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ORIGINAL ARTICLE

High-dose methotrexate combined with rituximab improves the survival rate of patients with primary central nervous system lymphoma

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Summary

Purpose: *To explore the efficacy of high-dose methotrexate (HD-MTX) combined with rituximab (R) in the treatment of primary central nervous system lymphoma (PCNSL).*

Methods: *108 PCNSL patients were randomly divided into Rituximab group (n=54) or control group (n=54). The patients in Rituximab group were treated with HD-MTX + R chemotherapy, while those in control group were given HD-MTX combined with whole brain radiotherapy (WBRT). The therapeutic effect, incidence rate of adverse reactions and the SF-36 score were compared between the two groups.*

Results: *The overall response rate was overtly higher in Rituximab group than that in control group (81.5% vs. 57.4%). After treatment, the scores of physical function, physical competence, health condition, social function and emotional function in the SF-36 scale were notably higher in Rituximab group than those in control group. The 1-year overall survival (OS) rate was 83.3% (45/54) and 63.0% (34/54), 1-year progression-free survival (PFS) rate was 70.4% (38/54) and 46.3% (25/68), 3-year OS rate was 57.4% (31/54) and 31.5% (17/54), and 3-year PFS rate was 27.8% (15/54) and 14.8% (8/54) in Rituximab group and control group, respectively. The results of log-rank test showed that the OS and PFS rates in Rituximab group were obviously better than those in control group.*

Conclusion: *Compared with HD-MTX combined with WBRT, HD-MTX combined with R can remarkably improved the quality of life and survival rate of patients with PCNSL, with tolerable adverse reactions and is worthy of popularization and application in clinical practice.*

Key words: *methotrexate, lymphoma, rituximab, central nervous system tumor, efficacy*

Introduction

Primary central nervous system lymphoma (PCNSL), which accounts for about 3-5% of primary intracranial tumors, is a rare aggressive non-Hodgkin lymphoma (NHL) restricted to the central nervous system, involving only the brain, spinal cord, eyes, or pia mater, and has high disability and fatality rates [1,2]. Besides, it ranks first among various intracranial tumors in terms of incidence rate and has been on the rise in recent years, and the patients tend to be younger. The pathological type of over 95% of PCNSL is diffuse large B-cell lymphoma (DLBCL) [3,4]. High-dose methotrexate (HD-MTX)-based regimens are now widely accepted as the preferred choices for the treatment of new-onset PCNSL patients, which can be combined with whole-brain radiotherapy (WBRT) or other targeted and therapeutic drugs including rituximab (R), cytarabine and temozolomide [5-7]. Studies have reported that R is able to effectively improve the prognosis of patients with systemic DLBCL [8-

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10]. However, no consensus has been reached in research on the efficacy of HD-MTX combined with R in treating PCNSL.

In this study, therefore, the efficacy and safety of HD-MTX combined with R were compared with those of HD-MTX combined with WBRT in the treatment of PCNSL, hoping to provide a strong basis for the choice of treatment regimens.

Methods

Study subjects

The clinical data of 108 PCNSL patients were retrospectively analyzed.

Inclusion criteria: patients definitely diagnosed with PCNSL according to the WHO classification criteria of tumors of the hematologic and lymphoid tissues and the results of clinical diagnosis, laboratory examination and imaging examination, those not receiving chemotherapy, radiotherapy or targeted therapy, those able to complete 4 chemotherapy cycles, those given R with positive CD20 expression, those who were conscious and able to express themselves correctly, and those who were HIV-negative and had no other immunodeficiencies.

Exclusion criteria: patients with severe liver and kidney dysfunction or other systemic diseases, those with contraindications for drugs used in this study, or those with expected survival time less than 3 months.

Among these patients, there were 69 males and 39 females, aged 39-77 years (mean 58.33±10.25). At the time of onset, the clinical manifestations of patients were related to the lesion location, probably with many systemic symptoms, including dizziness, headache, nausea, limb activity disorder, impaired vision, memory deterioration, slow response or drowsiness, and personality changes. The general data like age, gender, LDH, cerebrospinal fluid protein content, the presence or absence of tumor cells or symptoms and Karnofsky performance status (KPS) score showed no statistically significant differences between the two groups ($p>0.05$), which were comparable (Table 1). All patients enrolled were informed and signed the informed consent in accordance with Declaration of Helsinki. This study was approved by the Ethics Committee of Qilu Hospital of Shandong University.

All patients underwent computed tomography (CT) scan and magnetic resonance imaging (MRI) examination, 17 patients had magnetic resonance spectroscopy (MRS) examination, and 26 patients had positron emission tomography (PET)-CT examination. Based on the

Table 1. Demographics and general clinical data of all studied patients

Parameters	*Rituximab group (n=54)* *n (%)*	*Control group (n=54)* *n (%)*	*p value*
Gender (Male/Female)	37/17	32/22	0.423
Age (years)	57.64±10.08	59.11±10.13	0.451
Number of tumor			0.564
1	30 (55.6)	26 (48.1)	
≥2	24 (44.4)	28 (51.9)	
LDH			0.541
Normal	34 (63.0)	38 (70.4)	
Elevated	20 (37.0)	16 (29.6)	
CSF Protein			0.583
Normal	25 (46.3)	21 (38.9)	
Elevated	29 (53.7)	33 (61.1)	
CSF tumor cells	22 (40.7)	17 (31.5)	0.317
Symptoms			0.814
Headache	25 (46.3)	32 (59.3)	
Nausea	19 (35.2)	22 (40.7)	
Limb movement disorder	13 (24.1)	10 (18.5)	
Memory deterioration	10 (18.5)	8 (14.8)	
Personality change	9 (16.7)	13 (24.1)	
Blurred vision	3 (5.6)	1 (1.9)	
Lalopathy	1 (1.9)	2 (3.7)	
Drowsiness or lags in response	3 (5.6)	4 (7.4)	
Karnofsky score			0.335
70-90	31 (57.4)	26 (48.1)	
50-70	23 (42.6)	28 (51.9)	

LDH: lactate dehydrogenase; CSF: cerebrospinal fluid

images of CT scan, the lesions showed low-density, high-density or mixed-density appearance with generally irregular morphology, and the CT findings were not specific. The images of MRI displayed that the tumors were mostly in a round, oval, and "fisted" shape, with iso- or slightly hypo-intense signal on T1 images and iso- or slightly hyper-intense signal on other images. Among the 108 patients, there were 56 (51.9%) cases of single tumor and 52 (48.1%) cases of multiple tumors. In 67 (62.0%) patients, the tumors involved the deep part of the brain parenchyma. Most of the tumors were supratentorial and most common in frontal, temporal, occipital, basal ganglia and paraventricles, and paraventricular lesions tended to grow bilaterally. Few tumors were infratentorial and more common around the cerebellar vermiform, brainstem and the fourth ventricle. There was 1 case in lumbar spine. The images of enhancement scan showed that the lesions were lumpy or nodular and obviously uniformly enhanced, or were unevenly enhanced, or had adjacent meningeal enhancement. Moderate to severe peritumoral edema was observed in most cases, and midline shift was detected in 7 cases. According to the images of MRS examination, choline peak was increased, while creatine peak and nitrogen-acetylaspartate peak were decreased. The images of PET-CT showed that the lesions were nodular, clumpy, small lamellar, or irregular, with abnormally high 18F-FDG uptake, obvious radioactive concentration, standard uptake value (5.0-32.0), and normal concentration in lymph nodes in other parts of the body.

Therapeutic methods

The patients in control group were treated with HD-MTX (Sichuan Huiyu Pharmaceutical Co., Ltd., NMPN: H20044467, 5 mg/each) in combination with WBRT, i.e., the patients were intravenously injected with MTX at a dose of 3 g/m^2, and subjected to sequential WBRT (5 times a week, the total dose: not higher than 36 Gy, 2.0 Gy/time) for 4 consecutive cycles of treatment, with 4 weeks as 1 treatment cycle. If there were residual lesions, local radiation was conducted at 10.0 Gy.

The treatment regimen of HD-MTX combined with R was adopted in Rituximab group. In other words, the patients were given MTX at 3 g/m^2 and R at 375 mg/m^2. After administration, the urine was fully alkalized. At 12 h after medications, salvage treatment was performed using calcium folinate. Meanwhile, the changes in MTX blood concentration and indexes of blood routine and liver and kidney function during chemotherapy, such as 24-h urine output, were closely monitored. Besides, corresponding symptomatic and supportive treatment was carried out during chemotherapy. If leukopenia and thrombocytopenia occured during chemotherapy, cell colony stimulating factor or platelet promoting treatment was administered. The treatment lasted for 4 cycles, with 4 weeks as 1 treatment cycle.

Observation indexes

Efficacy was evaluated based on the consensus criteria for evaluation on therapeutic response to PCNSL by the International Primary CNS Lymphoma Collaborative Group (IPCG), including complete response (CR), partial response (PR), progressive disease (PD) and stable disease (SD) [12]. Enhanced MRI was the standard evaluation method, with no lesions enhanced as CR, 50% reduction of lesions enhanced as PR, 25% increase in tumors or new lesions as PD, and lesions between PD and tumor progression as SD. Overall response rate (%) = [(CR + PR + SD)/total cases] ×100%. The lymphocytes in the cerebrospinal fluid of patients was measured and counted before and after treatment.

As per the Common Terminology Criteria Adverse Events Version 4. 0 (CTCAE v4. 0), the adverse reactions including hematologic toxicity, liver and renal dysfunction, gastrointestinal reactions and mucositis in the two groups of patients were observed and recorded. The quality of life of patients was assessed using a short-form 36 health survey questionnaire (SF-36). This questionnaire covers the assessments of physical function, physical competence, health condition, social function, and emotional function, with 100 points for each item. The higher the score, the better the quality of life.

After treatment, patients could have reexaminations in our hospital at any time in the case of any discomfort such as nausea and headache. At the same time, patients should undergo head-enhanced MRI reexamination every 2 months for 2 years and then every half year. Tumor recurrence was diagnosed based on the presence of tumor recurrence features observed on MRI. The follow-up ended in October 2019. Overall survival (OS, the time from the date of the start of treatment to the date of the death or the deadline of follow-up) and progression-free survival (PFS, the time from the date of the start of treatment to the date of the tumor recurrence/progression or last follow-up) were used as observation indicators.

Statistics

SPSS 22.0 statistical software was utilized for statistical analyses. Measurement data were expressed as mean±standard deviation, and t-test was employed for the comparison between two groups. Enumeration data were expressed as ratio (%), and two-way ANOVA was used for comparison among groups. Survival curves were plotted using Kaplan-Meier method, and log-rank test was employed to evaluate differences between groups. $P<0.05$ suggested that the difference was statistically significant.

Results

Comparison of clinical efficacy between two groups of patients after treatment

The results of head-enhanced MRI examination performed after treatment displayed that the lesions were round nodules or masses, with relatively slight peritumoral edema and space-occupying effect and clear boundary. In Rituximab group, there were 17 cases of CR, 27 cases of PR, 21 cases of SD and 10 cases of PD, with an overall response rate of 81.5% (44/54). In control group, there were

8 cases of CR, 23 cases of PR, 16 cases of SD and 7 cases of PD, with an overall response rate of 57.4% (31/54). The overall response rate was overtly higher in Rituximab group than that in Control group, (p=0.010) (Table 2).

Comparison of incidence rate of adverse reactions between two groups of patients

The common adverse reactions in patients were hematologic toxicity, gastrointestinal reactions, liver and renal dysfunction, and mucositis. In Rituximab and Control group, grade I-III hematologic toxicity was detected, which was attenuated after symptomatic treatment, and no severe infection or bleeding were found. Besides, there were 11 and 26 cases of gastrointestinal reactions, 10 and 22 cases of liver dysfunction (manifested as elevated transaminase level or alkaline phosphatase level, and alleviated after treatment with hepatoprotective drugs), 8 cases of renal dysfunction (manifested as slightly increased proteinuria and urea nitrogen, which returned to normal after drug withdrawal) in the two groups. Other common adverse reactions were mucositis and respiratory infection. In comparison with those in Control group, the incidence rates of gastrointestinal reactions, liver and renal dysfunction, and mucositis clearly declined in Rituximab group (p=0.003, p=0.011, p=0.015, p=0.017), while the incidence rates of hematologic toxicity and respiratory infections showed no statistically significant differences (p>0.05) (Table 3).

Comparison of improvement of quality of life between two groups of patients

After treatment, the scores of physical function, physical competence, health condition, social function and emotional function in the SF-36 scale

Table 2. Clinical effective rates of the two studied groups

	Rituximab group n=54 *n (%)*	*Control group n=54* *n (%)*	*p value*
CR	17 (31.5)	8 (14.8)	
PR	27 (50.0)	23 (42.6)	
SD	21 (38.9)	16 (29.6)	
PD	10 (18.5)	7 (13.0)	
ORR	44 (81.5)	31 (57.4)	0.010

CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; ORR: overall response rate

Table 3. Comparison of adverse reactions of patients in the two groups

Parameters	*Rituximab group (n=54)* *n (%)*	*Control group (n=54)* *n (%)*	*p value*
Anemia	8 (14.8)	14 (25.9)	0.152
Leukopenia	16 (29.6)	21 (38.9)	0.311
Thrombocytopenia	7 (13.0)	12 (22.2)	0.223
Gastrointestinal reactions	11 (20.4)	26 (48.1)	0.003
Liver dysfunction	10 (18.5)	22 (40.7)	0.011
Renal dysfunction	8 (14.8)	19 (35.2)	0.015
Mucositis	9 (16.7)	20 (37.0)	0.017
Respiratory infection	13 (24.1)	10 (18.5)	0.639

Table 4. Comparison of SF-36 life quality scores of patients in the two groups

Parameters	*Rituximab group (n=54)*	*Control group (n=54)*	*p value*
Physical functions	72.1±8.7	65.6±7.8	0.001
Physical competence	71.2±7.6	64.9±7.3	0.001
Health condition	67.4±7.9	62.8±6.9	0.003
Social function	74.4±6.6	68.1±6.2	0.001
Emotional function	76.8±8.2	72.7±7.5	0.008

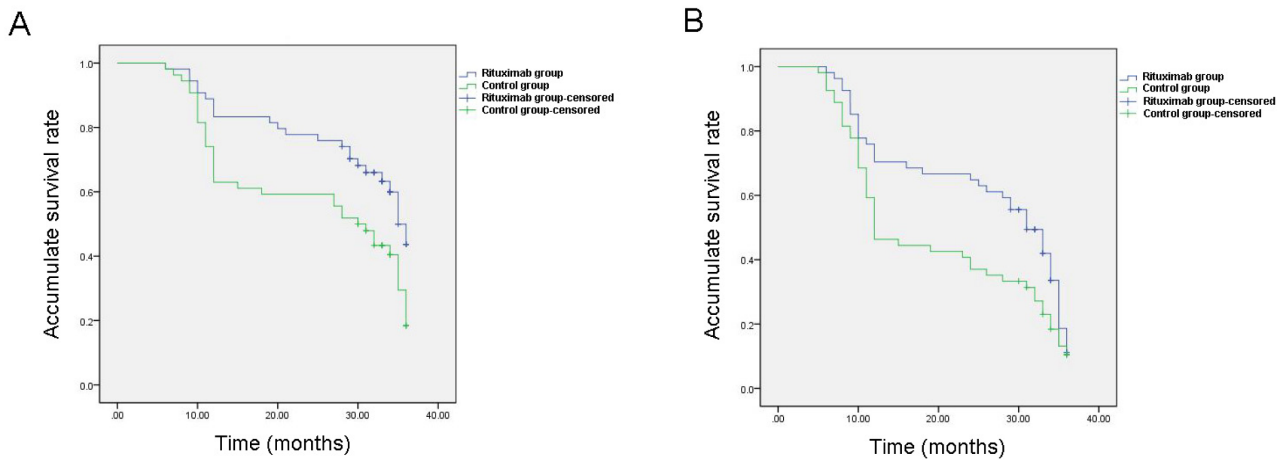

Figure 1. Kaplan-Meier survival curves of patients in Rituximab group and Control group. The overall survival rate **(A)** and progression free survival rate **(B)** of patients in Rituximab group were significantly higher than those of Control group (p=0.013, p=0.043).

were notably higher in Rituximab group than those in Control group (p<0.05) (Table 4).

Results of patient survival during follow-up

Up to October 2019, the patients were followed up for 6-36 months (median 25.3). The 1-year OS rate was 83.3% (45/54) and 63.0% (34/54), 1-year PFS rate was 70.4% (38/54) and 46.3% (25/68), 3-year OS rate was 57.4% (31/54) and 31.5% (17/54), and 3-year PFS rate was 27.8% (15/54) and 14.8% (8/54) in Rituximab group and Control group, respectively. Survival curves were plotted by Kaplain-Meier method (Figure 1). The results of Log-rank test revealed that the OS and PFS of patients were clearly superior in Rituximab group to those in Control group (p=0.013, p=0.043).

Discussion

PCNSL accounts for about 2.2% of all central nervous system tumors and has an increasing incidence rate in recent years, with DLBCL as the majority [13]. It is mainly manifested by neurological symptoms and signs at onset, and its prognosis is worse than that of systemic NHL. At present, there is no standard treatment method for this condition. Based on the literature, the median survival time is 10-16 months, and the integrated regimen of systemic chemotherapy, intrathecal chemotherapy and WBRT can significantly improve the efficacy and prolong the OS to 40-50 months, which are currently the most commonly used treatment modalities [14].

In accordance with the results of retrospective or prospective studies, MTX is considered as the most effective and important drug in the treatment of PCNSL. Literature recommends that MTX should be intravenously infused within 3 h rapidly at a dose above 3 g/m^2, so as to reach the therapeutic concentration in cerebrospinal fluid [15]. R, an anti-CD20 chimeric antibody, is deemed to be able to improve prognosis and prolong PFS and OS in treating DLBCL [16], approved for the treatment of DLBCL by the US FDA in 2006. However, as to whether R can improve the prognosis of patients with PCNSL, there are inconsistent results in different studies. The biggest controversy comes from whether R can pass through the blood-brain barrier (BBB). In a study conducted in 2003, 4 patients were intravenously injected with R, and the concentration of R in the vein and cerebrospinal fluid was detected, and the results revealed that the concentration of R in the cerebrospinal fluid was about 0.1% of that in the vein, suggesting that a small amount of R is capable of passing through the BBB, but its effect remains unknown. A retrospective study with small sample-size noted that the application of R can not change the OS and PFS of patients, or the results achieved are different but not statistically significant. The data in the study by Birnbaum et al demonstrated that the application of R can improve CR, but the differences in OS and PFS were not statistically significant [10]. In 2014, researchers of Johns Hopkins University compared 54 patients receiving HD-MTX from 1995 to 2012 with 27 patients undergoing HD-MTX + R from 2008 to 2012, and found that the CR rate was 36% in HD-MTX group and 73% in HDMTX + Rituximab group, the median PFS and median OS in HD-MTX group were 4.5 months and 16.3 months, and the median PFS in HDMTX + Rituximab group was 26.7 months. The administreation of R every month for 1 year after CR was achieved could reduce the recurrence [17]. A research by Madle et al [18] showed that

the application of R achieves a relatively moderate effect, without evident prolongation of PFS but with prolongation of OS of patients with PCNSL. Kansara et al [19] conducted a retrospective study on 86 patients and discovered that there were no significant differences in OR and CR between HD-MTX group and HD-MTX + Rituximab group, and differences were found in the median OS and median PFS, but they were not statistically significant.

In this study, it was found that the overall response rate in Rituximab group was significantly higher than in Control group (p=0.010). Targeted therapy with R can directly reach the lesion to exert its effect, with less inhibition from the BBB, increasing the concentration of drug in the central nervous system, enhancing the inhibitory effect on tumor cells and improving the therapeutic effect [20]. Moreover, targeted therapy has less toxic side effects, and can reduce damage to other tissues [21]. The results of this study manifested that the incidence rates of gastrointestinal reactions, liver and renal dysfunction, and mucositis in patients were significantly lower in Rituximab group than in Control group. Reducing the incidence rate of adverse reactions and improving efficacy can raise the quality of life of patients, which are the best results and ultimate goals of tumor treatment. In this study, the SF-36 score of patients in Rituximab group was significantly higher than in Control group (p<0.05). The quality of life has a close association with the therapeutic effects and side effects in patients, which indirectly reflects the efficacy in tumor treatment. The results of follow-up uncovered that the OS and PFS in Rituximab group were obviously better than in Control group (p=0.013, p=0.043).

As the molecular biology technology develops, precise therapy based on different biological characteristics will be conducive to improving the prognosis of PCNSL. This study was retrospective, with limited number of patients enrolled, short follow-up time, and incomprehensive content of the follow-up. Hence, multicenter and large-sample prospective randomized studies are needed in the future to verify the conclusion made in this study.

Conclusions

In comparison with HD-MTX + WBRT, HD-MTX + R remarkably improves the quality of life and survival rate of PCNSL patients, with tolerable adverse reactions, and is worthy of popularization and application in clinical practice.

Conflict of interests

The authors declare no conflict of interests.

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