while 8 (28.6%) died with the disease. Outcome data were unavailable in 11 (39.3%) patients. The median OS time was 7 months (1-161). Statistical survival analysis pointed out that achieving CR remission as response to the initial treatment is associated with an improved OS (p=0.027) (Figure 1). Other survival analysis to compare the impact of all initial treatment methods on OS was statistically insignificant (p>0.05).

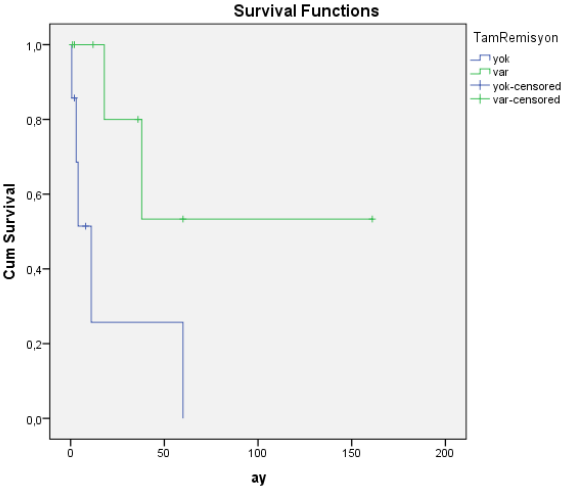

Figure 1: Overall Survival of patients with and without Complete Remission

DISCUSSION

Primary central nervous system lymphoma (PCNSL) is a rare, highly malignant disease with dismal prognosis (5). Current knowledge is generally based on the data gathered from small prospective clini-

cal trials (3, 5). While immunodeficiency is the only defined risk factor for the disease, optimal treatment modality remains still unknown (3). In this study it was aimed to obtain more information about the nature of the disease and to determine factors which may have been associated with an improved OS. As the consequence of the statistical survival analysis it was found out that achieving CR during the initial treatment improves OS significantly.

Primary central nervous system lymphoma (PCNSL) compromises approximately 1% of all NHLs (2). In our study the frequency of PCNSL was 7% of NHLs in our research centers. The identified number of PCNSL patients through our database was 28 which was approximate with other retrospective studies based on similar purpose in the literature. Dubuisson et al. (7) included 32 cases in their retrospective research about PCNSL, while Maekawa et al. (2) identified 31 patients from archives in their retrospective study. In our study the median age was 53 (25-76) which is comparable with the literature. In comparison with the studies carried out by Dalia et al. (4), Maeawa et al. (2), Dubuisson et al. (6) whose median age of the patients are 69,67, 61 respectively; our patients population could be considered younger. Furthermore the most common symptom presented by patients was focal deficit in these researches, while the most common symptom seen in our patients was headache (66.7%). Though, focal symptoms were presented in 15 (53.8%) cases in our research. Most of the lesions located in our patients were solitary which is consistent with the literature (3).

As our study results emphasized initial treatment is critical to improve OS. That is why in the other retrospective studies with the similar content, the optimal initial treatment method was investigated. The study carried out by Dalia et al. (4) resulted with the recommendation of HDMTX in the initial therapy. We had the similar purpose in our study. However we reached the conclusion that none of the treatment method was significantly more effective in comparison with other treatment modalities. Although surgical resection is least recommended treatment method containing high risk factors for the patients and is restricted for those with ventricular dilatation or impending herniation (3,4), we found out that 19 (67.8%) patients in our study were treated surgically as the part of initial treatment. The median OS time in our research was 7 months, which was also comparable with the estimated time of 9 months in the literature (6).

Primary central nervous system lymphoma (PCNSL) is a rare disease accounting for only 1.5%-3% of all brain tumors (2). To increase the number of cases we conducted our study in multiple centers. Carrying out a multicenter study enabled the increase of cases but on the other side complicated gathering the data. Along with it, obtaining the data retrospectively became the limitation factors of the research.

Consequently, in the study it is estimated that achieving CR as the response to initial treatment significantly improves the OS. Further retrospective researches with a bigger group of cases will contribute to determine the optimal initial treatment method and improve prognosis of the disease.

Ethics Committee Approval: This study was approved by Trakya University Faculty of Medicine Scientific Researches Ethics Committee.
Informed Consent: Written informed consent was obtained from the participants of this study.
Conflict of Interest: The authors declared no conflict of interest.
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