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Salvage chemotherapy with R-BAD (rituximab, bendamustine, cytarabine, and dexamethasone) for the treatment of relapsed primary CNS lymphoma

TO THE EDITOR: Primary central nervous system lymphoma (PCNSL) involves extranodal lymphomas arising exclusively in the central nervous system (CNS). It accounts for 2%–3% of newly diagnosed primary CNS tumors and systemic non-Hodgkin's lymphomas [1, 2]. Although survival outcomes have improved with the introduction of high-dose methotrexate (MTX)-based regimens, with or without cranial irradiation, relapse is still common. Approximately 35%–60% of patients show relapse and most relapses occur within the first 2 years following diagnosis [3, 4]. The prognosis of relapsed PCNSL remains poor, with limited treatment options. Furthermore, the aggressive course of relapsing PCNSL dramatically decreases performance status, particularly in elderly patients [5]. Here, we describe an elderly patient with recurrent/relapsed PCNSL who was successfully treated with four cycles of R-BAD (rituximab, bendamustine, cytarabine, and dexamethasone) as a salvage treatment.

A 70-year-old man presented with acalculia and agraphia in December 2011. He had a 3.2-cm mass in the left parietal periventricular white matter with perilesional edema on contrast-enhanced magnetic resonance imaging (MRI). A Leksell frame-based stereotactic biopsy of the mass was performed on December 14, 2011, revealing diffuse large B-cell lymphoma. At the time of diagnosis, the Eastern Cooperative Oncology Group (ECOG) performance status and Karnofsky performance score were 1 and 90, respectively. Laboratory test results revealed elevated serum lactate dehydrogenase (LDH) levels (536 IU/L, reference range < 472 IU/L), but other parameters were within normal limits. Lumbar puncture revealed a cerebrospinal fluid (CSF) glucose level of 67 mg/dL and a total protein level of 63 mg/dL. The brain lesion did not involve the deep structures. The International Extranodal Lymphoma Study Group (IELSG) score was observed to be 3 and the Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic score was class 3. No evidence of systemic lymphadenopathy or ocular involvement was detected.

An initial treatment with three cycles of high dose MTX (3,500 mg/m^2) led to a 6-month regression of the CNS lymphoma. The first primary CNS lymphoma relapse was treated with whole-brain radiation therapy, 180 cGy in 17 fractions; this led to a 9-month regression. The patient revisited the emergency department in October 2013 with nausea and short-term memory impairment. MRI revealed recurrent lymphoma with ependymal seeding from the sec-

ond relapse. He was treated with four cycles of high dose cytarabine (2,250 mg/m^2 for 3 days), and the subsequent brain MRI revealed regression of the CNS lymphoma. The patient was followed-up in the outpatient department, and images of the brain were taken regularly. He visited the outpatient department in September 2015 due to sudden blindness in his left eye. An ophthalmological examination revealed lymphomatous infiltration of the optic nerve, and brain MRI revealed thickening and enhancement of the left optic nerve, which was considered a third relapse of the primary CNS lymphoma. The patient was retreated with R-BAD chemotherapy including 375 mg/m^2 rituximab on day 1, 75 mg/m^2 bendamustine on days 2 and 3, 800 mg/m^2 cytarabine on days 2–4, and 20 mg dexamethasone on days 1–4. The blindness in his left eye recovered to baseline visual acuity after the first cycle of the R-BAD regimen. Brain MRI after four cycles of R-BAD chemotherapy revealed full regression of the lymphoma infiltration (Fig. 1). The R-BAD therapy was well tolerated by the patient; however, grade 4 neutropenia without fever and thrombocytopenia were observed during the chemotherapy. The patient is now receiving the planned sixth cycle of R-BAD chemotherapy with follow-up imaging of the brain. Until now, he has not shown any focal neurological symptoms or cognitive impairment.

The prognosis of patients with refractory or relapsed PCNSL is usually poor. No standard treatment approach is available for patients with relapsed/refractory PCNSL because of the heterogeneity of the therapies and the lack of large, prospective clinical trials [6].

Although rituximab, a chimeric monoclonal antibody against the CD20 antigen, improves survival in patients with systemic non-Hodgkin's lymphoma, its benefit in the treatment of PCNSL has not been firmly established yet. Many studies have suggested that compared to CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) chemotherapy, adding rituximab to the CHOP chemotherapy regimen does not significantly decrease the CNS relapse rate of systemic, diffuse large B-cell lymphoma. These studies concur with a pharmacokinetic study demonstrating that rituximab levels in the CSF after intravenous administration were only 0.1% of their corresponding levels in the serum [7]. Therefore, it is unlikely that rituximab can cross the brain-blood barrier (BBB) to access lymphoma cells in the CNS. However, several retrospective series in patients with relapsed PCNSL have demonstrated that rituximab is effective in patients with PCNSL. A pilot study of refractory/relapsed PCNSL demonstrated that four of 12 patients had a radiographic response to intravenous rituximab monotherapy [8]. Two more retrospective studies demonstrated the efficacy of rituximab when it was added to a MTX-based regimen, indicating some activity in patients with PCNSL; this is associated with increased complete response rates that may eventually lead to prolonged overall survival without significant toxicity [9, 10]. This result may reflect the partially disrupted BBB in patients with PCNSL, which may allow the antibody to reach some of the lymphoma cells in the brain. This supports the inclusion of rituximab in the PCNSL treatment regimen.

Bendamustine is a bifunctional purine analog/alkylating agent that appears to lack cross-resistance to other alkylating chemotherapies. Tissue distribution studies of intravenous [^{14}C]-bendamustine in mice, rats, and dogs demonstrated that radioactivity was distributed broadly throughout the tissues, including the brain tissue [11]. According to a case study of breast cancer that metastasized to the brain and was treated with bendamustine, this drug may also penetrate the CNS [12]. A small trial demonstrated a 50% response

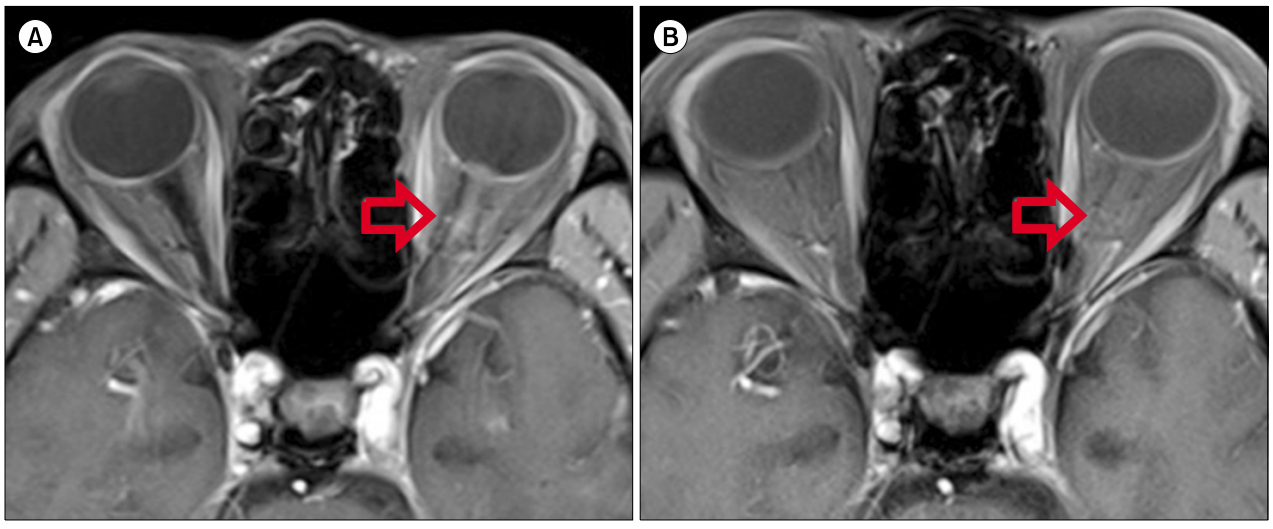

Fig. 1. **(A)** Gadolinium-enhanced, T1-weighted magnetic resonance imaging shows mild thickening and enhancement of the left optic nerve. **(B)** The optic nerve thickening was resolved after three cycles of R-BAD (rituximab, bendamustine, cytarabine, and dexamethasone) chemotherapy.

rate to bendamustine in 12 patients with MTX-refractory recurrent PCNSL [13].

Given the data from a number of trials and clinical series that have documented rituximab and bendamustine activity in patients with CNS lymphomas as monotherapy or a combined regimen, we hypothesized that the incorporation of rituximab and bendamustine into the cytarabine regimen for recurrent PCNSL may benefit patients with recurrent/relapsed primary CNS lymphoma.

We observed that R-BAD chemotherapy had a remarkable effect in our patient who had been previously treated with high doses of MTX and cytarabine, whole brain radiation therapy, and corticosteroids. Furthermore, the treatment was well tolerated. The patient is now receiving an additional cycle of this regimen along with further follow-up and we are deciding whether additional cycles are needed for the treatment.

Although the patient tolerated the R-BAD chemotherapy, he experienced grade 4 neutropenia and thrombocytopenia; however, he spontaneously recovered from these conditions. Therefore, longer follow-up periods and more number of treated cases are required to evaluate the toxicity of this regimen. In other studies of R-BAD chemotherapy for non-PCNSL hematologic malignancies, the most common toxicities were neutropenia and thrombocytopenia, as observed in our case. Common non-hematological toxicities included fatigue, infection, nausea, and liver toxicity [14, 15]. Thus, careful monitoring of these symptoms during R-BAD chemotherapy may be required.

In this case, we showed that the R-BAD regimen was effective as a salvage therapy in an elderly patient with recurrent/relapsed PCNSL. Although this is a single case report, we propose that R-BAD chemotherapy is an effective and well-tolerated salvage treatment regimen for patients with relapsed/refractory primary CNS lymphoma. Larger, prospective trials are needed to yield higher-grade evidence and enable stronger recommendations for PCNSL salvage treatments.

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