Original Article

Comparison of chemotherapy including intrathecal methotrexate combined with irradiation and irradiation alone for the treatment of primary central nervous system lymphomas

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Background

Chemotherapy has been useful in the treatment of primary CNS lymphoma as well as irradiation. In particular, methotrexate (MTX) is known as an effective agent. We compared retrospectively the effects of combined chemotherapy/irradiation and irradiation alone, and we examined several factors for possible correlations with leukoencephalopathy development.

Methods

Seventeen immunocompetent patients with primary central nervous system (CNS) lymphoma were treated by chemotherapy including intrathecal methotrexate (MTX), combined with irradiation, or irradiation alone. Group A received intrathecal MTX (3-10mg), intravenous VP-16 (100mg/m^2), and dexamethasone (10mg/m^2) as well as conventional irradiation or stereotactic radiosurgery. Group B received only conventional irradiation.

Results

Sixteen patients (8 patients in each group) were assessable. All 16 patients had a complete or partial response. Group A had statistically significant prolongation of the survival time ($p=0.0382$) compared with group B. Two patients in group A developed leukoencephalopathy, and two patients died of leukoencephalopathy. Multiple regression analysis revealed significantly between the development of leukoencephalopathy and total dose of MTX.

Conclusions

Chemotherapy, including intrathecal MTX, combined with whole-brain irradiation prolonged the survival time of primary CNS lymphoma patients. The incidence of leukoencephalopathy was related to the total dose of MTX, so careful patient monitoring is required.

(Key words : lymphoma, methotrexate, intrathecal, leukoencephalopathy)

Introduction

In recent years, marked increases in the incidence of primary central nervous system (CNS)

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lymphomas in the United States[1] and Japan[2] have been reported. The incidence increased significantly in immunosuppressed patients, as well as in immunocompetent patients[3-5]. Traditional treatment with radiotherapy provides rapid clinical and radiographic responses, but improves median survival time to only 10 to 18 months[5-13]. Intravenous high-dose methotrexate (MTX) therapy performed before irradiation is more effective than irradiation only[14-18]. However, MTX penetrates the CNS poorly, reaching subtherapeutic levels and resulting in only a transient response with conventional chemotherapy administration. Recently it was reported that rapid infusion of high-dose MTX therapy may improve patient survival[19]. Intra-arterial administration of MTX combined with osmotic disruption of the blood-brain barrier is also effective for drug delivery[20]. However, these systemic therapies require multiple blood and urine tests. The concentration of serum MTX must be monitored, and leucovorin rescue may be necessary. Careful observation for complications is required, especially in myelosuppressed patients. Additionally, general anesthesia used during intra-arterial administration may cause complications. Because of these complications, we studied a regimen that is easier to implement. We compared retrospectively the effects of combination therapy, including intrathecal MTX, intravenous VP-16, and irradiation, with the effects of irradiation alone. We also investigated the correlation of intrathecal MTX with leukoencephalopathy as delayed neurotoxicity.

Material and Methods

Patient Population

From January 1994 until January 2001, all 17 non-AIDS patients with newly diagnosed as primary CNS malignant lymphoma at Jichi Medical School Hospital or were referred to affiliated institutions were eligible for treatment with chemotherapy and cranial irradiation. We explained this study to all patients, although written informed consent was not obtained from each patient before enrollment. A surgical specimen and a cerebrospinal fluid (CSF) cytology sample were obtained from each patient by biopsy or tumor removal and lumbar puncture, before the therapy was performed. Histological examination was performed according to the criteria of the Working Formulation for Clinical Usage. There was no lower limit on the Karnofsky performance scale (KPS) score. All patients had ophthalmologic examinations to determine if ocular involvement was present. The possibility of systemic disease was eliminated with chest radiography, gallium scintigraphy, and computerized tomography (CT) of the abdomen and chest. Bone marrow biopsies were not routinely performed and depended on the physician's judgment. Evaluations for HIV-1 antibody were performed on every patient.

Therapy

We decided which therapy was performed to a patient depending on physician's judgment. Ten patients (group A) were eligible and participated in combined modality regimen. Group A received chemotherapy, including intrathecal MTX, followed by conventional irradiation. Eight patients (group B) received conventional irradiation alone.

All patients had a stereotactic biopsy or tumor removal (if herniation was anticipated

beforehand) ; tumor specimens were examined quickly. After the diagnosis of primary CNS malignant lymphoma was made, the Ommaya reservoir was inserted into the anterior horn of the right lateral ventricle of patients in group A. As a rule, chemotherapy preceded irradiation, and irradiation was started when a recurrence was observed. But, if tumor size was relatively large, irradiation was simultaneously performed. Chemotherapy consisted of : intrathecal (via the Ommaya reservoir) MTX (10mg) on days 1, 4, 8, 11, and15 ; intravenous dexamethasone (10 mg/m^2) on days 1, 2, 3, 4, and 5 ; and intravenous VP-16 (100mg/m^2) on days 1, 2, 3, 4, and 5. The duration of each chemotherapy cycle was greater than 1 month. Patients in group A received at least one cycle of chemotherapy unless the disease progressed. In group B, whole-brain irradiation and intravenous dexamethasone (10mg/m^2) for 10-20 days was started as soon as possible after the operation. Patients in group B received at least 45 Gy of whole-brain irradiation. The irradiation was fractioned into 1-2 Gy per session. There were 2 sessions per day for 5 days each week. After that, an additional 10-15 Gy boost of irradiation was locally administered if enhanced tumor areas remained. If enhanced tumor areas disappeared after 45 Gy of irradiation was completed, administration of a radiation boost depended on the physician's decision. For tumors with uveal involvement, the entire orbit was irradiated if possible.

Measurement of MTX Concentration in CSF

We measured the MTX concentration in the CSF of 5 patients 24 hours after administering MTX. CSF was obtained by lumbar puncture (n=3), except for patients who could not take the lateral position for lumbar puncture. CSF from these patients was obtained from the Ommaya reservoir (n=2).

Evaluation of Response

Karnofsky performance scale scores were measured at both the onset and the end of chemotherapy. MRI studies were obtained before the first chemotherapy and after completion of one cycle of chemotherapy including irradiation if performed. Before and after each cycle of chemotherapy and at the time of suspected recurrence, MRI studies were performed. A complete response was defined as the eradication of all tumor enhancement. A partial response was defined as tumor volume reduction of about 50% or more. Stable state was defined as tumor volume reduction of less than 50%. Progressive state was defined as the appearance of new lesions or an increase of 25% or more in the volume of the pre-existing tumor. The persistence of non-enhancing high intensity signals on T2-weighted images in areas remote from primary lesions with neurological disturbance was suspected to be leukoencephalopathy.

Statistical Analysis

The recurrence-free time and survival time from the date of diagnosis were plotted using the Kaplan-Meier product-limit method[21]. The difference in survival curves was examined for each of the potential prognostic factors by using the generalized Wilcoxon test[22]. The Mann-Whitney U test for nonparametric data was used to compare the two groups. Multiple regression

analysis was used to determine influential factors in developing leukoencephalopathy. Statistics were analyzed with StatView5J software (Abacus Concepts, Berkeley, CA).

Results

Patient Characteristics

Nine patients received the combined regimen (group A), and 8 patients received irradiation alone (group B). There was no difference in the patient characteristics at many points between the two treatment groups (Table 1), although we could not eliminate the difference of prognostic effect for any reasons(histological type, CSF cytology and so on). Eight of the

Table 1 Patient characteristics of 17 primary CNS lymphoma

Factor	Group A (n=9)	Group B (n=8)	Total
Sex			
male	4	4	8
female	5	4	9
Age(years)			
range	31-76	36-71	31-76
mean	61.1	58.4	59.8
<60	3	4	7
≧60	6	4	10
Initial KPS score			
mean	52.2	52.5	52.4
<60	5	4	9
≧50	4	4	8
Tumor location			
deep	6	8	14
superficial	3	0	3
Tumor multiplicity			
solitary	6	5	11
multiple	3	3	6
Histological type			
B-cell diffuse large	7	8	15
T-cell	2	0	2
CSF cytology			
positive	1	2	3
negative	8	6	14
Uveal involvemcnt			
positive	3	1	4
negative	6	7	13
Mode of diagnosis			
resection	4	2	6
biopsy	5	6	11

patients were men and 9 were women. The mean age was 61.1 years in group A and 58.4 years in group B. All patients had one or more tumors that were assessable on enhanced T1-weighted MRI or CT studies obtained before treatment. The lesions were solitary in 11 patients and multiple in 6. Fourteen of the 17 patients had tumors in deep cerebral structures such as basal ganglia, thalamus, and periventricular regions. Three of the 17 patients had tumors that were superficial. Diagnosis was established using a surgical specimen (Table 1). Eleven of the 17 patients had a stereotactic biopsy and 6 patients had a tumor resection. None of the 6 patients who had a tumor resection experienced severe, permanent, postoperative deficits. There were no complications after stereotactic biopsy. Based on histological examination, 15 tumors were classified as non-Hodgkin's B-cell diffuse large cell type and 2 tumors were classified as T-cell type. Uveal involvement was observed in 4 of the 17 patients. Cytological studies revealed malignant cells in the CSF of 3 of the 17 patients. Previously identified prognostic factors such as tumor location, initial KPS score, and age were compared between the two groups. There were no statistically significant differences in any of these factors.

Response to Therapy

One patient in group A had developed cirrhosis of the liver before she developed primary CNS malignant lymphoma. This patient died 5 months after the first cycle of chemotherapy because of liver dysfunction not related to the chemotherapy. This patient was excluded from the follow-up evaluation, leaving 16 patients that were assessable (Table 2). Eight of these patients were treated with combined therapy (group A), and 8 patients were treated with irradiation alone (group B).

All patients in group A had a significant response ; 4 patients had a complete response and4 patients had a partial response. Two patients received 1 cycle, 1patient received 2 cycles, 2 patients received 3 cycles, 1 patient received 4 cycles, 1 patient received 5 cycles, and 1 patient received 6 cycles of this chemotherapy. Five patients in group A received whole-brain irradiation. Two of the 5 patients received whole-brain irradiation simultaneously with chemotherapy, 2 patients received irradiation after 1 cycle of chemotherapy, and one patient received irradiation after 2 cycles of chemotherapy. One patient who achieved a complete response after simultaneous chemotherapy and irradiation developed a primary site recurrence and had stereotactic radiosurgery(16.1 Gy, 50% area). Two of the remaining 3 patients did not have a recurrence after chemotherapy, so they did not receive irradiation therapy. We could not expect their good response to chemotherapy. One patient from group A had uveal involvement and received 40 Gy of irradiation in the post eyeball area only.

All patients in group B had a significant response to whole-brain irradiation ; a complete response occurred in 6 patients and a partial response occurred in 2 patients. Boost irradiation to the local tumor region was performed in5patients from group B who had solitary tumors.

The mean initial KPS score for the entire study group was 52.4. After completion of the therapy in group A, the KPS scores improved in 6 patients for a mean of 71.3 (Table 2). After completion of the therapy in group B, KPS scores improved in4patients for a mean of 56.3. The improvement in KPS scores within each group was not statistically significant (Mann-Whitney

Table 2 Therapeutic data of 16 primary CNS lymphoma

Factor	Group A (n=8)	Group B (n=8)	Total
Chemotherapy cycle of drug			
1-2 cycle	3		3
3-4 cycle	3		3
≧5 cycle	2		2
Whole-brain irradiation dose (Gy)			
40-49	4	5	9
50-59	1	2	3
60-65	0	1	1
not performed	3	0	3
Local boost dose (Gy)			
≦10	2	1	3
11-20	0	4	4
Stereotactic radiosurgery	1*	0	1
Tumor response to chemotherapy			
complete	4		4
partial	4		4
Tumor response after irradiation			
complete	3	6	9
partial	1	2	3
not performed	4	0	4
Final KPS score			
mean	71.3	56.3	63.8
<50	2	3	5
≧50	6	5	11
Tumor recurrence			
primary site	2	3†	5
remote neuraxis	2	2	4

* 16.1Gy in 50% isodose area

† A patient relapsed concurrently in spinal cord

U test, p=0.345 for group A and p=0.753 for group B). There were no statistically significant differences between the initial KPS scores of both groups (p=0.875) or between the final KPS scores of both groups (p=0.318).

Concentration of Methotrexate in CSF

The concentration of MTX in CSF was measured in 5 patients who received 10 mg of intrathecal MTX (Fig 1). The maximum concentration ranged from 9.6 to 42μM (mean 26 μM) at 24 hours after initiation. The MTX remained above the minimum therapeutic concentration (1μM) in the CSF[23]of all 5 patients until 30 hours after the administration of MTX.

Toxicities

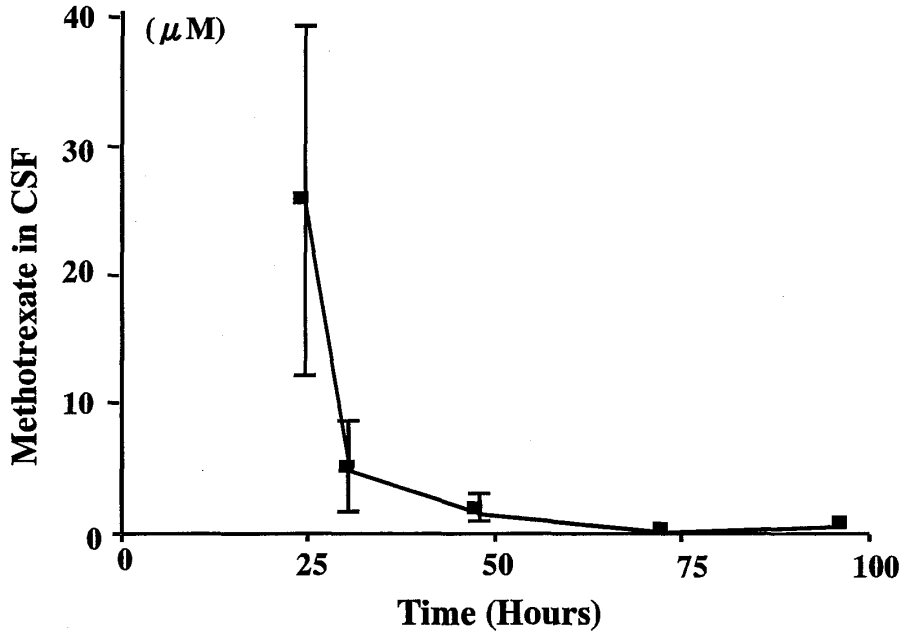

Figure 1. The time-course changes in methotrexate (MTX) concentration in the cerebrospinal fluid (CSF) of the intrathecal MTX-treated group ; plotted as the mean±SD.

A total of 27 cycles of chemotherapy were administered to the 8 patients in group A. Neuroimaging studies with contrast enhancement were repeated in all patients several times. Neuroimaging studies were repeated more often in patients who developed new neurological signs or symptoms after the initial treatment. Two patients in group A showed progressive and diffuse changes in the white matter on MRI studies with progressive neurological deterioration (Table 3). These patients were more than 60 years of age, and one of them experienced tumor recurrence after development of leukoencephalopathy. Clinical symptoms included dementia, loss of activity, gait disturbance, and epilepsy. The results of multiple regression analysis showed significantly correlation between total administered dose of MTX and occurrence of leukoencephalopathy, although no correlations between age, total dose of irradiation and occurrence of leukoencephalopathy (Table 4).We could not eliminate the possibility of other factor because the patients who received over 200mg i.t MTX had no leukoencephalopathy. Acute renal failure was not observed in all patients. Bacterial infection during 5 cycles of chemotherapy was observed in one patient who was immunosuppressed.

Recurrence-free Time and Survival Time

In group A, 4patients had a relapse 5 to 11 months after their initial diagnosis. Three of these

Table 3 Case of leukoencephalopathy

Case	Sex	Age	Total dose of IT MTX(mg)	Interval* (month)	Total dose of WBRT	Cause of death
1	M	65	320	33	50	Neurological detcrioration
2	F	62	130	4	45	Tumor recurrence

IT=Intrathecal MTX=methotrexate WBRT=Whole-brain radiation therapy

* Interval after initial treatment

Table 4 Multiple regression analysis and correlation coefficients of 3 factors in leukoencephalopathy

Factor	Standard correlation Coefficient	Standard error	t-value	*p*
Age	0.271	0.007	1.05	0.315
Total dose of IT methotrexate	0.673	0.001	2.21	0.047*
Total dose of WBRT	0.188	0.005	0.588	0.568

IT=Intrathecal WBRT=Whole-brain radiation therapy
Leukoencephalopathy : 1 if present, 0 if absent
R=0.597 * $p<0.05$

patients died from the relapsed tumor. The remaining patient died from the tumor recurrence after suffering from gradual neurological deterioration associated with leukoencephalopathy. Among the 4 patients that did not have a tumor relapse, one patient died from gradual neurological deterioration associated with leukoencephalopathy and one patient died from a bacterial infection during chemotherapy. Overall, 2 patients in group A survived and 6 patients died during the study period. In group B, 5 patients (including1patient who concurrently developed tumor recurrence in the primary site and spine) had a relapse 3 to 19 months after their initial diagnosis and all of these patients died from the relapsed tumor. The remaining 3 patients in group B had no recurrence and were alive at the end of the study.

The incidence of recurrence may be greater in group B(5 of 8 patients,) than in group A(4 of 8 patients), but there is no convincing evidence because of the small numbers involved. The location of recurrent tumors differed between the 2 treatment groups. In group A, 2 of 4 patients developed lesions in regions remote from the primary site, and 2 of 4 patients developed lesions in the primary site. Neither of the 2 patients from group A who received boost irradiation developed primary site recurrence. On the other hand, 3 of 5 patients in group B developed lesions in the primary site, including one patient who relapsed in both the brain and spine. Two of 5 patients in group B that had a tumor recurrence developed lesions in regions remote from the primary site. Only one of the 5 patients in group B who received boost irradiation developed primary site recurrence.

There was a statistically significant difference in the overall survival time (Fig 2) of the two groups ($p=0.0382$). The median survival time in group A was 22 months and the median survival time in group B was 7 months.

Discussion

To prevent the complications of high-dose MTX administration and to avoid intra-arterial administration that requires general anesthesia, we studied an easier regimen that many institutions would be capable of implementing. All patients in our study responded to this therapy. The median survival time of 8 patients who received combined chemotherapy including intrathecal MTX and irradiation was 22 months. The prolonged survival time was statistically significant ($p=0.038$) when compared with the survival time of the 8 patients who received irradiation alone (median survival time, 7 months).

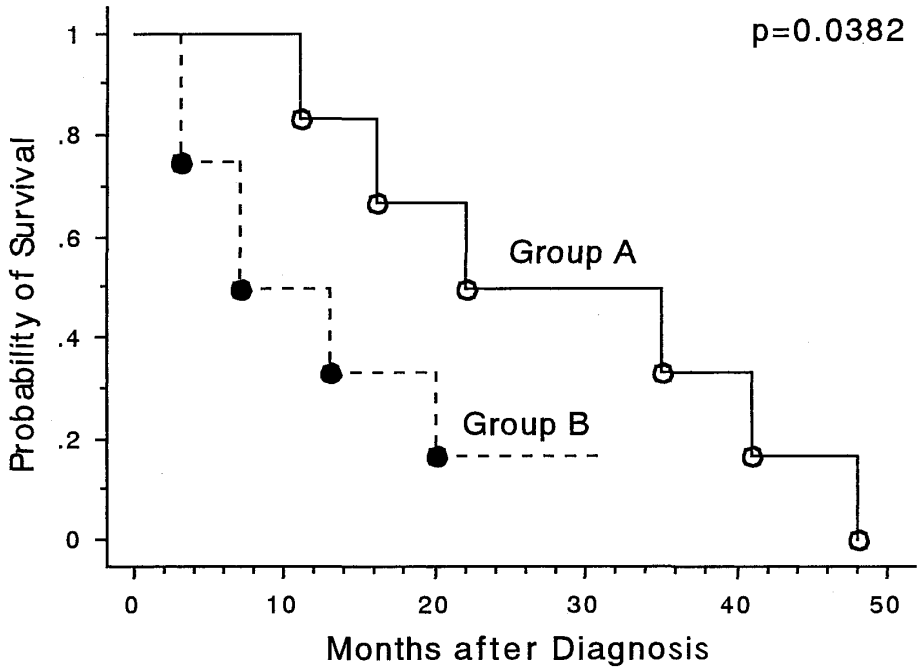

Figure 2. Overall survival for each therapeutic group was plotted using the Kaplan-Meier product-limit method.

These results were worse than those achieved in previous studies[17,19,24,25], although better than results noted for whole-brain irradiation alone. One reason may be the small number of patients enrolled in this study. We also suspect that MTX delivery into tumor lesions was insufficient. In a previous study, therapeutic levels of high-dose MTX were not sustained for more than 24 hours[26]. Previous studies also reported that intra-Ommaya MTX delivery created therapeutic levels in CSF that persisted for 48 hours, and that 2 doses may be administered per week[27,28]. These results were one reason why we employed the intra-Ommaya regimen in this study. The time-course curve of MTX concentration in CSF was significantly larger than the time-course curves reported in previous intravenous high-dose MTX studies[19,26,29]. The MTX concentration remained above the minimum therapeutic concentration (1μM) in the CSF[23] of all 5 patients that we tested until 30 hours after MTX administration. For 18% of the primary intracerebral malignant lymphoma lesions, contrast-enhanced images revealed ependymal contact with the ventricular wall[30], so we expected that intrathecal administration would be useful for the delivery of MTX. However, MTX penetration into the CNS parenchyma from the CSF may be poor. Certainly, intraventricular and intrathecal MTX infusion protocols fail to achieve therapeutic concentrations, except in the superficial 2 to 3 mm of CNS parenchyma[25]. Sufficient MTX penetration into the parenchyma may not be achieved by intrathecal MTX administration, particularly in patients with deep lesions.

As well as being a systemic lymphoma treatment[31-34], VP-16 was studied as a treatment for recurrent or refractory primary CNS lymphoma. Intensive chemotherapy, including VP-16, and followed by hematopoietic stem-cell rescue was a feasible and effective treatment[35]. The overall probability of survival at 3 years was 63.7%. Intra-arterial chemotherapy using a combination of etoposide and cisplatin was performed safely and resulted in a complete

response after 2 or 3 cycles[36,37]. This suggests that systemic chemotherapy with intra-arterial administration is able to remove areas that may cause recurrence. However, such therapy is associated with high-frequency hearing loss in primary CNS lymphoma patients[38]. In the present study intravenous administration of VP-16 was chosen because it is easy to manage ; however, intravenous delivery of this agent may be less effective than intra-arterial delivery. Additionally, intravenous administration may increase the frequency of myelosuppression. If VP-16 is adopted in a regimen of chemotherapy, the method of administration should be intra-arterial rather than intravenous, and combinations with other agents as neo-adjuvant chemotherapy should be considered.

Leukoencephalopathy is a serious complication of intraventricular MTX administration. Many investigators have described a bilateral demyelinating process of the juxtaventricular white matter ; this leukoencephalopathy may be caused by transependymal diffusion of MTX from the CSF into surrounding brain tissue[39-42]. Conventional irradiation alone can cause leukoencephalopathy and make co-operate with MTX[43-45]. Delayed neurologic sequelae of treatment usually occur more than 1 year after completion of chemotherapy[43]. In the present study, the overall incidence of leukoencephalopathy was 12.5% (2 of 16 patients). The duration between the initial treatment and the diagnosis of leukoencephalopathy ranged from 4 to 33 months. Three factors (age, total dose of intrathecal MTX, and total dose of whole-brain irradiation) were examined as possible factors in the development of leukoencephalopathy. Multiple regression analysis and correlation coefficients suggested that total dose of intrathecal MTX was significantly influential in leukoencephalopathy development. Previous studies used 12 to 15 mg doses of intrathecal MTX and a total MTX dose of about 70 to 105 mg ; but, the incidence of leukoencephalopathy in these studies was none or 11.5% for 1-year survivors[24,26]. Some investigators suggested that this apparently low incidence may be related to the administration of intrathecal and systemic chemotherapy before irradiation, which had been reported to be passively less neurotoxic than other combination modalities, such as simultaneous intrathecal MTX and irradiation[46-48]. Very careful monitoring for leukoencephalopathy is needed if intrathecal MTX administration is adopted with irradiation.

Conclusion

Chemotherapy, consisting of intrathecal MTX and intravenous VP-16, combined with whole-brain irradiation prolonged the survival time of primary CNS lymphoma patients significantly ($p=0.038$) when compared with irradiation alone. However, these results were worse than those achieved in previous studies, suggesting that the penetration of MTX into brain parenchyma was not sufficient, especially in deep tumors. The addition of some treatment modalities is required for further improvement. Because high incidence of leukoencephalopathy is significantly related to the total dose of MTX, we recommend careful observation for the development of leukoencephalopathy may be needed.

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Intrathecal methotrexate and intravenous VP-16 combined with irradiation for the treatment of primary central nervous system lymphomas

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要　約

我々は中枢神経原発悪性リンパ腫の患者で，放射線療法と化学療法を組み合わせた場合と，放射線療法単独の治療効果を回顧的に比較し，同時に副作用である白質脳症との相関も調べた。(方法)当院で治療した，16人の免疫不全のない中枢神経原発悪性リンパ腫の患者をメソトレキセートの髄腔内投与と，VP-16とデキサメサゾンの静脈内投与による化学療法と放射線治療を両方行う群（８人）と，放射線治療単独群（８人)に分け効果や副作用を比較した。(結果)両方の治療を受けた群で有意に生存期間が延長した（p＝0.038）が，この群のうち半数が白質脳症を発症し，メソトレキセートの総投与量と相関した（p＝0.047)。(結論）メソトレキセート髄腔内投与を含む化学療法と放射線治療の組み合わせは，中枢神経原発悪性リンパ腫患者の生存期間を延長するが，メソトレキセートの投与量と白質脳症の発症とは比例するため，注意深い観察が必要である。

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