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Primary Central Nervous System Lymphoma, Treatment Outcomes - 10 Year Experience. Single Center Study

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ABSTRACT

Background: Primary central nervous system lymphoma(PCNSL) is an aggressive, rare form of Non-Hodgkin lymphoma, characterized by the absence of systemic disease. There are limited data and no strictly defined guidelines for management of PCNSL. **Objective:** The aim of this study was to report a 10 year experience of PCNSL treatment, to evaluate treatment outcomes and asses Progression Free and Overall Survival of these patients. **Methods:** Study was conducted on the Haematology Clinic, Clinical center University of Sarajevo, BH, in the period from January 2012.-December 2022. Total sample of 24 patients were enrolled. All have undergone diagnostic surgery. Patients were treated with regimens based on High dose Methotrexate, with/without whole brain radiotherapy as consolidation. Treatment response was captured by imaging techniques. Patients who have relapsed were evaluated with imaging techniques and treated according to Methotrexate-based treatment protocols. **Results:** We have captured equal gender distribution. The median age of patients was 59.5 years (range 20-79). Pathohistological analysis confirmed DLBCL diagnosis in 22 patients, T cell lymphoma and anaplastic large cell lymphoma, each in 1 patient. Chemotherapy, chemotherapy combined with WBRT and radiotherapy were given to 5, 18 and 1 patients, respectively. The overall complete response rate (CR) was 87,15%. Those receiving combined modality-treatment had higher CR than those receiving chemotherapy (94,4% versus 60%). Out of 24 patients, 11 of them relapsed. The median time to relapse was 29 months (from 1 to 105). After second line of the treatment, CR was 54,5%, while 45,45% of patients died during the treatment. 4 patients relapsed for the second time with median time to relapse of 9 months (from 2 to 77). 2 year OS rate was 67%, and the median OS rate was 45,9 months. 2 year PFS rate was 31%. **Conclusion:** The OS and PFS rates indicate the usage of new drugs and consolidation with autologous stem cell transplantation in patients with PCNSL in order to achieve better treatment outcomes.

Keywords: PCNSL, treatment outcomes, High dose Methotrexate.

1. BACKGROUND

Primary central nervous system lymphoma (PCNSL) is a rare, aggressive form of extranodal Non Hodgkin Lymphoma, which main characteristic is absence of systemic disease (1). Unlike other brain tumors, PCNSL responds with high rates of complete remission to chemotherapy and radiation, but despite that, survival outcomes are very poor (2). Dominant histopathological type of PCNSL is Diffuse large B cell lymphoma, and other types include T cell lymphoma, Burkitt Lymphoma and low grade lymphoma (3). Treatment of PCNSL includes induction therapy, followed by consolidation therapy. Induction therapy includes protocols which are based on High Dose Methotrexate (HD-MTX), com-

bined with other therapeutic agents. Different treatment modalities can be used as consolidation therapy, such as nonmyeloablative chemotherapy, polichemotherapy regimen followed by autologous stem cell transplantation, and whole brain radiotherapy. In the recent past, new therapeutic agents were discovered, such as a CD-20 monoclonal antibody-Rituximab. Adding Rituximab to other therapeutic agents has shown improvement in survival rates comparing it with protocols without Rituximab (5-7). Despite being highly effective treatment modality in consolidation phase, the usage of whole brain radiotherapy is limited due it's irreversible neurotoxicity (8). Chemotherapy followed by autologous stem cell transplantation is used as an alternative to whole brain radiotherapy. This therapeutic modality gives best results when it is combined with alkylating agents such as Thiotepa, but it's usage is limited due it's high costs (9). Even though patients with PCNSL respond to the treatment with high response rates, more than 50% of them relapse. Choice of the treatment in those patients depends on the age, performance status, presence of comorbidities in the moment of relapse, and initial response to the specific treatment of each patient (3). Since there is no study about PCNSL in Bosnia and Herzegovina, we wanted to see what outcomes our patients had in order to improve the treatment for patients with newly diagnosed PNSL in our country.

Therefore, we conducted a retrospective study which included newly diagnosed PCNSL patients, who were treated with protocols based on HD-MTX, with or without radiotherapy.

2. OBJECTIVE

The aim of this study is to report a 10 year experience of treatment of PCNSL, to evaluate treatment outcomes and to asses Overall Survival of these patients.

3. PATIENTS AND METHODS

Patients and methods

In this retrospective study we have analyzed 24 patients with newly diagnosed PCNSL, who were treated at our Clinic in the period between January 2012 and December 2022. We have obtained all the necessary data from medical records. Recorded data included age, gender, primary localization of the process, surgical procedure, lab parameters such as complete and differential blood analysis, levels of LDH, CRP, proteins, MRI findings, other radiological findings (US, CT, PET/CT, RTG). All histo-pathological slides were reviewed. The diagnosis of DLBCL was confirmed by highly experienced pathologists., and presence of systemic disease was excluded by performing other radiological procedures. The outcome of each patient was obtained from the medical records, or direct follow-up with the patient/family of the patient. The study was approved by the institutional research ethics board.

Statistical analysis

Overall survival was estimated using Kaplan-Meier curve. It was calculated from the day of diagnosis to the date of death from any cause, and Progression Free Survival was calculated from the day of the treatment to the date of relapse or death from any cause. Statistical analysis was performed using IBM Statistics SPSS version 25.0.

4. RESULTS

This study has analyzed 24 patients who were treated at our Clinic in the period between January 2012 and December 2022. The sex distribution was equal 50%male and 50% female. Median age was 59,5 years (from 20 to 79 years.) Localization of the lesions, performed surgical procedures and patho-histological diagnosis are presented in Table 1. Initially MRI was performed to all 24 patients, and in order to exclude systemic disease, PET/CT was performed in 9 patients, Abdominal ultrasound, CT of the abdomen, CT of the thorax and RTG of the lung and the heart in 13, 6, 8 and 8 patients, respectively.

As first line treatment, patients were treated with protocols based on HD-MTX, with or without radiotherapy. Protocols, treatment modalities and response rates are presented in Table 2. Out of 19 patients treated with RTOG 93-10 protocol, 17 achieved complete response. 2 patients were treated with combination of HD-MTX/AraC, and one of them achieved complete response. 3 patients were treated with Study-G-PCNS-SG-1 protocol, combination of HD-MTX/Ifosfamide and radiotherapy alone, all of them achieved complete response.

Out of 24 patients, 3 of them died during the first line treatment. After they received the therapy, patients were evaluated with MRI, CT and PET/CT, 18, 2, 1 respectively.

Relapse

Number of 11 (45,83%) patients relapsed after the first line of the treatment. The median time to relapse was 29 months (from 1 to 105 months). Patients were evaluated with MRI (8 patients) and PET/CT (2 patients) in order to confirm relapse. During the second line of the treatment, 5 patients have died, and 6 of them achieved CR which was confirmed with MRI and PET/CT.

Number of 4 patients relapsed after second line of the treatment, which was confirmed by MRI (3 patients) and PET/CT (1 patient). The median time to second relapse was 9 months (from 2 to 77 months). Third line of the treatment included combination of HD-MTX/AraC which was administered to 3 patients, and HD-MTX which was administered to 1 patient. Out of 3 patients receiving HD-MTX/AraC, 2 of them achieved CR, and one of them died during the treatment. Patient who was treated with HD-MTX only, also died during the treatment.

Survival

The median overall survival was 45.9 months (95% CI 22,7 to 69,3), and 2 year OS was 67% (95% CI 42,1 to 88,5). Data shown in Fig. 1. The median PFS was 29.6 months (95% CI 27.5 to 30.5) and 2 year PFS was 31% (95% CI 18.4 to 53.3). Data shown in Fig. 2.

5. DISCUSSION

Results of our study showed that patients achieved highest CR rate (94,4%, p=0,111) when combined modality of treatment (chemotherapy and radiotherapy) is administered to them. Similar results are reported in

different studies, where CR rate is achieved in 60% to 75% (7, 10). Even though our patients were not treated with protocols which include Rituximab, there was no difference in results from those reported earlier. CR rate in patients who were treated with chemotherapy alone was 60% (p=0,111), and other studies reported that patients treated with Rituximab based regimens achieved CR rate of 64% to 66% (7, 11).

Treating patients with relapse of PCSNL is still a challenge. Our analysis showed that in the second line of the treatment, 5 patients received therapy according to the Study-G-PCNS-SG-1 protocol, 3 patients were treated with RTOG 93-10, and one patient was treated with combination of HD-MTX/AraC. Previously published studies showed that treating relapse of PCNSL with higher dose of radiotherapy (≥30Gy) are linked to the higher CR rates (12). New modalities of treatment are being developed for patients with PCNSL relapse. They include Bruton tyrosine kinase inhibitors. Studies have shown encouraging results, where patients achieved CR rates of 64% to 73,3% (13, 14). Our study showed better rate of 2 year OS (67%) than that of 2 year PFS (31%), because patient with relapse lived long due to the response on the second line of the treatment. Our results follow those reported earlier, even though one of the study showed better 2 year OS (81%) in patients who were treated with combination of chemotherapy followed by autologous stem cell transplantation (15). Published prospective studies are showing encouraging results; patients who were treated with protocols similar to RTOG 93-10 (excluding radiotherapy due its toxicity) and in conjunction with Rituximab, resulted in PFS rate of 63% (11), while other study with similar regimen showed 2 year PFS of 0.57 (16).

Retrospective design and small number of patients are limitations of this study which doesn't allow us to come up with statistically significant conclusions regarding outcomes of the treatment.

6. CONCLUSION

Previously presented Survival rates indicate the need of using new drugs and autologous stem cell transplantation as consolidation therapy in patients with PCNSL in order to achieve better treatment outcomes.

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