Original Article

Treatment of Primary Central Nervous System Lymphoma with High-dose Methotrexate and Radiotherapy in HIV-negative Patients

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Abstract

Background: We assessed the outcome of high-dose methotrexate (HD-MTX) chemotherapy with or without radiotherapy (RT) in primary central nervous system lymphoma (PCNSL) patients.

Methods: Fifty-one HIV-negative patients with an average age of 50.3 years were treated with chemotherapy regimen included 2500 mg/m^2 MTX with Leucovorin rescue and 1.4 mg/m^2 vincristine (day two), which was administered every other week for 6 weeks. Only the patients who were younger than 60 years received RT. All patients received two cycles of 3000 mg/m^2 cytarabine at the end of the treatment for two successive days.

Results: Diffuse large B-cell lymphoma was the most common histologic subtype (90.2%), and twenty-six (51.0%) patients had multiple brain lesions. The median survival of patients who were younger than 60 years was 37 months. For patients who were older than 60 years, the median survival was 20 months. The median survival of men and women were 30 and 34 months, respectively. There was no significant difference in survival of patients in terms of age and sex. Overall, sixteen patients (31%) out of fifty-one patients died, five of them were older than 60 years and eleven were younger than 60 years. Twenty-five (49%) of all patients experienced relapse, and 10 (40%) of them died after rechemotherapy.

Conclusions: The base of our chemotherapy regimen was HD-MTX as the regular doses of MTX cannot penetrate the blood brain barrier (BBB). Our results indicated that the combination of HD-MTX with RT may not influence the outcome of PCNSL; thus, RT cannot be the first line therapy.

Keywords: Central nervous system, lymphoma, methotrexate, radiotherapy

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Introduction

Primary central nervous system lymphoma (PCNSL) is a rare variant of non-Hodgkin's lymphoma (NHL) that can affect the brain, spinal cord, meninges and eyes without any sign of systemic involvement.[1]

Incidence of this disease is increased in the last three decades among both immune compromised and immune competent individuals, with current incidence rate of four per one million population.[1,2] The most important predisposing factor for PCNSL is immunodeficiency (including HIV infection), iatrogenic immunosuppression and congenital immunodeficiency syndromes like ataxia-telangiectasia and Wiskott-Aldrich syndrome.[1,3] The pathogenesis of PCNSL is unclear and does not respond to current therapy in systemic NHL (R-CHOP).[4] In recent years, different therapeutic protocols have been developed for treatment of lymphoma. High-dose methotrexate (HD-MTX) chemotherapy is the most effective treatment, which results in a response rate of 80% – 90% and two-year survival rate of 60% – 65%.[5] Radiotherapy (RT) results in high response rates but rapid relapse. In addition, RT is associated with delayed neurotoxicity, especially in elderly patients, which is a recognized complication in 90% of patients who are older than 60 years.[6,7] Adding MTX-based chemotherapy has improved survival in these patients. Chemotherapy with HD-MTX followed by RT is the most commonly used therapeutic approach for patients with newly diagnosed PCNSL, resulting in a 5-year survival rate of 22% – 40% in comparison to 3% – 26% rate reported with RT alone.[3,5] However, patients receiving this combined treatment are at risk for delayed neurotoxicity.[8]

Therefore, current treatment is a systemic chemotherapy with or without RT. We evaluated the effect of chemotherapy with HD-MTX and RT on survival of patients with PCNSL from the time of diagnosis to 8-year follow-up period, and assessed the role of age and sex in the outcome of these patients. Eventually, we concluded that RT is not the first step in PCNSL treatment.

Materials and Methods

Between 2004 and 2012, nine hundred and fifty-two patients with PCNSL symptoms, underwent either open biopsy or stereo-

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taxic in two hospitals (Arad Hospital and 501 Army Hospital) in Tehran, Iran. Eighty-two patients were confirmed to have PCNSL by stereotaxic biopsy and four patients with open biopsy. At the end, we chose 51 out of 86 patients for their therapy. Written informed consent was obtained from all patients. We conducted a retrospective study of these patients, and examined long-term survival and morbidity rates among patients who were treated with either combination chemotherapy and RT or chemotherapy alone. Patients, who aged between 16 and 80 years, were eligible for the study. All patients were HIV negative, and had positive pathology and immuno-histochemical staining for NHL in the brain. All patients underwent CT scan of chest, abdomen and the pelvis, whole body bone scan, bone marrow aspiration and biopsy as part of their initial work-up.

The enrolled patients were divided to two groups; younger than 60 years old and older than 60 years old. The former were treated with a combination of chemotherapy and RT and the latter were treated with chemotherapy alone to reduce cognitive complications related to RT in older patients. The chemotherapy regimen included 2500 mg/m^2 MTX with Leucovorin rescue (starting18 hours after MTX infusion) and 1.4 mg/m^2 vincristine (day two), which was administered every other week for 6 weeks. In younger patients (< 60), chemotherapy was followed by daily RT for 3 weeks to a total of 4500 rad. Both groups received 3000 mg/m^2 Cytarabine for two successive days (3 weeks apart). MTX plus 100 mg Cytarabine (15 to 20 mg) was intrathecally injected to all the patients with meningeal involvement. Urine output of more than 100 (mL/h) and a urine pH of 7 had been maintained, during and after infusion of MTX, IV hydration and urine alkalization. The chemotherapy regimen is summarized in (Table1). The patients were monitored from 2004 to 2012, and their median overall survival (OS) was assessed. Follow-up studies included physical and neurological examinations, 24-hour urine collection for creatinine clearance with each cycle of chemotherapy, complete blood count, cranial MRI after every other cycle of chemotherapy, ophthalmology examination and CSF cytology.

Statistical Analysis

Data were available as mean and standard deviation (SD) for continuous variables and number (%) in case of categorical variables. Kaplan-Meier curves were computed to display the distribution of OS. Survival period was measured from the date of diagnosis to the date of first relapse, death or last follow-up. To show differences in the survival period among various sex and age groups, Cox regression model and Kaplan-Meier survival curve were implemented. The Log Rank (Mantel-Cox) test was used for comparing the survival periods between groups. The *P*-value less than 0.05 was considered as statistically significant. All analyses were performed using SPSS for Windows v.13.0 (SPSS Inc., Chicago, IL, USA) and R software (v.3.0.2.)

Results

Patient Characteristics and Pathology

In this study, 51 patients with a histological diagnosis of PCNSL received 2500 mg/m^2 MTX with Leucovorin rescue (starting 18 hours after MTX infusion) and 1.4 mg/m^2 vincristine (day two) treatment with or without RT between July 2004 and July 2012. Their common presenting symptoms included headache, hemiparesis, convulsion, neurocognitive defects, ocular symptoms and a combination of the mentioned symptoms. Patient's characteristics are presented in Table 2. The median age was 50.3 years (SD = 15.1 years). Most of patients were lower than 60 years old (n = 35; 68.6%). Thirty-one patients were male and twenty were female. Diffuse large B-cell lymphoma (DLBCL) was the most frequent histologic subtype (90.2%). Four patients had a high grade B-cell lymphoma (7.8%), and one patient had a low-grade lymphoma (LGL) (2%). Twenty-six (51.0%) patients had multiple brain lesions (Table 2). All patients were HIV negative, and just one patient had spinal fluid involvement. All patients had a 24-hour creatinine clearance of 50 mL/min or higher.

Patients Outcome

Twenty-five patients (49%) experienced relapse in the same site of initial tumor (Figure 1). They were treated with HD-MTX again, but ten of them died after chemotherapy. Overall, sixteen patients (31%) out of fifty-one patients died, five of them were older than 60 and eleven younger than 60 years (Figure 2). Twenty-four of surviving patients were under the age of 60 and eleven of them were older than 60 years. Median OS time of 51 patients was 32 months (Figure 3). In patients younger than 60 years the median survival old was 37 months, but 20 months in those older than 60 years. Figure 4 displays the Kaplan-Meier survival curve for age groups (under and over 60 years old). Log-rank test revealed that there was no significant difference in the median survival period between these two age groups (P = 0.92). The median survival of men and women was 30 and 34 months, respectively. Figure 5 presents the Kaplan-Meier survival curve in terms of sex. Log-rank test revealed that there was no significant difference in the median survival period between males and females (P = 0.544). The patient's outcome is summarized in Figure 2.

Discussion

PCNSL is one of the most aggressive malignancies with the poorest prognosis among NHLs.[5] MTX plays a major role in systemic chemotherapy regimens for PCNSL treatment. Dose of MTX is

Table 1. Chemotherapy regimen for PCNSL in the current study

Treatment protocol	Cycles
Chemotherapy (all patients) HD-MTX 2500 mg/m^2 (day one) Vincristine 1.4 mg/m^2 (day two) With Leucovorin rescue 18-hoursafter HD-MTX	Six cycles with 1 week interval between cycles (1, 3, 5, 7, 9, 11)
RT4500 RADs (< 60 years old patients)	Daily for three weeks
Cytarabine 3000 mg/m^2 (all patients)	Two cycles; two successive days with three weeks of interval between cycles

Table 2. Patient Characteristics and Pathology

Characteristic	N (%)
Sex	
Male	31 (60.8)
Female	20 (39.2)
Age, years	
< 60	35 (68.6)
≥ 60	16 (31.4)
Mean (SD)	50.3 (15.1)
Pathology	
DLBCL	46 (90.2)
High grade B-cell lymphoma	4 (7.8)
LGL	1 (2.0)
Site of CNS involvement	
Cerebellum	4 (7.8)
Left frontal	5 (9.8)
Right frontal	4 (7.8)
Corpus callosum	4 (7.8)
Left parietal	2 (3.9)
Brain stem	6 (11.9)
Multiple brain lesion	26 (51.0)

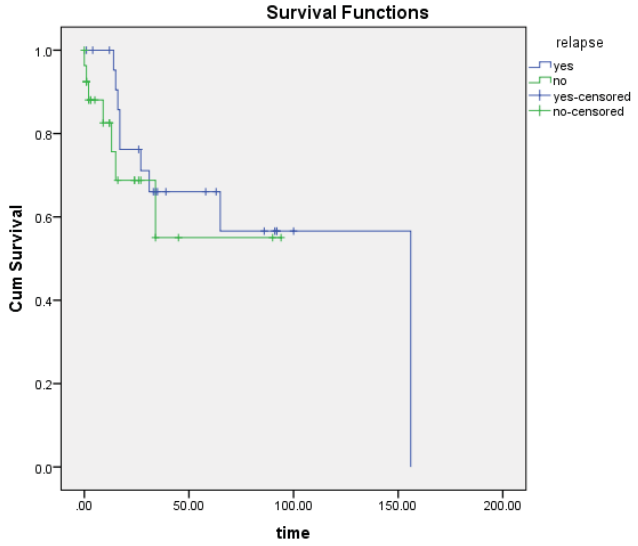

Figure 1. Kaplan-Meier survival curve for relapse

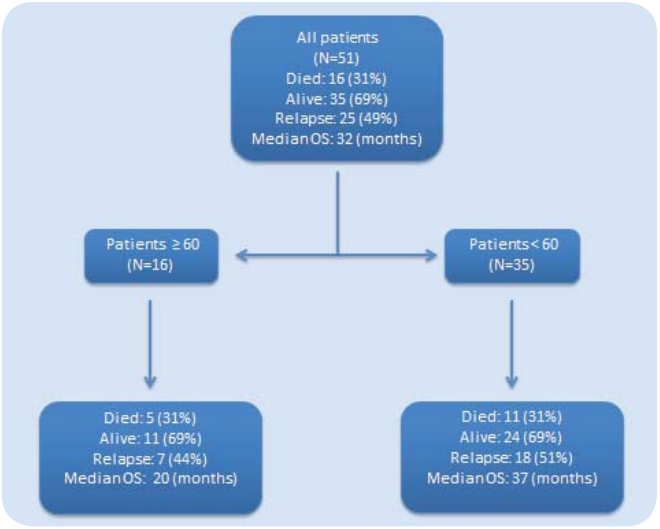

Figure 2. A diagram of the patients participating in the study and the outcome of their related treatment

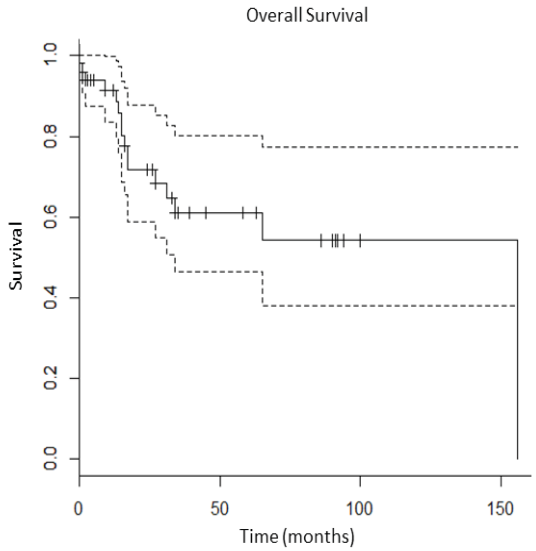

Figure 3. OS and 95% confidence intervals, analysis were performed using Kaplan-Meier method for all 51 patients.

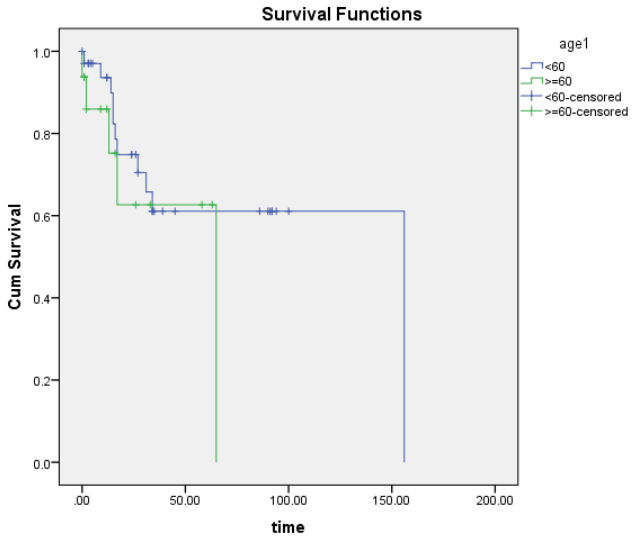

Figure 4. Kaplan-Meier survival curve for age groups (< 60 vs. ≥ 60)

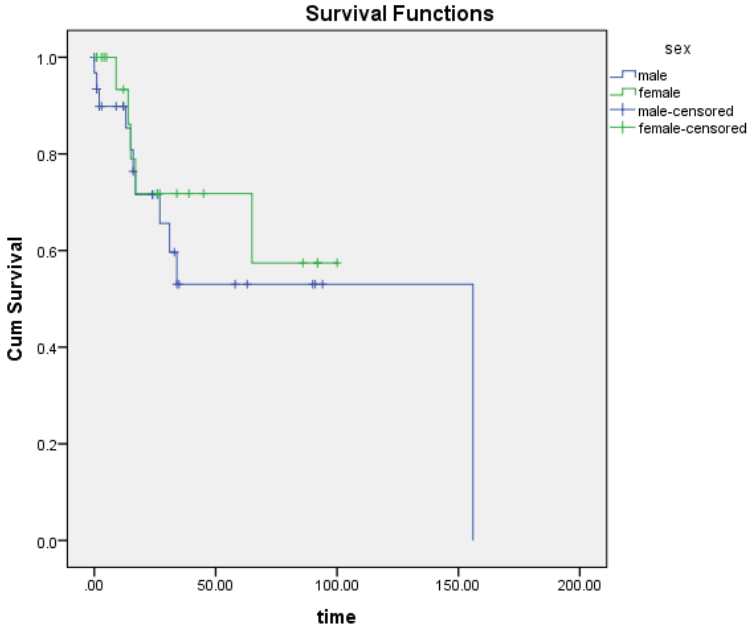

Figure 5. Kaplan-Meier survival curve for sex groups (male vs. female)

important because, HD-MTX (over 1 g/m^2) passes through the Blood Brain Barrier (BBB) and penetrates to the brain.[5,9] Inclusion of ARA-C has resulted in a better response and survival.[10] A number of studies have been conducted to get an optimized dose and better survival, such as the study of Sandor, et al.[11] They administered a higher dose of MTX (8.4 g/m^2) in combination with vincristine and thiotepa without RT. The progression-free survival (PFS) rate was only 16.5 months, and more than 70% of patients experienced relapse. BBB disruption with the administration of intra-arterial MTX (2.5 g/m^2) without RT is one of the protocols resulting in a median survival of 40 months.[12] A lower dose of MTX (2.5 g/m^2) had a high response rate before RT chemotherapy with an OS of at least 30 months.[13] In the present study, we used the intravenous HD-MTX (2.5 g/m^2) to treat the patients.

Although addition of HD-MTX to RT improves the prognosis and leads to three times longer median survival periods compared with RT alone, it causes a high risk of delayed neurotoxicity, especially in patients who are older than 60 years.[14] According to other studies, RT is not an effective therapy for PCNSL and does not affect the survival, so it can be withheld for elderly patients.[8,15] Omission of RT resulted in reduced PFS and neurotoxicity but the OS was not compromised in younger patients.[16] Therefore, RT has been omitted as the first line therapy of PCNSL, because chemotherapy is the first option in younger patients.

In our study, which is a report of the PCNSL with the highest number of samples from Iran, we treated the patients with HD-MTX chemotherapy regimen with RT (just for patients younger than 60 years) in an 8 year follow-up period. Their average survival period was calculated, and reported as 32 months. According to their treatment the survival time was 37 months for patients younger than 60 years and 20 months for those older than 60 years, separately. There were no significant differences in mean survival time between these two age groups (P = 0.92).

Another study from Iran has been conducted by Keihani.[17] He evaluated the administration of RT before or after chemotherapy in 23 PCNSL patients, and concluded that chemotherapy prior to RT was more efficacious than RT prior to chemotherapy with 100% two-year survival, and provided improved disease free survival. In our study, there was no significant difference between OS of patients who were older and younger than 50 years of age (P = 0.64). According to Glass, et al. before RT, HD-MTX was so helpful and increased the survival period to 33 months.[18] In Abery, et al. study, the survival period for patients with RT alone was 21.7 months, however it was 42.5 months for those who had also received chemotherapy regimens. In addition, in a 5 year follow-up, the survival rate was 3% – 4 % and 22.3 %, respectively.[19] Also in another study of Abery, et al. they showed that HD-MTX in addition to a combination of Procarbazine, vincristine and RT and two cycles of Cytarabine at the end can increase the survival up to 60 months.[7] According to these studies, the use of RT is controversial and further studies are required.

Fifty percent of patients who were older than 60 years who deferred RT, experienced relapse, and most of them died due to progressive tumor.[7] This relapse proportion was 44% in the current study. Forty-nine percent of all patients experienced a relapse, 10 (40%) of whom died after relapse. Overall, 62.5% of deceased patients (10 out of 16) had experienced relapse before death.

In conclusion, according to lack of difference in OS time between patients younger and older than 60 years, therefore RT therapy does not influence the outcome of PCNSL, and is not the first line therapy. Moreover, there is no significant difference in the mean survival period between males and females (P = 0.544), so the gender will not affect treatment. Since PCNSL is a rare disease, most of the studies are retrospective. Nowadays, the use of new diagnostic methods and treatment of patients with immunodeficiency has increased the incidence of PCNSL, so we can see more prospective studies resulting in a better survival. New regimens include systemic as well as intrathecal rituximab, temozolamide, topotecan, BMT and combination therapy. In order to improve disease control and outcome for all patients, we can

choose the best regimen to treat PCNSL.

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