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ORIGINAL ARTICLE

A nonradiation-containing, intermediate-dose methotrexate regimen for elderly patients with primary central nervous system lymphoma

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Abstract To assess the efficacy, acute toxicity, and delayed neurotoxicity of intermediate-dose methotrexate (MTX)-containing chemotherapy without whole-brain radiotherapy in the treatment of elderly patients with primary central nervous system lymphoma (PCNSL), we conducted a retrospective analysis of elderly patients ($N = 17$; median age 67) with newly diagnosed PCNSL who were treated with chemotherapy alone at Tsukuba University Hospital from January 2005 to December 2009. Induction therapy consisted of intravenous intermediate-dose MTX (1 g/m^2), ranimustine, procarbazine, methylprednisolone, and intrathecal MTX and cytarabine. Patients who achieved complete response (CR) or partial response (PR) received 5 cycles of maintenance therapy every 6 weeks. All patients in this study achieved CR or PR and received maintenance therapy. Overall survival (OS) and progression-free survival (PFS) were 100 and 80% at 1 year, and 61 and 43% at 2 years, respectively. The median OS and PFS were 36 and 20 months, respectively. Delayed neurotoxicity did not develop in any patient before lymphoma progression. In terms of response rate, OS, and PFS, the nonradiation-containing, intermediate-dose MTX-containing protocol used in elderly Japanese patients was comparable to previous protocols that consisted of more intensive chemotherapy. Acute and delayed toxicities were manageable and quality of life was maintained until progression.

Keywords PCNSL · Radiation · Methotrexate · Elderly · Dementia

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1 Introduction

Primary central nervous system lymphomas (PCNSL) (also termed primary diffuse large B cell lymphoma of the CNS in version 4 of the WHO classification) represent about 3% of all nonHodgkin lymphomas and about 3% of all primary brain tumors [1]. Historically, whole-brain radiotherapy (WBRT) was the modality of choice, but the outcome of PCNSL treated with WBRT alone was not favorable [2].

Recently, high-dose methotrexate (MTX)-based therapy with or without WBRT has become the standard therapy [1]. Supporting this is one meta-analysis of 19 prospective clinical studies, which reports that MTX $\geq$ 3 g/m^2 improves overall survival (OS) [3]. However, high-dose MTX-containing therapy is often associated with side effects such as neurotoxicity, myelosuppression, renal failure, and mucositis and requires long-term hospitalization. Combination with WBRT further worsens neurotoxicity, particularly in patients older than 60 years. It has been reported that neurotoxicity occurs in 19–83% of elderly patients treated with chemoradiotherapy [4–6].

Most cases of nonAIDS-related PCNSL are diagnosed in patients aged between 45 and 70 years [7–10], with the majority aged over 60 years [11]. In such elderly patients, quality of life (QOL) is one of the most important issues in the treatment of PCNSL as well as survival. Therefore, in

elderly PCNSL patients, WBRT should be avoided and a reduced MTX dose might be sufficient at the initial treatment.

The European Organization for Research and Treatment of Cancer (EORTC) multicenter phase II study, which evaluated the efficacy of relatively low-dose MTX without WBRT, demonstrated a low frequency of delayed neurotoxicity [12]. However, given that several polymorphic genes have been identified as encoding MTX-metabolizing enzymes [13], its pharmacokinetics and pharmacodynamics might differ among different ethnic groups. A modified version of the EORTC's protocol was started in elderly Japanese patients with PCNSL at Tsukuba University Hospital in 2005. We retrospectively analyzed the efficacy, acute toxicity, and delayed neurotoxicity of intermediate-dose methotrexate-based chemotherapy without WBRT in this cohort.

2 Patients and methods

2.1 Patients

Consecutive patients with newly diagnosed PCNSL aged over 60 years, or aged 55–60 years if they had poor performance status, were treated with the protocol described below from January 2005 to December 2009 at Tsukuba University Hospital. Stereotactic surgery or tumor resection under craniotomy was performed and diagnosis was made on the basis of histological and immunohistochemical studies. Two patients were excluded from this analysis: 1 patient initially diagnosed as having multiple sclerosis and treated with 9 courses of corticosteroid pulse therapy was subsequently diagnosed as having PCNSL; the other had a large herniating cerebral lesion and fell into a coma 2 days after the initiation of induction chemotherapy and finally died of infection 2 months later. One 58-year-old woman who had a poor performance status (Eastern Cooperative Oncology Group performance status score 4) and was considered inappropriate for the treatment with 3.5 g/m^2 MTX, the standard dose for patients aged under 60 years, was treated with this protocol and included in the cohort. According to the guideline published by the Ministry of Health, Labour and Welfare of Japan, this retrospective study was approved by the institutional review board at Tsukuba University Hospital.

2.2 Treatment protocol

The protocol reported by the EORTC Brain Tumor Group [12] was modified because of the difference in drug availability in Japan (Table 1).

Intravenous ranimustine was substituted for the oral lomustine used in the original protocol. Routine supportive treatments were given. In short, patients with normal cardiac and renal function were given 2–3 l of hydration per day. Urine alkalization with sodium bicarbonate was started 1 day before the administration of MTX. Urine pH was monitored 3 times a day during MTX administration. These supportive treatments were continued until the serum MTX concentration decreased to below 0.1 μmol/l.

Table 1 Chemotherapy protocol

Induction chemotherapy
IV MTX 1 g/m^2 days 1, 10, and 20
IV ranimustine 40 mg/m^2 day 1
PO pocarbazine 60 mg/m^2 days 1–7
IV or PO methylprednisolone 120 mg/m^2 every other day from days 1 to 20 and 60 mg/m^2 from days 21 to 45
IT MTX 15 mg + cytarabine 40 mg days 1, 5, 10, and 15
PO leucovorin 25 mg initiated 24 h after MTX administration every 6 h for 3 days
Maintenance chemotherapy: 5 more cycles every 6 weeks from day 45 in the case of CR or PR
IV MTX 1 g/m^2 day 1
IV ranimustine 40 mg/m^2 day 1
PO procarbazine 60 mg/m^2 days 1–7
IT MTX 15 mg + cytarabine 40 mg day 1
PO leucovorin 25 mg initiated 24 h after MTX administration every 6 h for 3 days

IV intravenous, *PO* per os, *MTX* methotrexate, *IT* intrathecal, *CR* complete response, *PR* partial response

Six weeks after the initiation of induction chemotherapy, response to treatment was evaluated using magnetic resonance imaging (MRI) with contrast enhancement according to the following criteria: complete response (CR), indicated by the absence of any contrast enhancement on the MRI of the brain, and partial response (PR), indicated by at least 50% reduction in the product of the perpendicular diameters of the contrast-enhanced area with no new lesions. Five courses of maintenance therapy were administered every 6 weeks for patients who achieved CR or PR (Table 1). When disease progression was observed, the protocol was stopped, and salvage or palliative therapy was selected.

2.3 Follow-up and assessment

Acute toxicity was evaluated according to version 4 of the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) (http://evs.nci.nih.gov/ftp1/CTCAE/About.html). To evaluate QOL after the chemotherapy, we referred to changes in the Barthel Index (BI) [14] and in the Manual Muscle Test (MMT) score [15] of each patient's paralyzed side at disease presentation through the period of progression. The BI assesses motor function and activities of daily living (ADL) and is often used for functional evaluation of rehabilitation after

cerebral infarction (full score 100, lowest score 0). The MMT score grades muscle power from 0 to 5, with a score of 0 representing no muscle contraction and a score of 5, normal muscular power. In addition to these, we evaluated dementia progression. All these evaluations were performed by referring to past clinical records. In the survival analysis, overall survival (OS) was defined as "death as a result of any cause" and progression-free survival (PFS) as "disease progression or death as a result of PCNSL". In each survivor, day 0 was defined as the day on which the induction therapy was initiated [16]. Survival curves were calculated by Kaplan–Meier survival analysis using StatCel2 software (OMS publishing, Saitama, Japan).

Table 2 Patient characteristics ($N = 17$)

Characteristics	
Age (years)	
Median	67
Range	58–78
Sex	
Male	10
Female	7
Histology	
DLBCL	17
Meningeal involvement	0
Ocular involvement	0

DLBCL diffuse large B cell lymphoma

3 Results

3.1 Response and survival

The characteristics and outcomes of the 17 patients with newly diagnosed PCNSL are summarized in Tables 2, 3, and 4. No patient had ocular or meningeal involvement. All the patients completed induction therapy and achieved significant response. Seven (41%) patients achieved CR, and 10 (59%) PR. Thus, all the patients received maintenance therapy. Thirteen patients finished the maintenance therapy, and 2 (patients 16 and 17) are continuing it as of the submission of this manuscript. Lymphoma progression was observed in 2 patients (patients 1 and 9) during the maintenance therapy; therefore, they received salvage therapies.

One-year PFS was 80% [95% confidence interval (CI) 60–100%] and 2-year PFS 43% (95% CI 14–73%), with the median PFS being 20 months. One-year OS was 100% and 2-year OS 61% (95% CI 34–88%), with the median OS being 36 months (Fig. 1).

3.2 Acute toxicity of induction chemotherapy

The acute and severe toxicities that occurred during the induction therapy are summarized in Table 5. The most frequent toxicity was myelosuppression. Four patients (24%) developed grade 3 thrombocytopenia or neutropenia, and 6 patients (35%), grade 4. Grade 3 anemia occurred in 2 patients (12%). Two patients (12%) had grade 3–4 aspartate

Table 3 Lesion site, diagnostic procedure and histology of patients

UPN	Solitary/multiple	Lesion site	Diagnostic procedure	Histology	CD20	CD79a	CD3	CD10	BCL-2	BCL-6	MUM-1	CD5
1	Solitary	T	Tumor resection	DLBCL	+	+	−	−	NA	NA	NA	NA
2	Solitary	C	Tumor resection	DLBCL	+	+	−	NA	NA	NA	NA	NA
3	Multiple	F, T, CC	Rt frontal lobectomy	DLBCL	+	+	−	−	−	NA	NA	NA
4	Solitary	F	Stereotactic surgery	DLBCL	+	+	−	−	−	NA	NA	NA
5	Multiple	F, T	Stereotactic surgery	DLBCL	+	+	NA	NA	NA	NA	NA	NA
6	Solitary	F	Stereotactic surgery	DLBCL	+	+	−	NA	NA	NA	NA	NA
7	Solitary	T	Tumor resection	DLBCL	+	+	−	NA	NA	NA	NA	NA
8	Solitary	T	Stereotactic surgery	DLBCL	+	+	−	NA	NA	NA	NA	NA
9	Solitary	B	Stereotactic surgery	DLBCL	+	+	−	−	NA	NA	NA	NA
10	Solitary	T	Stereotactic surgery	DLBCL	+	+	−	−	NA	NA	NA	NA
11	Multiple	F, T, CC, B	Stereotactic surgery	DLBCL	+	+	−	+	NA	NA	NA	NA
12	Multiple	F, T, C, B, S	Stereotactic surgery	DLBCL	+	NA	NA	NA	NA	NA	NA	NA
13	Solitary	F	Tumor resection	DLBCL	+	+	NA	NA	NA	NA	NA	NA
14	Solitary	F	Partial Tumor resection	DLBCL	+	NA	−	+	NA	+	+	NA
15	Solitary	T	Tumor resection	DLBCL	+	NA	NA	NA	NA	NA	NA	NA
16	Multiple	F, CC, B	Stereotactic surgery	DLBCL	+	+	−	−	+	+	+	NA
17	Solitary	B	Stereotactic surgery	DLBCL	+	+	−	−	+	NA	+	NA

F frontal lobe, *T* temporal lobe, *C* cerebellum, *CC* corpus callosum, *B* basal ganglia, *S* brainstem, *NA* not applicable

Table 4 Patients and outcomes

UPN	Age	Sex	Response	PFS (day)	OS (day)	BI/cognitive disturbance before induction	BI/cognitive disturbance after induction
1	61	M	CR	98	525	100/2	100/0
2	63	M	PR	1311+	1311+	95/0	100/0
3	68	M	CR	434	839	95/0	100/0
4	58	F	PR	612	1407+	60/2	100/0
5	62	F	PR	300	413	10/3	95/0
6	67	M	PR	1048	1075	25/3	70/2
7	74	M	CR	1777+	1777+	100/0	100/0
8	78	F	CR	433+	433	25/1	40/0
9	66	M	CR	199	372	50/3	90/1
10	60	F	CR	368	435	10/4	90/1
11	74	F	PR	806+	806+	25/3	100/0
12	64	M	PR	438+	622+	10/4	75/2
13	67	M	PR	451+	451+	45/2	90/2
14	71	F	PR	339+	339+	100/0	100/0
15	64	M	PR	238+	238+	100/0	100/0
16	73	F	PR	191+	191+	0/3	5/1
17	78	M	CR	187+	187+	25/1	60/0

UPN unique patient number, *DLBCL* diffuse large B cell lymphoma, *PFS* progression-free survival, *OS* overall survival, *BI* Barthel Index, *CR* complete response, *PR* partial response, "+" alive at the cutoff point

transaminase (AST) and alanine transaminase (ALT) elevations that were reversible without specific therapy. This liver dysfunction was recorded 3–9 days after the initiation of induction therapy and did not occur during maintenance therapy. One patient had grade 2 renal toxicity that was reversible. Stomatitis occurred in almost all the patients but without grade 3 or 4 toxicity. One patient had pneumonia (grade 3) during myelosuppression, which was managed and cured with antibiotics. Four patients (24%) had progressive cognitive disturbance soon after the initiation of the induction chemotherapy. However, this apparent worsening was transient and recovered within 3 days to a level above that shown initially in all the patients except one (patient 10), who recovered on day 48. In total, the median duration of progressive cognitive impairment was 3 days. This transient decline was assessed as being due to transient cerebral edema, although high-dose steroid therapy every 2 days might also have had some influence, particularly in Pt 10, because she recovered soon after the steroid therapy was completed.

Toxicities of maintenance therapy were rare and mild. The median hospitalization for the maintenance therapy was 4 days.

3.3 Improvement of QOL and delayed neurotoxicity

Ten (59%) patients already had cognitive disturbances due to lymphoma at presentation of the disease (Table 4).

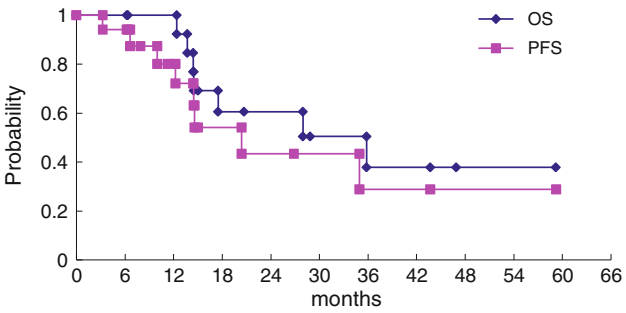

Fig. 1 Kaplan–Meier curve showing patients' overall survival (OS) and progression-free survival (PFS)

These were equivalent to the grade 2–4 cognitive disturbances described in version 4.0 of the CTCAE. After induction therapy, 4 patients recovered completely. Three patients recovered to the grade 1 level, while 3 patients still had grade 2 cognitive disturbances at the time of the last follow-up (Table 4).

We evaluated ADL improvement using the BI (Table 4). In all patients, the ADL improved and were maintained after the induction chemotherapy; the median BI scores before and after the induction therapy were 45 and 95, respectively. Unless they had lymphoma progression, no patients showed any decrease in BI scores throughout the period of maintenance therapy (Fig. 2). This was also true for the MMT scores of the paralyzed side (Fig. 3).

Table 5 Severe acute toxicities during the induction therapy ($N = 17$)

Grade	Thrombopenia	Neutropenia[a]	Anemia	Hepatitis[b]	Renal toxicity[b]	Cognitive disturbance
3	2 (12)	2 (12)	2 (12)	1 (6)	–	4 (24)
4	2 (12)	4 (24)	–	1 (6)	–	–

Patients' number and percentage are shown

[a] One patient developed grade 3 pneumonia

[b] Grade 2 hepatitis and renal toxicity occurred in 2 (12%) and 1 (6%) patient(s), respectively

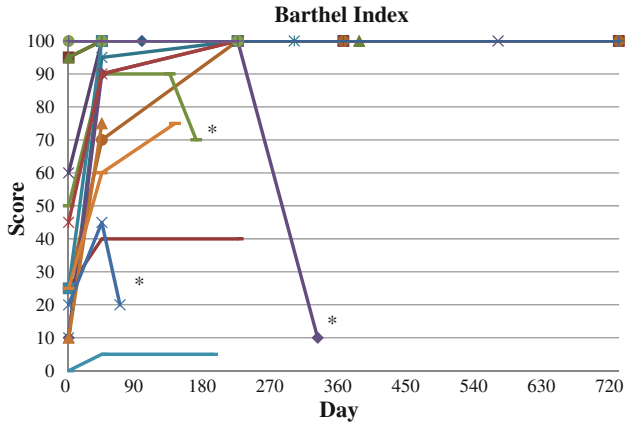

Fig. 2 Changes in patients' Barthel Index scores. Barthel Index scores were assessed from disease presentation through the period of progression. *Asterisk* Decline at the time of relapse. The other patients experienced no decline until disease progression

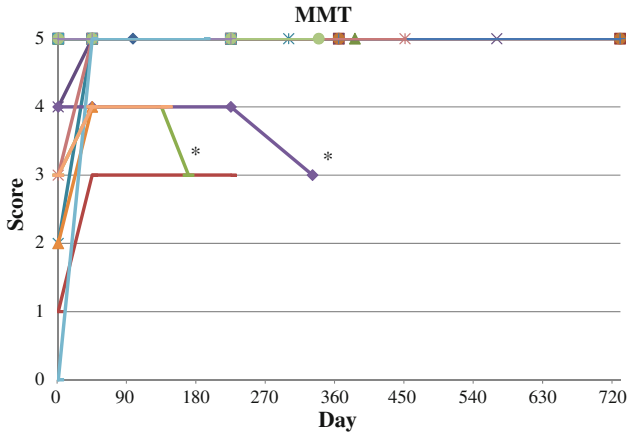

Fig. 3 Changes in manual muscle test (MMT) of paralyzed side. MMT was assessed from disease presentation through the period of progression. *Asterisk* Decline at the time of relapse. The other patients experienced no decline until disease progression

Patient 9 received 45 Gy WBRT because of relapse after 2 courses of maintenance therapy, progressed dementia and ataxia during radiation. He achieved CR after WBRT but died of progressive neurotoxicity and respiratory failure without lymphoma progression 115 days after the initiation of radiation.

4 Discussion

Delayed neurotoxicity, which is commonly associated with leukoencephalopathy, is one of the most serious complications in the treatment of PCNSL. It is typically characterized by rapidly progressive dementia followed by gait disturbance and incontinence. In general, delayed neurotoxicity occurs in elderly patients who are treated with chemoradiotherapy [17, 18]. In particular, those aged over 60 years are susceptible to this complication, and therefore, those who survive quite often have a very poor QOL. In one study, all of the patients aged over 60 years who underwent chemoradiotherapy developed clinical neurotoxicity [19].

To the best of our knowledge, 6 studies of elderly PCNSL treated with chemotherapy alone have been reported (Table 6). As mentioned, our protocol was based on one of these, the EORTC's study [12], which used a relatively low-dose MTX without WBRT.

In both the current cohort and that of the EORTC's study, systemic MTX used in the initial treatment and in total was much less than that used in other studies. Nevertheless, comparable OS was achieved, although the higher doses of intrathecal MTX used in both cohorts might have affected the outcome. The incidences of dementia varied among the previous reports. In the EORTC's study, 3 (8%) of the 38 patients developed delayed neurotoxicity. In our cohort, no patients showed progression or new development of dementia. Also notable in this protocol was the very low incidence of impaired QOL and the short admission period for the maintenance therapy.

Further studies are needed to determine whether intrathecal MTX is indeed required in place of systemic MTX. Nevertheless, adverse events are very likely to be lower after intrathecal MTX plus intermediate-dose systemic MTX than after high-dose systemic MTX. As a conclusion, systemic MTX could be reduced for the treatment of elderly PCNSL.

Abrey et al. [5] reported that addition of 45 Gy WBRT to 3.5 g/m^2 MTX resulted in increased incidence of dementia

Table 6 Comparison of reported outcomes of elderly PCNSL with those of the present study

Study	No. of Pt	Median age (years)	Initial treatment	PFS, median (months)	OS, median (months)	Dementia (%)	Systemic MTX, total (g/m^2)	IT MTX, total (mg/body)
Freilich [22]	13	74	MTX 1–3.5 g/m^2 + IT + PCZ ± VCR/TTP/AraC	–	30.5	0	4–17.5	60–72
Ng [23]	10	72.5	MTX 8 g/m^2	18	36	0	41.5	0
Abrey [5]	22	70	MTX 3.5 g/m^2 + IT + PCZ + VCR	–	33	5[a]	17.5	60
	12	67	+ RTX 45 Gy	–	32	83	17.5	60
McAllister [24]	38	>60	IA MTX[b] 5 g/m^2 + CPA + VP-16 + PCZ + dexamethasone	18.0 (in responders)	16.3	0	60	0
Illerhaus [25]	30	70	MTX 3 g/m^2 + CCNU + PCZ	5.9	15.4	6.7[a]	27	0
Hoang-Xuan [12]	*50*	*72*	*MTX 1 g/m^2 + IT + CCNU + PCZ + mPSL*	*6.8*	*14.3*	*8*	*8*	*135*
Present study	*17*	*67*	*MTX 1 g/m^2 + IT + MCNU + PCZ + mPSL*	*20*	*36*	*0*	*8*	*135*

The present study and the EORTC report cited within the text are given in italics

No. of Pt number of patients, *PFS* progression-free survival, *OS* overall survival, *MTX* methotrexate, *IT* intrathecal (administration), *PCZ* procarbazine, *VCR* vincristine, *TTP* thiotepa, *AraC* cytarabine, *RTX* radiotherapy, *IA* intra-arterial, *CPA* cyclophosphamide, *VP-16* etoposide, *CCNU* lomustine, *MCNU* ranimustine, *mPSL* methylprednisolone

[a] The dementia progressed after whole brain irradiation because of relapse or MTX toxicity

[b] Intra-arterial MTX after blood–brain barrier disruption with intra-arterial mannitol

(from 5 to 83%) without a significant change in OS (Table 6). Taken together, 3.5 g/m^2 of MTX plus WBRT should be avoided, at least for elderly patients.

The PFS and OS were longer and the development of dementia was less frequent in this cohort than in that of the EORTC's study, although we are unable to make a straightforward comparison. If we would compare them, the younger median age of the patients of this cohort (5 years younger) might account for the better PFS and OS (Table 6). Differences between European and Asian populations in pharmacokinetics and pharmacodynamics of MTX and the effect of ranimustine instead of lomustine might also have affected the outcomes of the present study.

Recently, rituximab has been explored for PCNSL in MTX-containing regimens with [20] or without [21] radiation. Although its efficacy remains to be defined by randomized trials and the mechanisms for rituximab to cross blood–brain barrier should also be elucidated, reported results apparently indicate that the incorporation of rituximab may be promising. We are currently planning a prospective study of a protocol combining rituximab with the one described in the paper.

In conclusion, a 2-year overall survival rate of 61% without acute or delayed therapy-related neurotoxicities such as dementia was achieved by a nonradiation-containing, repeated intermediate-dose MTX regimen in Japanese patients. Because of its efficacy and toxicity balance, this may be one of the protocols of choice for elderly patients with PCNSL, leaving a question of rituximab incorporation.

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