

Original Article

A single institutional retrospective evaluation for younger patients with primary central nervous lymphomas on a modified R-MPV regimen followed by radiotherapy and high dose cytarabine

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We conducted a retrospective analysis of patients younger than 60 years (N = 10, median age 54.5) with newly diagnosed primary central nervous system lymphoma (PCNSL) at the University of Tsukuba Hospital from January 2008 to November 2016. All the patients were scheduled to receive a single regimen without registration to any clinical trials. This was based on a phase 2 study by Memorial Sloan-Kettering Cancer Center (MSKCC); induction chemotherapy with rituximab, methotrexate, procarbazine, and vincristine (R-MPV) (five to seven cycles), followed by whole-brain radiotherapy (rd-WBRT) (23.4 Gy) and two high-dose cytarabine (HD-AC) cycles as a consolidation. The median age was 54.5 years, and median follow up duration was 33.1 months. The 3-year overall survival (OS) and progression-free survival (PFS) were 69% (95% CI 31–89%) and 56% (95% CI 20–81%). The median OS and PFS were not reached, respectively. Acute and delayed toxicities were manageable. In particular, OS and PFS of seven patients who achieved CR by the R-MPV induction chemotherapy were significantly superb (3-year OS, 100%; 3-year PFS, 80%), implying that a large proportion of patients in CR after the completion of this treatment may achieve durable disease control.

On the other hand, all of the three patients who had progressive disease during this treatment died of disease progression within 1 year after diagnosis without achieving CR. Identifying the patients having a risk of failure in the R-MPV induction chemotherapy is important, and may allow us to consider a potentially more effective regimen.

Keywords: R-MPV induction therapy followed by consolidation rdWBRT and HD-AC, primary central nervous system lymphoma, CR after completion of treatment

INTRODUCTION

Primary central nervous system lymphoma (PCNSL) is diffuse large B-cell lymphoma (DLBCL) that arises within the brain or eyes. It accounts for around 2-3% of primary malignant brain tumors and less than 1% of non-Hodgkin lymphomas (NHL) in adults.¹ Historically, whole-brain radiotherapy (WBRT) was the sole treatment for PCNSL but the outcome of PCNSL treated with WBRT alone was not favorable.²

Combined modality therapy (CMT) using high-dose methotrexate (HD-MTX) and WBRT was first described in 2000 and since then has demonstrated improvement of

response rate and prognosis.³ Now, there is consensus that CMT is superior to radiotherapy alone, although this was not confirmed in a randomized trial.³ As a result, HD-MTX in combination with WBRT has been chosen as the backbone in most of the currently used regimens.³ Although this CMT strategy results in high rates of disease remission, the majority of patients eventually progress and only a minority (20-40%) are cured of their disease. Additionally problematic is the delayed neurotoxicity associated with CMT that is clinically evident in approximately one-third of patients, particularly in those at higher ages.

Recently, encouraging response rates have been achieved with rituximab-containing regimens in several clinical trials.^{4,5,6,7,8}

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In a study of the 90Y-labeled anti-CD20 antibody, single photon emission computed tomography (SPECT) imaging with ¹¹¹In ibritumomab tiuxetan was performed in 6 patients before treatment with 90Y ibritumomab tiuxetan, and high uptake in the tumors in central nervous system was shown in 4 out of these 6 patients with PCNSL.⁹ This report suggests that rituximab may achieve therapeutic concentrations in regions of a brain tumor manifesting contrast enhancement secondary to blood brain barrier (BBB) disruption.⁹ Ultimately, this may support the rationale for incorporation of rituximab into induction regimens for PCNSL.

Among the rituximab containing regimens, the multicenter phase 2 study, which evaluated the efficacy of rituximab, methotrexate, procarbazine, and vincristine (R-MPV) followed by consolidation reduced-dose whole-brain radiotherapy (rdWBRT) and high-dose cytarabine (HD-AC) in PCNSL, demonstrated a high response rate (objective response rate (ORR), 95%; 3-year overall survival (OS), 77%; 3-year progression-free survival (PFS), 51%), while the frequency of delayed neurotoxicity was low.⁴ However, reproducibility of this regimen has not been sufficiently confirmed, particularly in younger Japanese patients with PCNSL. Although efficacy of the R-MPV regimens in Japanese PCNSL patients was reported in a meeting abstract (Nakazaki K, *et al.*, 2015; Harada Y, *et al.*, 2013), any detailed information has not been published.^{10,11} We retrospectively analyzed the efficacy, acute toxicity, and delayed neurotoxicity of younger Japanese patients with PCNSL, treated by the R-MPV induction therapy, followed by reduced- or standard-dose WBRT (23Gy or 45Gy) and HD-AC consolidation at the University of Tsukuba Hospital in 2008-2016.

MATERIALS AND METHODS

Patients

Between January 2008 and November 2016, a total of twelve consecutive patients with newly diagnosed PCNSL aged younger than 60 years, who were treated with the R-MPV induction therapy followed by consolidation rdWBRT and HD-AC at the University of Tsukuba Hospital, were identified from the medical records.⁴ Two patients were excluded from this analysis: one was initially infected with HIV and the other was treated with gamma-knife radiosurgery prior to diagnosis of PCNSL. The remaining ten patients were analyzed in a retrospective manner. Stereotactic surgery or tumor resection under craniotomy was performed for biopsy. Diagnosis was made on the basis of histological and immunohistochemical studies at the central pathological facility within the hospital. This retrospective study was approved by the institutional review board at the University of Tsukuba Hospital.

Treatment and response evaluation

We modified the original R-MPV regimen. The dose of rituximab in R-MPV was reduced from 500 mg/m² to 375

mg/m². Treatment started with induction R-MPV chemotherapy (1 cycle=14 days), as follows: day 1, rituximab 375 mg/m²; day 2, methotrexate 3.5 g/m² (over 2 hours), vincristine 1.4 mg/m². Procarbazine was administered at 100 mg/m²/d on days 1 through 7 (odd cycles only).⁴ Patients with evidence of lymphoma cells in cerebrospinal fluid (CSF) received 10 mg of intraspinal MTX and cytarabine in each cycle. All patients who had grade 4 neutropenia received prophylactic lenograstim (2μg/kg/d, subcutaneously for 3 to 5 days) after each cycle.

Response was assessed using magnetic resonance imaging (MRI) with contrast enhancement according to the following criteria: complete response (CR) was determined by the absence of any contrast enhancement on the MRI of the brain, and partial response (PR) by at least a 50% reduction in the contrast-enhancing lesion seen on MRI as compared with baseline imaging. Patients were evaluated for response after five cycles of R-MPV. If CR was achieved, the patients went on to receive rd-WBRT (23.4 Gy fractionated at 1.8 Gy over 13 fractions) 3 to 5 weeks after completion of chemotherapy (Table 2, patient 5, 6, 8, and 10). If judged as a partial response, the patient received two additional cycles of R-MPV and was re-evaluated by MRI. If the patient achieved CR after seven cycles of induction chemotherapy, they then went on to receive rdWBRT (Table 2, patient 2). If small but persistent enhancing abnormalities, which were difficult to ascertain whether these represented residual nodules of tumor or scar tissue, were seen on MRI after 5 cycles of the R-MPV induction therapy, the patients also received two additional cycles of the R-MPV induction therapy and were re-evaluated. If the image of the abnormality did not change on MRI after the additional cycles of the R-MPV induction therapy, we categorized these as CR and rdWBRT was given to them (Table 2, patient 1, 4). After radiotherapy, two courses of consolidation HD-AC were given at 3 g/m²/d on

Table 1. Patient characteristics (N = 10)

Age (years)	
Median	54.5
Range	47-59
KPS	
Median	70
Range	40-90
Sex	
Male	4
Female	6
Histology	
DLBCL	10
Menigeal involvement	0
Ocular involvement	0

KPS Karnofsky performance score
DLBCL diffuse large B cell lymphoma

days 1 and 2 of each cycle (d1-28). Prophylactic lenograstim was given after each cycle.

Routine supportive treatments were given. In short, patients with normal cardiac and renal function were given 2–3 l of hydration per day during HD-MTX. 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 mol/l.

Three patients had progressive disease after cycle 1 (patient 3), 3 (patient 9), and 5 (patient 7) of the R-MPV induction therapy. Then, the induction therapy was stopped, and salvage WBRT or palliative therapy was selected for these patients.

Follow-up and assessment

All these evaluations were performed by referring to clinical records. In the survival analysis, OS was defined as “survival without death as a result of any cause” and PFS as “survival without 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. Acute and delayed toxicities were evaluated according to the National Cancer Institute’s Common Terminology Criteria for Adverse Events (CTCAE) (version 4; <http://evs.nci.nih.gov/ftp1/CTCAE/About.html>).

Kaplan–Meier survival curves were analyzed with the log rank test using the EZR.¹²

RESULTS

Patient characteristics

The characteristics and outcomes of the ten patients with newly diagnosed PCNSL are summarized in Tables 1 and 2. The median age was 54.5 years, and median follow up duration was 33.1 months. No patients had ocular or meningeal involvement. In total, all ten patients were assessed for response to induction chemotherapy with R-MPV.

In three patients, the period between the first visit to a physician because of symptoms related to PCNSL and treatment was remarkably longer than that of other patients (Table 2; patient 3, 5, and 9). Patients 3 and 5 were initially diagnosed as having multiple sclerosis and treated with several courses of corticosteroid pulse therapy, and were subsequently diagnosed as having PCNSL. As a result, start of therapy was postponed. The induction therapy of patient 9 was postponed due to infection that was suspected to be associated with meningitis.

Response and survival

Four patients (40%) (patients 5, 6, 8, and 10) achieved CR by the fifth cycle of the R-MPV induction therapy (Table 2). One patient (patient 2) with a PR after the fifth cycle received the additional two cycles of the induction therapy and then achieved CR on MRI (Table 2). The other two patients (patients 1 and 4) who had minimal abnormalities at the post cycle 5 evaluation also received two additional cycles of the R-MPV induction therapy (Table 2). The images did not change after the additional cycles in both cases, and thus, we categorized these abnormalities as CR (Table 2). All these seven patients maintained CR at the

Table 2. Patients and outcomes

UPN	Age	Sex	The period between the first examination and treatment	Completion of the induction therapy (5 x R-MPV)	Evaluation after 5x R-MPV	Additional R-MPV	Evaluation after additional R-MPV	Radiation	Evaluation After radiation therapy	OS (day)	PFS (day)
1	58	F	18	Yes	CR*1	Yes (2) *2	CR	rdWBRT	CR	1406+	1406+
2	49	F	27	Yes	PR	Yes (2) *2	CR	rdWBRT	CR	2246+	2246+
3	59	F	251	No	NA	NA	NA	NA	NA	13	13
4	51	F	29	Yes	CR*1	Yes (2) *2	CR	rdWBRT	CR	2531+	2531+
5	47	M	97	Yes	CR	No	NA	rdWBRT	CR	1333	823
6	54	F	35	Yes	CR	No	NA	rdWBRT	CR	1261+	1261+
7	52	F	12	Yes	PD	No	NA	WBRT (36Gy)	PD	278	116
8	55	M	38	Yes	CR	No	NA	rdWBRT	CR	728+	728+
9	58	M	72	No	NA	NA	NA	WBRT(39.6Gy)	PD	158	58
10	58	M	27	Yes	CR	No	NA	rdWBRT	CR	255+	255+

UPN unique patient number, PFS progression-free survival, OS overall survival, CR complete response, PR partial response, PD progression disease, NA not available, WBRT whole brain radiotherapy, rd reduced dose, “+” alive at the cutoff point

*1 Patients had minimal abnormalities, which were difficult to evaluate whether these were tumor or scar tissue,

*2 Patients received two additional cycles of the R-MPV induction therapy.

completion of the R-MPV induction therapy. They received rdWBRT at 23.4 Gy. After radiotherapy, these patients received two consolidation HD-AC therapies. As a result, six of these seven patients remain alive at the time of submission of this manuscript and are free of disease progression. In one male patient achieving CR (patient 5), lymphoma progressed at 22 months after completion of the therapy. Then, he received high-dose chemotherapy using etoposide, cytarabine, and melphalan (BEAM) with autologous stem cell transplant (ASCT), but he experienced disease relapse within six months and died 1 year after ASCT.

The other three patients (30%) (patients 3, 7 and 9) did not achieve CR by the R-MPV induction therapy (Table 2). One patient (patient 7) with progressive disease after the induction therapy received WBRT at only 36 Gy because the patient refused further doses of radiation. After radiotherapy, the patient died because of disease progression. Two patients (patients 3 and 9) progressed before the completion of the R-MPV induction therapy. Patient 3 died because of early progression after the first cycle of the R-MPV induction therapy. Patient 9 had disease progression after the third cycle of the induction therapy and then received WBRT at 39.6 Gy as salvage therapy. This subject subsequently died of disease progression.

For all ten patients, 3-year PFS was 56% (95% CI 20–81%), with the median PFS not reached (Figure). The 3-year OS was 68.6% (95% CI 31–89%), with the median

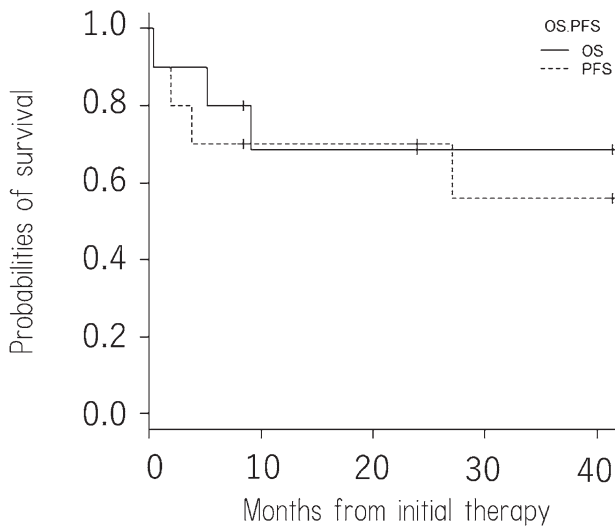


Fig. Overall survival (OS) and Progression free survival (PFS) after induction therapy.

Table 3. Severe acute toxicities during the induction therapy (N = 10)

Grade	Anemia	Thrombopenia	Neutropenia ^a	Hepatitis	Renal toxicity	Cognitive disturbance
3	3 (30)	0	1 (10)	3 (30)	0	1 (10)
4	0	0	4 (40)	0	0	0

Patients' number and percentage are shown

^a Three patients developed grade 3 febrile neutropenia

OS not reached (Figure). OS and PFS of patients who achieved CR at the completion of the induction chemotherapy were favorable (3-year OS, 100%; 3-year PFS, 80%).

Acute toxicity of induction chemotherapy

The median number of R-MPV cycles was five (range, one to seven). The acute and severe toxicities that occurred during the induction therapy are summarized in Table 3. The most frequent toxicity was myelosuppression. Five patients (50%) developed grade 3 or 4 neutropenia. Grade 3 anemia occurred in three patients (30%). Two patients (20%) had grade 3 aspartate transaminase (AST) and alanine transaminase (ALT) elevations, and one patient (10%) had grade 3 gamma-glutamyl transpeptidase (γ GTP) elevation. These liver dysfunctions were recorded 3–9 days after the initiation of the induction therapy and were reversible without specific therapy. Three patients had febrile neutropenia (grade 3) during myelosuppression, which was managed and cured with antibiotics. One patient (patient 6) (10%) had cognitive disturbance and gait disorder soon after completion of all treatment without lymphoma progression, which were reversible.

DISCUSSION

Several studies on PCNSL treated with immunochemotherapy in combination with WBRT have been reported.^{4,13-16} Although there are limitations in comparison across different cohorts, the OS and PFS of patients in this cohort are excellent (Figure, 3-year OS, 69%; 3-year PFS, 56%) and are comparable to those of the phase 2 study of MSKCC (3-year OS, 77%; 3-year PFS, 51%).

Unfortunately, three of ten patients (patients 3, 7, and 9) died of disease progression. Among these three patients, 2 patients (patients 3 and 9) had rapid progression of disease before the completion of the R-MPV induction therapy (Table 2). The initiation of induction therapies was delayed in these patients, which may partly account for the treatment failure. In general, histological diagnosis can be difficult at the early period of the clinical course if the lesion is located deep in the brain structure. Detection of somatic mutations in cell-free DNA (cfDNA), a recently developed method, may represent a minimally invasive tool helping for diagnosis.¹⁷

Several specific clinical parameters, such as MSKCC and IELSG prognostic score systems, were reported to predict the treatment outcome of PCNSL patients.^{18,19} We previously

found that *MYD88* L265P mutations had a negative impact on the clinical outcome of elderly PCNSL patients.²⁰ The impact of *MYD88* L265P mutation should be examined for younger patients treated with the R-MPV regimen followed by consolidation rdWBRT and cytarabine.

Newly developed targeted drugs may provide treatment options in PCNSL patients. Ibrutinib, a selective covalent BTK inhibitor, is effective in patients with some B-cell malignancies by inhibiting the NF- κ B pathway activity.^{21,22,23} The effectiveness of ibrutinib for CNS relapse of B-cell lymphomas was demonstrated.²⁴ Recently, several studies have been conducted to show the effects on refractory/recurrent CNS lymphoma patients (NCT02203526, NCT02315326).^{25,26} Additionally, lenalidomide, an IMiD class biological agent, may also be effective for PCNSL via down-modulation of MUM1/IRF-4.²⁷ A phase-2 trial combining rituximab and lenalidomide for recurrent PCNSL is ongoing (NCT01956695).²⁸

In addition, there has been increasing interest in the role of high-dose chemotherapy (HDC) followed by ASCT in PCNSL as a consolidation approach in first-line therapy.²⁹ Antonio Omuro *et al.* previously conducted a single center phase 2 study in newly diagnosed PCNSL utilizing the R-MPV induction therapy and HD-AC, followed by consolidation HDC-ASCT with thiotepea, busulfan, and cyclophosphamide (TBC).³⁰ In their series, excellent disease-free control and OS (3-year OS, 81%; PFS, 79%) were observed, with an acceptable toxicity profile and minimal neurotoxicity.³⁰ Interestingly, a small phase 2 study suggested that HDC-ASCT could replace consolidation radiotherapy, with a 3-year OS of 77%.³¹ Thus, HDC followed by ASCT may be proposed as an alternative consolidation therapy instead of radiotherapy in PCNSL, especially for patients who achieved CR after the induction phase.

In conclusion, a 3-year overall survival rate of 100% was achieved by the R-MPV regimen followed by consolidation rdWBRT and cytarabine in Japanese patients achieving CR at the completion of this treatment. The effectiveness of the treatment was an important factor contributing to these favorable results. Further study is needed to identify the factors that predict the tolerance and response before treatment. Therapy can potentially be revised or newly invented to a potentially more effective regimen in patients who are destined to respond poorly to the initial treatment.

AUTHOR CONTRIBUTIONS

K.H., M.S.-Y., and S.C. designed and performed research, analyzed data, and wrote the paper; Y.O., T.K., N.K., Y.Y., N.O., and Y.H. designed and performed research; S.T., E.I., T.Y., and A.M. provided patient data.

CONFLICT OF INTEREST

S.C. received research funds from the Mitsubishi Tanabe Pharma Corporation, which sells MTX in Japan, the Nippon Shinyaku Corporation, which sells AraC, and the Chugai

Pharmaceutical Corporation which sells procarbazine and rituximab. No other research support was provided for this study.

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