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Reduced neurotoxicity with combined treatment of high-dose methotrexate, cyclophosphamide, doxorubicin, vincristine and prednisolone (M-CHOP) and deferred radiotherapy for primary central nervous system lymphoma

Tomotsugu Ichikawa[a,*], Kazuhiko Kurozumi[a], Hiroyuki Michiue[b], Joji Ishida[a], Yoshinobu Maeda[c], Eisei Kondo[c], Akihiro Kawasaki[a,d], Isao Date[a]

[a] Department of Neurological Surgery, Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences, 2-5-1 Shikata-cho, Kita-ku, Okayama 700-8558, Japan
[b] Department of Physiology, Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences, 2-5-1 Shikata-cho, Kita-ku, Okayama 700-8558, Japan
[c] Department of Hematology and Oncology, Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences, 2-5-1 Shikata-cho, Kita-ku, Okayama 700-8558, Japan
[d] Faculty of Human Development, University of Toyama, 3190 Gofuku, Toyama 930-8555, Japan

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ABSTRACT

Objective: Although high-dose methotrexate and whole-brain radiation therapy (WBRT) is the current standard for primary central nervous system lymphoma (PCNSL), it has a limited response rate and produces radiation-induced neurotoxicity. We report the effect of a combined treatment of high-dose methotrexate, cyclophosphamide, doxorubicin, vincristine and prednisolone (M-CHOP) for immunocompetent patients with PCNSL.
Methods: We analyzed 24 patients who had received M-CHOP administered in 28-day cycles with or without WBRT. The response rate to M-CHOP, overall survival (OS), and recurrence-free survival (RFS) were analyzed.
Results: Nine patients were treated with M-CHOP plus WBRT and 15 patients were treated with M-CHOP alone. Twenty-one patients achieved a complete response and three patients achieved a partial response to M-CHOP, for a 100% response rate. With a median follow-up of 70 months, the median OS and RFS were 33 and 13 months, respectively. The median OS for patients treated with M-CHOP plus WBRT and M-CHOP alone was 33 and 32 months, respectively. Of the 13 patients whose age was above 65 years, the median OS for the M-CHOP plus WBRT group (two patients) and the M-CHOP alone group (11 patients) was 14 and 32 months, respectively. Toxicities related to M-CHOP were mostly hematologic and generally mild to moderate. Two patients whose age was above 65 years in the M-CHOP plus WBRT group developed neurotoxicity.
Conclusion: Combined treatment with M-CHOP was well tolerated and produced a high response rate. Deferring WBRT was associated with reduced neurotoxicity without worsening the prognosis, especially in elderly patients.

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1. Introduction

Primary central nervous system lymphoma (PCNSL) is a rare variant of non-Hodgkin's lymphoma that involves the brain parenchyma, leptomeninges, eyes, and spinal cord. It comprises approximately 2–7% of primary central nervous system tumors. Its incidence has been increasing in the immunocompetent, elderly patient population over the past several decades [1,2].

Treatment of PCNSL typically consists of high-dose methotrexate (MTX)-based chemotherapy with the addition of whole brain radiation therapy (WBRT). In recent studies with high-dose MTX-based chemotherapy followed by WBRT, response rates have been from 46 to 100% and overall survival (OS) has been between 32 and 60 months [3–9].

* Corresponding author. Tel.: +81 86 235 7336; fax: +81 86 227 0191.
E-mail address: tomoichi@cc.okayama-u.ac.jp (T. Ichikawa).

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Although this treatment strategy has improved disease control and survival in patients with PCNSL, most patients eventually experience a relapse, and uncontrolled PCNSL remains the primary cause of death. Currently, multiple treatment regimens using high-dose MTX alone or in combination with other chemotherapeutic agents have been reported, with complete response (CR) rates without WBRT ranging from 11 to 78% [5,8–13]. This means that a considerable number of patients still depend on WBRT for a CR. However, the addition of WBRT significantly increases the risk of treatment-related neurotoxicity, particularly in elderly patients [5,14,15].

Therefore, a treatment regimen that is both more effective, with high response rates, and less toxic, is required to improve patient outcomes. Efforts have been made to implement chemotherapy alone as a first-line therapy and to defer WBRT until progression or relapse. Such efforts include high-dose MTX-based multi-agent chemotherapy [5,8]. Thus, trials assessing the efficacy of multi-agent chemotherapy with high-dose MTX should be useful.

In the present study, we report the effect of combined chemotherapy with high-dose methotrexate, cyclophosphamide, doxorubicin, vincristine and prednisolone (M-CHOP) to achieve high response rates in the initial treatment. The effect of deferring radiation therapy after induction of complete remission by first-line M-CHOP chemotherapy is also evaluated.

2. Materials and methods

2.1. Patient selection

We studied 24 newly diagnosed immunocompetent patients with PCNSL between 1995 and 2010. Four patients were previously diagnosed and treated with intraocular lymphoma. Pathological diagnosis was based on stereotactic biopsy (11 patients), endoscopic biopsy (1 patient), partial resection (8 patients), or vitrectomy for preceding intraocular lymphoma (4 patients). All 24 patients had a diffuse, large B-cell type of PCNSL. Pretreatment evaluation included 24-h urine collection for creatinine clearance (minimum required: 50 mL/min); complete ophthalmologic examination; computed tomography (CT) scans and/or FDG-PET scans of the chest, abdomen, and pelvis; and a baseline neurocognitive evaluation. Adequate bone marrow, renal, and liver function were required for participation. Patients exhibiting evidence of systemic lymphoma or other active malignancies were excluded. All patients were human immunodeficiency virus (HIV-1) seronegative. None had received any prior therapy for PCNSL. There were no limits with regard to age or performance status. All patients provided written informed consent before treatment, and the protocol was approved by the institutional review board.

2.2. Induction Chemotherapy

Induction chemotherapy consisted of three to six four-week cycles of high-dose methotrexate, cyclophosphamide, doxorubicin, vincristine and prednisolone (M-CHOP). A dose of MTX at 3.5 g/m^2 was administered intravenously over 3 h on Day 1 of each cycle, with standard pretreatment hydration and alkalinization of urine (target urine pH > 7.0). The MTX dose was reduced, if necessary, according to creatinine clearance measures; the maximal dose reduction was 50%. Leucovorin rescue (15 mg every 3 h) was begun 6 to 24 h after MTX infusion and continued for at least 72 h or until the serum MTX level fell below 1×10^{-8} M. In addition to this, 750 mg/m^2 of cyclophosphamide, 50 mg/m^2 of doxorubicin, and 1.4 mg/m^2 of vincristine (maximum dose: 2.0 mg) were administered on Day 1 of each cycle. The cyclophosphamide dose was reduced, if necessary, according to the general condition and myelotoxicity of the former cycle; the maximum dose reduction was 50%. Prednisolone 60 mg/body was administered on Days 1 and 2, and tapered off by seven days. Between 1995 and June 2004, all patients received four to six consecutive cycles of M-CHOP, regardless of their responses to therapy.

Between July 2004 and 2010, patients who attained a CR after one to four cycles of M-CHOP received two additional courses of M-CHOP. Patients who attained less than a CR after four courses of M-CHOP were given the option to receive one to two additional cycles of M-CHOP before WBRT.

2.3. Radiation therapy

Between 1995 and June 2004, all patients who completed M-CHOP received WBRT to a total dose of 36–60 Gy (1.8–2.0 Gy/fraction X 20–30 daily) regardless of their responses to initial M-CHOP therapy. Between July 2004 and 2010, patients who attained a CR after M-CHOP had not received WBRT. WBRT was started three to five weeks after the completion of M-CHOP.

2.4. Response evaluation and toxicity

Patients were evaluated for responses after each cycle of M-CHOP and WBRT. Radiographic responses were based on analysis of gadolinium-enhanced magnetic resonance imaging (MRI) studies using the NCI standardized response criteria [16]. The primary end points were a radiographic response to initial chemotherapy and survival from the diagnosis. A CR was defined as the eradication of all tumor enhancement; partial response (PR) as a decrease of 50% or more in tumor size; progressive disease as an increase of 25% or more in tumor size or the appearance of any new lesion; and stable disease as situations that did not meet any of the previous criteria. Toxicity was graded by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.0

2.5. Follow-up and neuropsychological testing

All patients have been observed longitudinally with surveillance MRI scans and neurological examinations were performed every month for three years and every three months thereafter. The standardized neuropsychological test battery included verbal and nonverbal memory [The Rey Auditory Verbal Learning Test (RAVLT), Rey-Osterrieth Complex Figure Test (ROCFT)], executive function [Wisconsin Card Sorting Test (WCST)], intelligence [WAIS-R, Raven's colored progressive matrices (RCPM)], speech function [Standard Language Test of Aphasia (SLTA), word fluency test (WFT)], cognitive function [Mini Mental State Examination (MMSE)], and frontal lobe function [frontal assessment battery (FAB)]. Treatment-related neurotoxicity was defined as progressive neurologic or cognitive impairment, as documented on serial clinical examinations in the absence of recurrent lymphoma.

2.6. Statistical methods

Statistical analysis was performed using SPSS statistical software (version 20; SPSS, Inc., Chicago, IL, USA). Survival was measured from the time of diagnosis. The median follow-up was 70 months (range: 14–125 months). Estimates of recurrence-free survival (RFS) and OS from time of diagnosis were made using the Kaplan and Meier method. Comparisons of survival curves were made using the log-rank test. $P < 0.05$ was considered statistically significant.

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