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FEASIBILITY AND EFFICACY OF INDIVIDUALIZED RADIATION THERAPY FOR PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA: RADIATION TREATMENT PLANNING ACCORDING TO TREATMENT RESPONSE BY RADIOGRAPHIC ASSESSMENT

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Abstract:

Background: To assess the feasibility and efficacy of individualized treatment selection in radiation therapy (RT) for primary central nervous system lymphoma (PCNSL) according to treatment response by radiographic assessment.

Methods: The details of recurrence and change in performance status (PS) were assessed in 31 patients with histologically confirmed PCNSL treated between 2000 and 2016. During the treatment period, radiographic assessment was conducted, and RT planning (RTP) was determined individually by treatment response.

Results: At a median follow-up of 28.2 months, 9 patients were alive 7 of whom were relapse-free. The two-year overall survival (OS) and progression-free survival (PFS) rates were 69.3% and 52.7%, with median survival times (MSTs) of 36.5 months and 24.4 months, respectively. The two-year local recurrence rate was 40.5% and the median time to local recurrence from treatment initiation was 27.9 months. All patients were scheduled to receive whole-brain RT (WBRT) and subsequent partial-brain RT (PBRT), with a median total dose to the tumor bed of 46 Gy and a median WBRT dose of 30 Gy. Eight patients received reduced-dose WBRT (rd-WBRT) (< 30 Gy), and 13 patients who could not achieve a complete response (CR) during the RT period received additional boost radiation after WBRT and PBRT, with a median dose of 6 Gy. Over 70% of local recurrence occurred within areas in which only WBRT was conducted (median dose of 30.3 Gy). The two-year occurrence rate of neurotoxicity over grade 2 was 49.5%. PS at 24 months after RT was maintained in 12 patients.

Conclusions: Individual RTP using radiographic assessment led to reasonable survival and disease control rates with mild treatment-related toxicity. For patients not receiving chemotherapy or lacking a CR after chemotherapy and WBRT, WBRT followed by PBRT and additional boost radiation for poor RT responders might be effective. However, even for patients with CR after chemotherapy, a WBRT dose of 30 Gy or higher might be necessary for local control.

Key words: Primary central nervous system lymphoma, Radiation therapy, Treatment response evaluation, Whole brain radiation dose, Boost irradiation

Background

Primary central nervous system lymphoma (PCNSL) is a rare form of extranodal non-Hodgkin's lymphoma that is typically confined to the brain, eyes, and cerebrospinal fluid, but without evidence of systemic spread. Recently, a rising incidence of PCNSL among men and women aged over 65 years of 1.7% and 1.6% per year has been recognized[1), 2)], which is reported to represent about 4.6% of intracranial neoplasms in Japan[3)]. Diffuse large B-cell lymphoma is the most common histological subtype of PCNSL and is expected to have good response to high-dose methotrexate (HD-MTX)-based chemotherapy and radiotherapy, as seen in other systemic lymphomas, though patient outcome is actually poor[4)], with a high rate of tumor recurrence[5)]. Considering the invasive characteristics and multifocal occurrence of PCNSL[6)], whole brain irradiation has been commonly prescribed.

Radiation monotherapy has been shown to have poor survival in this setting, with a median overall survival ranging from 11 to 18 months and a 5-year survival rate of less than 18%[5), 7)]. Therefore, recent standard treatments for PCNSL have included HD-MTX-based chemotherapy, followed by radiation therapy (RT)[8), 9)]. This combined treatment modality has prolonged survival[10-15)], but treatment-related neurotoxicity has become a major concern[10), 16-18)]. As age and WBRT are considered to increase neurotoxicity[10), 12), 16), 17), 19-22)]. efforts to solve this problem have been undertaken, with special focus on elderly patients[23)] by excluding WBRT[24), 25)], reducing the WBRT dose[26-29)], or irradiating the partial brain instead of the whole brain[30)]. Although excluding WBRT or reducing the WBRT dose resulted in a lower incidence of neurotoxicity without compromising outcome, some previous studies have shown that this resulted in suboptimal disease control[26), 31), 32)]. Therefore, the optimal WBRT dose and total RT dose for PCNSL patients remains uncertain.

At our institution, we prescribe the WBRT dose individually according to patient pre-RT conditions (age and chemotherapy response), carry out short-term radiographic assessments of treatment response, and then plan for boost radiation. Despite the rarity of PCNSL, we were able to followup 31 patients. The aim of this study was to retrospectively assess outcomes and late neurotoxicity using this individualized treatment strategy and to propose optimal planning of radiation therapy for PCNSL patients.

Methods

Study group

Immunocompetent patients with newly diagnosed, histologically confirmed PCNSL presenting at our institution between 2000 and 2016 were analyzed. Diagnosis was based on either stereotactic biopsy (17 patients) or surgical resection (either complete or partial, 14 patients). All patients underwent staging evaluation using cranial magnetic resonance imaging (MRI) before the initial treatment. To exclude evidence of systemic lymphoma, patients underwent any of the following radiographic assessments before treatment: abdominal, thoracic computed tomographic (CT) imaging, gallium scintigraphy, or ^{18}F-fluorodeoxyglucose-positron emission tomography imaging. Patients with lymphoma outside the brain and who were suspected

of having secondary central nervous system (CNS) lymphoma were excluded. When clinical suspicion of ocular involvement was present, slit lamp examination was conducted by ophthalmologists. Cytological analysis of cerebrospinal fluid (CSF) was performed in 8 patients. This study was approved by Nara Medical University Ethics Committee (approval number, 1212).

Surgery and chemotherapy

Surgery was limited to biopsy, with no further resection being performed when a diagnosis of malignant lymphoma was determined from frozen-section diagnosis. In the case of an uncertain pathological diagnosis from frozen sections during operation, further resection was performed. Pre-RT chemotherapy with 3.5g/m^2 of intravenous HD-MTX was planned for day 1, followed by 15-mg leucovorin rescue on days 2-5 of every other week. In some patients, the MTX dose was reduced in consideration of patient general condition. When tumor progression was determined by MRI, despite HD-MTX delivery, chemotherapy was interrupted and immediately switched to RT.

Radiation therapy

All patients were scheduled to receive WBRT and subsequent partial-brain RT (PBRT). Furthermore, in cases with residual contrast-enhanced (CE) lesions on MRI during the WBRT period, local boost radiation was added following PBRT. The whole brain, including the first 2 cervical vertebrae and the posterior half of the orbits, was irradiated by 2 opposed lateral fields using 6 or 10 MV X-rays. In cases where ocular involvement was suspected, the entire orbits were included in the WBRT field. After irradiating the whole brain (considering the area as a low-risk clinical target volume; CTV), the radiation field size was reduced; initially, fields were set with 1-2 cm margins from the area showing high-intensity on T2WI/FLAIR imaging on the pre-treatment MRI (considering the area a high-risk CTV). The boost-radiation fields were then reduced to the residual CE lesion with a narrow margin on MRI, which was conducted during the WBRT period (considering the area as the residual gross tumor volume; GTV). WBRT dose was determined according to response to chemotherapy and patient age at the initiation of RT. Boost dose and field characteristics were individually determined by considering the radiographic response during WBRT.

Response evaluation

Response to treatment was evaluated radiographically with cranial MRI or CT before starting the initial treatment, as well as at the completion of each treatment. When initially treated by surgery (other than biopsy), assessments were made before and after surgery. For HD-MTX chemotherapy, response assessments were made between MTX treatment courses. As for RT, we also assessed tumor response during the WBRT period, in addition to pre- and post-RT. Response criteria were defined as follows33): complete response (CR) was the complete resolution of CE lesions on MRI or CT; partial response (PR) was a $\geq$ 50% decrease in tumor growth; progressive disease (PD) was an unequivocal increase in tumor size; and, stable disease (SD) included all other situations. World Health Organization (WHO) performance status (PS)

was used to assess patient quality-of-life at the start and completion of RT, as well as 6, 12, and 24 months after the completion of RT. Acute treatment-related toxicities were scored using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0[34]. Treatment-related neurotoxicity was defined as progressive neurologic or cognitive impairment in the absence of recurrent lymphoma. Formal neuropsychological assessment was not performed, and neurotoxicity was assessed only on clinical grounds.

Statistical considerations

Overall survival (OS) was assessed from the start of treatment until death from any cause or the date of the last follow-up. Progression-free survival (PFS) was assessed from the start of treatment until the first instance of disease progression. OS and PFS were estimated with the Kaplan-Meier method, compared using the log-rank test, and modelled by the Cox proportional hazards method. We used the cumulative incidence method to estimate local failure rates, which were compared using Gray's test and modelled with the Fine-Gray method. Statistical significance was assessed at $p < 0.05$. All statistical analyses were performed with EZR software (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, EZR is a modified version of the R interface that is designed to add statistical functions frequently used in biostatistics.

Results

Patient characteristics

Thirty-one patients were analyzed with a median follow-up of 28.2 months (range : 1.68-78.70 months). Nine patients are alive at the last follow-up (June 2017), with a median follow-up time of 20.7 months (range : 8.78-48.50 months). Among the remaining 22 patients, 20 died in the follow-up period and 2 were lost to follow-up. The median patient age was 66 years (range : 36-84 years) and 74.2% were ≥ 60 years-old. All except 1 patient, who was not examined for Human Immunodeficiency Virus (HIV), were HIV negative. This tendency reflects Japan's typical patient population that has a low HIV-positive rate. At their first visit to our department, 18 patients (58.1%) were PS 3-4, PS 0-1 in 11 patients, PS 2 in 2 patients, PS 3 in 9 patients, and PS 4 in 9 patients. Four patients had symptoms such as visual impairment and diplopia at diagnosis, and were considered to have ocular involvement. Diffuse large B-cell lymphoma was the most common histologic subtype observed in 26 patients (83.9%); the remaining 5 patients had high grade B-cell lymphoma, but their subtypes were not specified. Lactate dehydrogenase levels were elevated in 17 patients. Multiple tumors were detected in 11 patients, and 20 patients had tumors that were deep lesions of the brain (such as basal ganglia, corpus callosum, brainstem, and/or cerebellum). The median tumor size at diagnosis was 50 mm (calculated as the sum of all CE lesions on the axial images of gadolinium-enhanced MRI). The details of the patient characteristics are shown in Table 1.

Table 1. Patients characteristics (n=31)

		N (%)
Age (y)	Median (range)	66 (36–84)
	≥ 60	23 (74.2)
	< 60	8 (25.8)
Gender	Male	18 (58.1)
	Female	13 (41.9)
WHO PS	0–1	11 (35.5)
	2	2 (6.5)
	3	9 (29.0)
	4	9 (29.0)
LDH	Elevated	17 (54.8)
	WNL	14 (45.2)
Surgery	Biopsy	17 (54.8)
	Resection	14 (45.2)
Multiple lesions		11 (35.5)
Involvement of deep structures*		20 (64.5)
Tumor size	≥ 40 mm	20 (64.5)
	< 40 mm	9 (29.0)
	unmeasurable	2 (6.5)
Initial treatment	Surgery	14 (45.2)
	Chemotherapy	12 (38.7)
	RT	5 (16.1)
Chemotherapy completion	Completed	14 (35.2)
	Interrupted	9 (29.0)
	No chemotherapy	8 (25.8)
Response to chemotherapy (n=23)	CR	6 (26.1)
	PR	11 (47.8)
	SD or PD	6 (26.1)
Total RT dose (Gy)	Median (range)	46 (34–55)
	≥ 46	12 (38.7)
	< 46	19 (61.3)
WBRT dose (Gy)	Median (range)	30 (0–40)
	≥ 30	23 (74.2)
	< 30	8 (25.8)

Abbreviations: *LDH* lactate dehydrogenase, *WNL* within normal limit, *HD-MTX* high dose-methotrexate, *RT* radiation therapy, *WBRT* whole brain radiation therapy, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease

*Deep structures include basal ganglia and/or corpus callosum and/or brainstem and/or cerebellum

Treatment

The initial treatment was surgery in 14 patients (partial–, subtotal–, or total–resection), HD–MTX–based chemotherapy in 12 patients, and RT in 5 patients. Two patients were initially diagnosed as having multiple sclerosis and underwent steroid pulse therapy (methylprednisolone 1 g/day for 3days) before the initial treatment. HD–MTX–based chemotherapy was delivered in 23 patients, with a median dose of 3.5 g/m^2 for 3 courses (range, 2.275–5.000 g/m^2 for 1–6 courses). In 8 patients, chemotherapy was not performed due to poor baseline cognitive function, poor PS, and comorbidities. Radiation monotherapy was conducted in case neither surgery nor chemotherapy was considered tolerable (n=5).

Thirty patients underwent WBRT with a median dose of 30 Gy (range, 24–40 Gy). PBRT of 10 Gy (range, 5.4–36.0 Gy) was delivered to 30 patients; among these, 13 patients with residual CE lesions, observed on MRI conducted during the WBRT period, were given boost radiation of 6 Gy (range, 4–10 Gy). One patient refused WBRT, with PBRT of 36 Gy being initially performed,

followed by a 10 Gy boost. Hence, a median total dose given to the tumor bed was 46 Gy (range, 34–55 Gy).

For each group divided by response to HD-MTX, the CR group received a total median dose of 37 Gy (median WBRT dose, 27 Gy), the non-CR group received 46 Gy (WBRT, 30 Gy), and those who did not receive HD-MTX received 50 Gy (WBRT, 40 Gy). The WBRT dose was reduced to lower than 30 Gy (median, 26 Gy; range, 0–28 Gy) in 8 patients: 6 who achieved a good PR~CR after the preceding chemotherapy, 1 who refused to receive a higher RT dose owing to concerns of late neurotoxicity, and 1 who was considered unable to tolerate WBRT owing to poor baseline cognitive condition. Radiographic assessments were made 2–10 times during the initial treatment. During the RT period, radiographic assessment was conducted on the day on which the median dose of 22 Gy (range, 10–50 Gy) was delivered.

Response and survival

By the last follow-up on June 2017, 9 patients were alive, and 20 patients were dead, with a median follow-up time of 28.2 months. The 2 patients lost in follow-up were considered dead for the statistical analysis. Among the 20 patients, 15 died from tumor progression or recurrence, while 5 died of pneumonia. As the exact relationship between pneumonia and PCNSL is equivocal, we included these 5 patients as PCSNL-related death (Table 2).

Table 2. Cause of death in 5 patients with mortality considered to be related to PCNSL

Case	
1	Died of pneumonia, which occurred in an immunosuppressed state caused by MTX for tumor recurrence.
2	Changed hospital after onset of cognitive dysfunction and the cause of death was reported as pneumonia.
3	General condition was bad at the start of RT with convulsions often seen. During the RT period, aspiration pneumonia had occurred due to convulsion, and eventually led to congestive heart failure and pulmonary edema.
4	(same as case 2)
5	Being followed-up in ambulatory care, but slipped at home and had difficulty walking. Eventually, this patient was admitted to hospital and developed pneumonia.

Abbreviations : *PCNSL* primary central nervous system lymphoma, *MTX* methotrexate, *RT* radiation therapy

The median follow-up time was 20.7 months for those patients who were still alive by the end of the follow-up period. By the end of chemotherapy, 6 of 23 patients (26.1%) had a CR, 11 (47.8%) had a PR, and 2 (6.5%) had SD. Tumor progression was observed among 4 patients (12.9%). All patients but one had tumor size reduction after the completion of RT; the only case with no change in CE lesion size was considered to be a post-operative change (scar) by discussion with neuroradiologists and neurosurgeons. Therefore, the overall response rate after RT was 96.8% (CR, 32.3%; PR, 64.5%). The median survival time (MST) was 36.5 months, and the 1- and 2-year Kaplan-Meier estimates of OS were 77.0% and 69.3%, respectively. The overall survival for the 31 patients from the initiation of either treatment is shown in Fig. 1. Younger age and good PS tended to improve OS, though not significantly; for patients under and at least 60 yearsold, the 2-year OS rates were 87.5% and 62.1%, and the MST was 48.1 months and 29.8 months, respectively (p=0.09, Fig. 2a). For patients with a PS of 0–2 and 3–4, the 2-year OS rates were

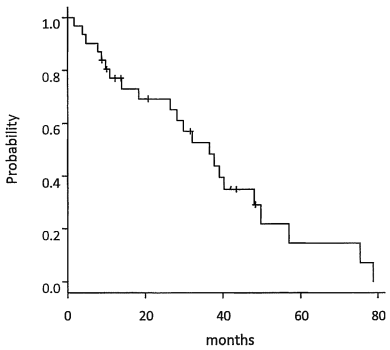

Fig. 1. Kaplan-Meier curve for overall survival for the entire study group.

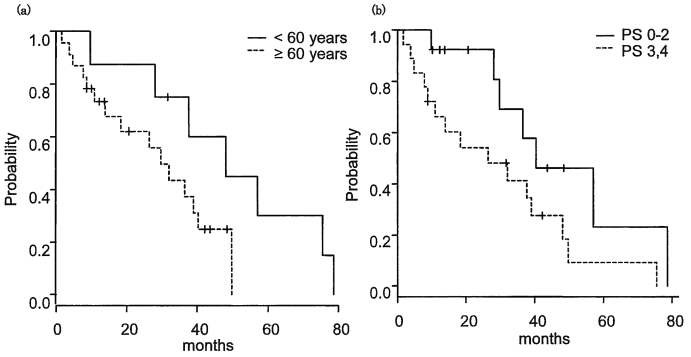

Fig. 2. (a) Overall survival curve according to age. Younger patients had better OS compared to those over 60 years-old (p=0.09).(b) Overall survival curve according to PS.Patients with PS 0–2 showed better OS compared to those who had PS 3–4 (p=0.06).

Table 3. Survival rates and MST by patients' characteristics

			OS	PFS	Local control			
		N	MST (Mo)	*p* value	MST (Mo)	*p* value	MST (Mo)	*p* value
Age	≥ 60	23	29.8	0.09	18	0.624	24.6	0.733
	< 60	8	48.1		31.3		31.3	
Sex	Male	18	39.1	0.344	27.9	0.118	27.9	0.584
	Female	13	18.4		10.4		17.2	
Performance status	0-2	13	40.3	0.0626	33.9	0.0676	33.9	0.165
	3,4	18	26.5		12.4		17.2	
LDH	elevated	17	36.5	0.883	24.4	0.255	24.6	0.711
	WNL	14	37.8		22.5		27.9	
Tumor location	deep	20	37.8	0.715	24.6	0.683	27.9	0.32
	peripheral	11	36.5		18		48.1	
Initial treatment	surgery	14	39.1	0.107	27.1	0.0163*	39.1	0.077
	chemotherapy	12	37.8		27.9		27.9	
	radiation	5	13.9		10.4		14.6	
HD-MTX	yes	23	36.5	0.254	27.9	0.269	33.9	0.74
	no	8	32.1		13.5		15.9	
chemotherapy completion	completed	14	36.5	0.42	27.9	0.255	27.9	0.694
	no chemotherapy or interrupted	17	32.1		12.4		17.2	
response to chemotherapy	CR+PR	17	36.5	0.488	27.9	0.525	27.9	0.167
	SD+PD	6	33.3		27.9		48.1	
WBRT dose	≥ 30 Gy	23	365	0.893	17.2	0.95	279	0.664
	< 30 Gy	8	33.8		24.6		24.6	

Abbreviations: *MST* median survival time, *OS* overall survival, *PFS* progression free survival, *Mo* month, *LDH* lactate dehydrogenase, *WNL* within normal limit, *HD-MTX* high dose-methotrexate, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, WBRT whole brain radiation therapy

* Indicated $p < 0.05$

92.3% and 54.2%, and the MSTs were 40.3 months and 26.5 months, respectively (p=0.06, Fig. 2b). Survival rates and MST according to patient characteristics are listed in Table 3.

The 2-year PFS rate was 52.7% (Fig. 3). The univariate analysis showed that initial treatment with chemotherapy significantly increased PFS (Table 3). Having a good PS and male gender tended to increase PFS, though this was not significant. When divided by chemotherapy completion, the prognosis tended to be better in patients who completed planned chemotherapy than in those who could not receive chemotherapy or in whom chemotherapy was interrupted because of poor response; the 2-year OS, PFS, and local recurrence rates for these patients were 85.1% and 56.1%, 77.1% and 33.1%, and 22.9% and 54.7%, respectively.

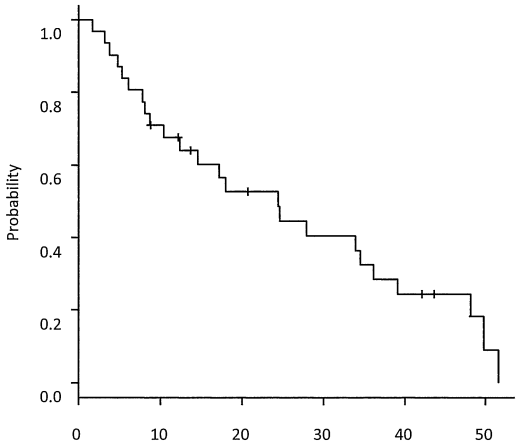

Fig. 3. Kaplan-Meier curve for progression-free survival for the entire study group.

Tumor recurrence

Sixteen patients had relapse after treatment completion, including 2 patients with out-of-field recurrences, whose recurrent sites were the cervical-thoracic and lumbar-sacral spinal cord, which occurred at 10.3 months and 6.1 months post-treatment, respectively. Of the 16 patients with tumor recurrence, 5 could not receive chemotherapy due to poor baseline condition. The chemotherapy responses of the other 11 patients were CR for 3, PR for 5, SD for 1, and PD for 2 patients. Recurrence was observed in 3 patients with a CR after chemotherapy, which occurred in the area where only WBRT was administered. According to total RT dose, recurrence rates were similar between the groups who did and did not receive RT doses higher than 46 Gy; the numbers of patients with tumor recurrence were 10/19 (52.6%) and 6/12 (50%) in these groups, respectively. As for rd-WBRT, the numbers of patients with tumor recurrence who did and did not receive rd-WBRT were 5/8 (62.5%) and 11/23 (47.8%), respectively. Fourteen patients had relapses in the brain, which were defined as local (in-field) recurrences. The details of patients with local recurrence are listed in Table 4.

The 2-year local recurrence rate was 40.5% (1-year, 25.8%) and the time to local recurrence ranged from 3.16-74.00 months, with a median time of 21.2 months. There were 31 in-field recurrences for 14 patients, and a median RT dose of 40 Gy was delivered to the recurrence sites. Most of these recurrences (71%) occurred in areas where only WBRT was conducted, with

Table 4. Details of patients with recurrence

Pt no	Age, Sex	Primary tumor location	Initial treatment	HD-MTX	Chemotherapy response	RT dose (Gy)				RT response	Dose irradiated to recurrent site ((Gy) × fractions) recurrence site[a]	
						total	WBRT	limited field	boost			
1	71, M	Left cerebellar hemisphere	HD-MTX	3.5g/㎡ 5courses	CR	36	24	12	-	NC	24	C
2	51, F	Left putamen~caudate ~pallidum	HD-MTX	3.5g/㎡× 6courses	CR	36	26	10	-	NC	26	C
3	66, M	Left corona radiata	HD-MTX	3.5g/㎡× 6courses	CR	38	28	10	-	CR	28	C
4	64, M	Right and left frontal lobe	surgery (partial resection)	3g/㎡× 3courses	PR	46	30	10	6	PR	30 × 4, 46 × 2	B*1, C*5
5	60, M	Right putamen	HD-MTX	4g/㎡× 6courses	PR	44	26	10	8	PR	36	B
6	47, M	Left striatum~frontal lobe, Right temporal lobe	HD-MTX	3.5 g/㎡× 5courses	PR	41.4	30.6	5.4	5.4	PR	30.6	C
7	36, M	Left frontal lobe~corpus callosum~thalamus	HD-MTX	3.5g/㎡× 5courses	PR	46	34	6	6	CR	46	A
8	84, M	Left occipital lobe~corpus callosum~hippocampus	HD-MTX	2.275g/ ㎡ (65% dose) × 3courses	PR	46	36	10	-	PR	46	A
9	71, F	Pituitary gland	surgery (partial resection)	3.5g/㎡× 1course	SD	48	36	12	-	CR	0	D
10	66, F	Left parietal lobe	surgery (total resection)	3g/㎡× 1course	PD	50	36	8	6	CR	36	C
11	51, M	Right frontal lobe	surgery (partial resection)	3.5g/㎡× 3courses	PD	55	30	16	9	PR	30	C
12	40, M	Right temporal ~parietal lobe	surgery (subtotal resection)	-	-	50	30	20	-	CR	30 × 3, 0 × 2	C*3, D*2
13	46, F	Right thalamus ~parietal lobe	surgery (partial resection)	-	-	40	40	-	-	PR	40 × 5	A*1, B*1, C*3
14	75, F	Left frontal lobe	RT	-	-	50	40	10	-	CR	40 × 3, 50 × 2	B*1, C*4
15	53, M	Left temporal~frontal lobe~corpus callosum	RT	-	-	52	40	6	6	PR	40, 52 × 2	A*2, C*1
16	75, F	Left putamen ~corona radiata	RT	-	-	50	40	10	-	PR	0	D

Abbreviations: *HD-MTX* high dose-methotrexate, *RT* radiation therapy, *WBRT* whole brain radiation therapy, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *NC* no change, *M* male, *F* female
aRecurrent site was divided into 4 groups based on pre-treatment MRI; *A* recurrence within CE lesion, *B* recurrence within T2-FLAIR high lesion, *C* recurrence outside either CE or T2-FLAIR high lesion, *D* out-of-field recurrence

a median dose of 30.3 Gy (range, 24–40 Gy). Six recurrences from 4 patients occurred within areas irradiated with a median dose of 46 Gy (range, 46–52 Gy), which were within the boost fields. 1 patient could not receive HD-MTX, and 1 received 65% of the typical MTX dose, due to poor baseline conditions. The 1 patient with decreased MTX dose did not receive WBRT. The remaining 2 patients showed a PR after HD-MTX treatment, and a PR and CR after RT. Five recurrences occurred within the area of the CE lesion determined by pre-treatment MRI, 4 within the area of the T2WI/FLAIR high lesion, and the remaining 22 occurred outside of the former radiographic areas. Though there were no significant improving factors for local control, patients who were initially treated by surgery tended to have better local control when compared to other treatments (p=0.08, Table 4).

Adverse events and PS change

Adverse events were evaluated based on CTCAE version 4.0. Acute toxicities such as radiation sickness, dermatitis, conjunctivitis, otitis media, and otitis externa were observed with severities no higher than grade 4 (Table 5). Grade 3 radiation dermatitis was seen in 2 patients and grade 3 conjunctivitis was observed in 1 patient.

Table 5. Acute toxicity

	Grade (Pt no.)			
	1	2	3	4
Dermatitis	18	4	2	0
Conjunctivitis	2	3	1	0
Nausea	5	0	0	0
Otitis media/externa	3	1	0	0

Eighteen patients (58.1%) developed late neurotoxicity greater than grade 2 (including 5 who were grade [3], which was defined as memory deterioration, aphasia, apraxia, loss of activity, or progression of primary existing cognitive impairment, after a median 26.8 months from the start of the initial treatment (range, 4–75 months). Of the 18 patients who developed cognitive impairment, 77.8% occurred within 2 years from treatment initiation, with the median time to occurrence being 15.2 months; 1- and 2-year occurrence rates were 22.9% and 49.5%, respectively. Among these patients, 11 had pre-existing cognitive impairments at the start of RT. There was no effect from age ($\geq$ 60 years-old vs. $<$ 60 years-old) and WBRT dose ($\geq$ 30 Gy vs. $<$ 30 Gy) on the occurrence of neurotoxicity, though the time to occurrence was longer in younger patients and those who underwent rd-WBRT.

At the end of RT, PS increased or did not change in 30 patients (1 died during RT); after 6 months, 23 patients had increased or maintained PS, whereas 5 had declined PS (PS declined due to tumor recurrence in 2 patients and 3 died from PCNSL and pneumonia) or died, and 3 were lost to follow-up. After 12 months, PS was either increased or maintained in 16 patients, whereas in 7 patients had PS declined or died (2 died from PCNSL between 6 and 12 months after RT), and 8 patients were lost to follow-up including 4 who did not reach the assessment period. After 24 months, PS was either increased or maintained in 12 patients, whereas 13 patients had declined PS or died (PS declined in 2 because of late neurotoxicity and leg deficiency, 4 died of PCNSL between 12–24 months after RT), and 6 patients were lost to follow-up, including 4 who did not reach the assessment period (Fig. 4). Among those whose PS increased by 24 months after the completion of RT, the median WBRT dose was 30 Gy; in contrast, the dose was 36 Gy in those who declined.

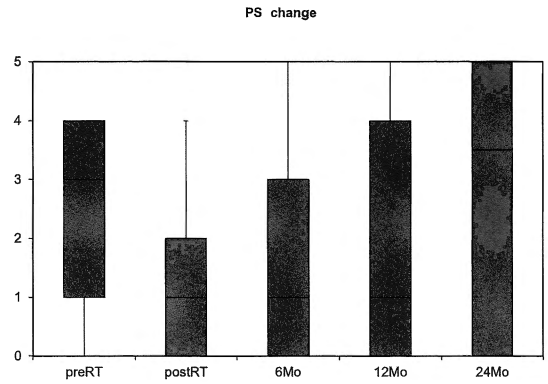

Fig. 4. Change in patient PS during the treatment course.

Discussion

In this study, we showed that individually prescribed WBRT, according to radiographic assessment, is a feasible and efficacious treatment strategy for PCNSL.

Treatment for PCNSL has been widely studied, yet its optimal treatment strategy has not been defined. Considering that more than 65% of patients are over 60 years old (35% of whom are over 70 years old)[3], patients often have poor PS at diagnosis, and their baseline conditions and responses to initial treatment significantly correlate with outcome, individual treatment selection is important for disease control and to maintain quality-of-life. For decades, radiation therapy has been the mainstay of treatment for patients with PCNSL. Because of its multifocal occurrence with diffuse brain infiltration[6], WBRT is preferred over PBRT. Shibamoto et al. reported the efficacy of PBRT with a radiation field using a 4-cm margin from the tumor bed; a patient group with a larger radiation field (> 4-cm margin) showed increased survival and a lower recurrence rate, which suggests that larger radiation fields are recommended for disease control[35]. However, the outcomes of patients treated with WBRT alone is unsatisfactory, with the median survival times ranging from 11-18 months and a 5-year survival rate of less than 18%[5, 7] The only prospective trial of radiation monotherapy that compared patients treated with WBRT at a dose of 40 Gy and either with or without a 20 Gy boost to the tumor bed, showed a tumor response rate of 81% with a median survival of 11.6 months in the boost group; this suggests that RT is an active treatment modality, though survival is poor when treated with RT alone, even with dose escalation[5]. WBRT dose is commonly suggested to be 40-50 Gy for radiation monotherapy, although its optimal dose remains controversial.

In the 1990s, the use of HD-MTX as a chemotherapy regimen for PCNSL increased[8, 9]. Former studies reported that the CR rate ranges from 29 to 52% on treatment with HD-MTX alone, with a median survival of approximately 2 years[24, 36]. Numerous studies using MTX as part of the treatment course have been conducted, including HD-MTX-based chemotherapy alone[28, 37-39], single-agent HD-MTX followed by WBRT[19], and HD-MTX in combination with other CNS-penetrating drugs followed by WBRT[10, 12, 22, 26, 38, 40]. Considering its efficacy, HD-MTX-based chemotherapy is suggested as the standard of care for PCNSL patients and its optimal dose is generally considered to be > 3 g/m^2, which is considered the tumoricidal level in both brain parenchyma and cerebrospinal fluid[41]. Recently, the efficacy of using rituximab, which has dramatic benefits in systemic lymphoma, and temozolomide, which is commonly used in the treatment of glioma, as the initial treatment or for recurrent PCNSLs have been explored and encouraging results have been reported[27, 39, 42, 43]. Combination therapy comprising HD-MTX-based chemotherapy and WBRT improves long-term disease control[40, 44], but increasing risk of late neurotoxicity is observed. Clinical symptoms of neurotoxicity can range from mild short-term memory loss to severe progressive dementia, which may deteriorate patient quality-of-life. Neurotoxicity induced death may occur in the most severe cases. While it is reported that 10% of patients who were treated with chemotherapy alone presented leukoencephalopathy[36], and another study showed that white matter abnormalities and global atrophy were found in patients treated with HD-MTX-based chemotherapy alone and frequently found in those who

received WBRT plus chemotherapy[17]. Moreover, treating patients with WBRT who received HD-MTX-based chemotherapy significantly increases this toxicity risk up to 30%[10), 12), 19), 21), 22)]

Age (> 60) is the most important risk factor of neurotoxicity; previous reports showed that in patients older than 60 years, 83% of long-term survivors developed neurotoxicity after combined modality treatment[10), 16)] From this point of view, omitting WBRT or dose-reduction has been proposed. In 1999, the largest phase III trial evaluating whether the omission of WBRT compromises OS was conducted[45)] The initial report at a median follow-up time of 31.8 months was published in 2010. Undergoing WBRT resulted in more frequent clinical and radiologic signs of late neurotoxicity, which was 49% and 71% in the WBRT group, and 26% and 46% in the group not receiving WBRT, respectively (not significant). Though the non-inferiority was not statistically significant, disease control tends to be improved with WBRT (median PFS, 18.3 vs 11.9 months; P=.14), and omitting WBRT was not associated with inferior OS (median OS, 32.4 vs 37.1 months; hazard ratio, 1.06; 95% confidence interval (CI): 0.80-1.40). The updated version at a median follow-up time of 81.2 months was published in 2015, reporting that PFS was significantly improved with WBRT[46)] There is another report that focused on younger patients (< 60 years-old), which suggested that deferring WBRT compromises PFS but not OS[31)] Particularly in elderly patients, there are several reports that suggest the addition of WBRT does not improve OS, but increased neurotoxicity[22), 40), 44)] Therefore, omitting WBRT in order to reduce the risk of late neurotoxicity has been considered, but poor outcomes is common in patients treated with chemotherapy alone[25), 42)] Several studies conclude that in elderly patients, WBRT should be withheld when a CR is achieved from initial chemotherapy until progression or recurrence is observed[10), 16), 37) 47-51)] In 2015, Kasenda et al. conducted the largest systematic review to focus on therapeutic management and outcomes in elderly patients[23)] According to that report, WBRT may improve outcomes; in particular, improvement in OS was observed in patients with lower Karnofsky PS (KPS). The authors also insist that when making therapeutic decisions, considering not only age but also KPS is necessary, as previously mentioned by Abrey et al.[52)]

Several studies have examined the efficacy of rd-WBRT. Bessell et al. compared CR patients receiving a WBRT dose of 45 Gy and 30.6 Gy and found the 3-year survival rate to be 92% and 60%, respectively. Moreover, a significant increase in the relapse rate and decrease in survival was observed, especially in patients under 60 yearsold[26)] This report suggests that rd-WBRT may be optimal for elderly patients, but in younger patients WBRT dose-reduction is not recommended. Another report suggested that deferring WBRT in younger patients (< 60 yearsold) resulted in poor PFS[31)] On the other hand, a group from Memorial Sloan-Kettering Cancer Center reported that reducing the WBRT dose to 23.4 Gy after achieving a CR to MTX-based chemotherapy did not compromise PFS but presented excellent disease control, with no evidence of delayed neurotoxicity, when compared to that in those who received 45 Gy[27)] In 2011, a retrospective study comparing patients who underwent consolidative WBRT of 30-36 Gy and over 40 Gy was conducted; no significant difference was observed in relapse rate (30% vs. 46%) or the 5-year PFS (50% vs. 51%)[53)] Morris et al. reported a 2-year PFS of 77% and a median PFS of 7.7 years in patients treated with rituximab, methotrexate, procarbazine, and vincristine (R-MPV) followed by rd-WBRT (23.4 Gy) and found minimal neurotoxicity[28)] Regarding

neurotoxicity, a group from Korea reported that low-dose WBRT with a tumor bed boost showed a lower rate of neurotoxicity[29] and a prospective study showed a significant decrease in neurotoxicity when the WBRT dose was reduced[54] In the RTOG 93-10 trial, a hyperfractionated radiation schedule of 36 Gy was compared to a conventional 45 Gy prescription. This regimen delayed, but did not eliminate, severe neurotoxicity from chemoradiation therapy[12), 55] Above all, WBRT dose may be safely decreased to 23.4-36.0 Gy with a conventional fractionation schedule in patients who achieved a CR after high-dose MTX-based first-line chemotherapy; in elderly patients, this is an option for postponing WBRT until tumor progression or recurrence.

Despite new therapeutic agents being developed, the recurrence rate for PCNSL remains high. Unlike other systemic lymphomas, PCNSL shows poor response to RT. One reason for this may be that the brain is considered an immune-privileged environment. The high rate of dissemination and recurrence within the central nervous system suggests the possibility of circulating micrometastasis within the cerebrospinal fluid. Considering this fact, irradiating the whole brain and spine may be one treatment option. There are several reports focusing on whole-spinal irradiation (WSI)[56-58] with some encouraging results showing long-term survival being presented. However, the number of patients treated in these reports was small and there might be some bias in that patients with high tolerability were selected to receive WSI. For WSI, the difficulty in conducting salvage chemotherapy due to myelosuppression, as derived from WSI, should be considered.

At our institution, we conduct RTP by considering each patient's treatment tolerability according to both baseline conditions and response to pre-RT chemotherapy. For patients older than 60 years and who show good response to HD-MTX (good PR or CR), rd-WBRT (of < 30 Gy) was administered; for other patients, WBRT (of ≥ 30 Gy, and < 40 Gy) was administered. Patients were then administered PBRT after WBRT, with a local boost added when CR was not achieved during the WBRT period (the median total dose radiated to the tumor bed was 46 Gy). A unique characteristic of our treatment methodology is the evaluation of tumor response, as derived from WBRT, to determine the appropriate dose of subsequent PBRT and local boost individually. As malignant lymphoma is known to be a radiosensitive disease and immediately shrinks due to radiation, we aimed to assess its response the next day, when approximately 20 Gy was delivered. In cases where it was difficult to decide whether the residual enhanced lesion was remaining tumor or a treatment-related change, we consulted neuroradiologists and neurosurgeons about the dose required and appropriate fields for boost radiation to control the disease during the brain tumor board.

For CR patients, it has been recommended to reduce the WBRT dose to 23.4-24.0 Gy to consider neurotoxicity[60]. We conducted rd-WBRT (median dose, 27 Gy) followed by PBRT in all cases. Despite relatively higher doses than typically recommended, local recurrence was observed in 50% of patients. The majority of recurrences occurred outside the initial CE or high-intensity T2WI/FLAIR lesions on pre-treatment MRI-i.e. outside of PBRT field. When confined to recurrences occurring in this area, a median dose of 28 Gy was delivered. In consideration of our results, the generally recommended dose of 23.4-24.0 Gy may be too low for achieving tumor control. In our opinion, an rd-WBRT dose of at least 30 Gy may be necessary, even for CR patients. Recently, Adhikari et al. reported a similar opinion with no mention of

the minimum radiation dose. Moreover, these authors conducted a phase II trial of response-adapted WBRT after HD-MTX-based chemotherapy[32] Patients with a CR were given rd-WBRT (23.4 Gy/13 fractions) and those with PR, SD, or PD were given standard dose WBRT (45 Gy/25 fractions). A higher risk of recurrence and progression, as well as early death, were found in the rd-WBRT group. The authors concluded that even for CR patients, rd-WBRT may be a suboptimal treatment.

For patients showing a poor response to initial HD-MTX, it is obvious that a high dose is required for the purpose of tumor control. However, as high doses can cause neurotoxicity, the dose and target area should be individually controlled. Considering the above, our RTP consists of WBRT, subsequent PBRT, and additional local boosts of radiation, with PBRT and local boost being determined according to the treatment response assessed during the WBRT period. There was a tendency for longer MST of OS, PFS, and local relapse-free survival in patients where local boost radiation was given, especially in groups that showed poor response to chemotherapy or groups that were unable to complete chemotherapy. This result shows the efficacy of adding boost radiation in this scenario.

Clinical symptoms of neurotoxicity were observed in 18 out of 31 patients (58.1%), with a median time to occurrence of 15.2 months, which seemed more frequent than other reports. Inclusion of 11 patients with existing cognitive impairments may be a reason for this result. In 12 out of 16 patients (75%), who were alive and able to be followedup 24 months after completion of RT, clinically assessed PS decreased or was unchanged, suggesting that treatment-related neurotoxicity was tolerable and patient quality-of-life was successfully maintained. Good PS and tumor control suggests our individualized RTP protocol is effective.

There are several limitations in this study. First, the study design was retrospective, and the sample size was small, including some cases with slightly short follow-up periods who are still vulnerable to recurrence. However, the inclusion of elderly patients and those with poor PS may reflect the typical population of PCNSL patients. Second, psychometric evaluations were not performed; using clinical assessments might lead us to incorrectly estimate late neurotoxicity incidence.

Conclusion

Since we show that reducing WBRT dose is effective in lowering the risk of late neurotoxicity, we suggest that a WBRT dose of 30 Gy or more is necessary to maintain reasonable tumor control, even for patients with a CR after HD-MTX. For those with unsatisfactory response after HD-MTX, subsequent PBRT and additional boost radiation, as determined individually according to treatment response, should be considered.

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Ethical statement

This study was approved by Nara Medical University Ethics Committee (approval number 1212).

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