Therapeutic Outcomes and Toxicity of High-Dose Methotrexate-Based Chemotherapy for Elderly Patients with Primary Central Nervous System Lymphoma: A Report on Six Cases

Akira Tempaku^a Yoshinobu Takahashi^{a,b} Hajime Kamada^a

^aDepartment of Neurosurgery, Hokuto Hospital, Obihiro, Japan; ^bDepartment of Neurosurgery, Kyoto Prefectural University of Medicine, Kyoto, Japan

Dear Editor,

Primary central nervous system lymphoma (PCNSL) is an intracranial malignancy that represents <5% of all brain tumors [1]. As the population ages, nearly half of the patients with PCNSL are aged >60 years with one-tenth of these aged ≥80 years [2]. High-dose methotrexate (HDMTX)-based chemotherapy has been developed against PCNSL and showed to improve the survival period of patients [3]. However, median overall survival of PCNSL patients aged >70 years has never been improved over the past 4 decades [2]. Since methotrexate is associated with severe renal toxicity, whether elderly patients with PCNSL should be treated with the same methotrexate dose as younger patients remains unclear.

From September 2010 to March 2015, 6 patients aged >80 years were treated for PCNSL at the Hokuto Hospital, Obihiro, Japan. The clinical characteristics of patients, treatments, and outcomes are summarized in Table 1. Upon surgical sample collection, all patients were diagnosed with diffuse large B-cell lymphoma. All patients

were treated with intravenously administered HDMTX at a dose of 3.5 g/m², according to the established protocol [4]. Leucovorin rescue was also administered to all patients. No methotrexate dose reduction was performed, and 4 patients received additional vincristine (1.4 mg/m²) and procarbazine (150 mg/day) treatment. Whole-brain irradiation therapy was performed in 3 patients for whom chemotherapy was insufficient. Three patients (50%) exhibited grade III or IV adverse events (National Cancer Institute–Common Toxicity Criteria Version 2.0) and 2 patients (33%) discontinued the therapy due to severe adverse events, which proved fatal because both patients died. Two patients achieved complete response, whereas 3 achieved partial response and 1 had progressive disease. The mean progression-free survival and overall survival were 19.5 and 24.7 months, respectively. As patients 1 and 2 did not survive, no secondary treatment other than HDMTX was administered on relapse. Patient 3 underwent additional irradiation (20 Gy).

Advanced age is associated with a poor PCNSL prognosis [5]. Moreover, poor performance status [5] and lower renal function [6] have been reported as negative prognostic factors. However, a recent study reported good outcomes of HDMTX in elderly patients with PCNSL exhibiting specific characteristics including higher Karnofsky performance status (KPS), lower serum LDH level, or no deep brain lesion [3]. In addition to age, the general physical condition and renal capacity were reported to influence the effect of HDMTX [5, 7]. In the present study, HDMTX-related death was observed in 2 patients, both of whom exhibited a low KPS and renal dysfunction. This result suggests that pretreatment KPS and renal function might strongly influence the outcome of HDMTX therapy in elderly patients with PCNSL. Our results support previous evidence that aging is not the only critical factor to assess, when considering the use of HDMTX to treat PCNSL. HDMTX is effective against PCNSL even in patients aged >80 years, as long as they do not present poor KPS or renal dysfunction.

Table 1. Characteristics and outcomes of patients with PCNSL

Patient	Age/sex	KPS	Ccr, mL/min	Therapy times	Radiation, Gy	Response	Toxicity grade (type)	Survival, months		Cause of death
1	85/F	40	44	1	no	PR	IV (thrombocytopenia) III (DIC, hyper Na)	0.6	deceased	MTX related
2	84/M	40	49	2	no	PR	IV (pancytopenia, DIC, thrombosis, hyper Na) III (pneumonia)	4.0	deceased	MTX related
3	83/M	80	57	6	20	PR	IV (pancytopenia) III (renal failure)	41.8	deceased	pneumonia
4	83/F	90	56	2	no	CR	I (anorexia)	71.4	alive	
5	83/M	70	53	4	15	PD	None	5.5	deceased	encephalocele
6	80/M	70	96	6	45	CR	None	24.7	deceased	jaundice

KPS, Karnofsky performance status; Ccr, creatinine clearance; Gy, Gray; PR, partial response; CR, complete response; PD, progressive disease; DIC, disseminated intravascular coagulation; hyper Na, hypernatremia; MTX, methotrexate.

tion. Conversely, elderly patients with poor KPS or renal dysfunction should be treated with reduced doses of MTX. Recent studies [2, 7] demonstrated that a 60 or 70% dose of MTX is useful to treat elderly patients with PCNSL. We would recommend administering 2–2.5 mg/m² of MTX to elderly PCNSL patients with decreased renal function. However, the evidence supporting the use of MTX treatment in elderly pa-

tients with PCNSL is limited, and future studies using lower doses should be performed.

Acknowledgement

We would like to thank the staff of the Hokuto Hospital for its support with the clinical treatment and care of the patients.

Disclosure Statement

The authors have no conflicts of interest to declare.

Funding Sources

This study was not supported by official or private funding.

References

- Olson JE, Janney CA, Rao RD, Cerhan JR, Kurtin PJ, Schiff D, et al. The continuing increase in the incidence of primary central nervous system non-Hodgkin lymphoma: a surveillance, epidemiology, and end results analysis. *Cancer*. 2002 Oct;95(7):1504–10.
- Mendez JS, Ostrom QT, Gittleman H, Kruchko C, DeAngelis LM, Barnholtz-Sloan JS, et al. The elderly left behind-changes in survival trends of primary central nervous system lymphoma over the past 4 decades. *Neuro-oncol*. 2018 Apr;20(5):687–94.
- Fritsch K, Kasenda B, Schorb E, Hau P, Bloehdorn J, Möhle R, et al. High-dose methotrexate-based immuno-chemotherapy for elderly primary CNS lymphoma patients (PRIMAIN study). *Leukemia*. 2017 Apr;31(4):846–52.
- Makino K, Nakamura H, Hide T, Kuroda J, Yano S, Kuratsu J. Prognostic impact of completion of initial high-dose methotrexate therapy on primary central nervous system lymphoma: a single institution experience. *Int J Clin Oncol*. 2015 Feb;20(1):29–34.
- Abrey LE, Ben-Porat L, Panageas KS, Yahalom J, Berkey B, Curran W, et al. Primary central nervous system lymphoma: the Memorial Sloan-Kettering Cancer Center prognostic model. *J Clin Oncol*. 2006 Dec;24(36):5711–5.
- Zhu JJ, Gerstner ER, Engler DA, Mrugala MM, Nugent W, Nierenberg K, et al. High-dose methotrexate for elderly patients with primary CNS lymphoma. *Neuro-oncol*. 2009 Apr;11(2):211–5.
- Welch MR, Omuro A, Deangelis LM. Outcomes of the oldest patients with primary CNS lymphoma treated at Memorial Sloan-Kettering Cancer Center. *Neuro-oncol*. 2012 Oct;14(10):1304–11.