**Small Case Series**

**Effect of Intravitreous Rituximab Injections in Patients With Recurrent Ocular Lesions Associated With Central Nervous System Lymphoma**

Most central nervous system (CNS) lymphomas, including primary intraocular lymphoma, are large B-cell neoplasms that express CD20. Although intravenously administered rituximab, which is a chimeric anti-CD20 human monoclonal antibody, contributes to prolonged survival in patients with systemic large B-cell lymphoma, the drug may not affect the prognosis of CNS lymphoma, possibly because the monoclonal antibody does not effectively penetrate the intact blood-brain barrier. Therefore, intravenous rituximab treatment of ocular lesions associated with CNS lymphoma also could not be expected to be beneficial because of the blood-ocular barrier.

Recent studies have shown that 1 intravitreous injection of rituximab is safe in rabbit eyes. Kitzmann et al also reported that 3 to 4 injections of rituximab did not cause significant ocular toxic effects in patients with primary CNS lymphoma. However, because their patients were all treated with either additional systemic treatment or ocular treatment, they could not draw conclusions about the effectiveness of intravitreous rituximab therapy. We report the effect of intravitreous injections of rituximab on ocular lesions in 2 patients with recurrent CNS lymphoma.

**Report of Cases.** Case 1. A 52-year-old woman with suspected primary intraocular lymphoma underwent a diagnostic vitrectomy on her right eye, and the vitreous specimen showed CD20-positive diffuse large B-cell lymphoma. Magnetic resonance imaging showed brain involvement. She underwent whole-brain radiotherapy at a dose of 40 Gy, with 30 Gy administered to the orbit, and systemic high-dose methotrexate therapy. After these therapies, a vitreous specimen from her left eye showed no malignant cells in May 2003. The vitreous opacity in the fellow eye resolved, and the brain involvement responded to therapy. Since then, she has experienced 3 ocular recurrences (May and November 2006 and August 2007) in her right eye, with cells in the anterior chamber and vitreous cavity. Brain magnetic resonance imaging did not show recurrent CNS lymphoma at each time point, and the patient did not want to undergo systemic treatment. Intravitreous methotrexate injections were administered but were discontinued because of the development of severe corneal epitheliopathy (8 injections for the first recurrence, 6 injections for the second recurrence, and 4 injections for the last recurrence). At the first 2 recurrences, her right eye was free of malignant cells, but at the last recurrence, malignant cells were present and significantly increased in October 2007. We then administered an intravitreous injection of rituximab (1 mg/0.1 mL). One week after the first injection, the malignant cells dramatically disappeared from the eye (Figure 1B). The patient subsequently received an intravitreous injection of rituximab weekly for 4 weeks. Except for anterior chamber inflammation, which subsided with topical corticosteroid treatment, no complications developed during and up to 2 months after treatment.

Case 2. A 55-year-old woman with blurred vision and dense vitreous opacities in both eyes in September 2003 had a vitreous specimen of her right eye that showed CD20-positive lymphoma. She underwent intravitreous methotrexate therapy (10 injections) bilaterally. No malignant cells were observed in a vitreous specimen from her left eye, but severe corneal epitheliopathy developed bilaterally. In June 2006, she experienced ocular recurrences bilaterally, with cells in the anterior chamber and vitreous cavity. She again underwent intravitreous methotrexate therapy bilaterally (8 injections). The malignant cells disappeared; however, severe corneal epitheliopathy developed. In October 2007, she experienced ocular recurrences bilaterally, with cells in the anterior chamber and vitreous cavity (Figure 2A). Findings from a fundus examination also revealed multiple diffuse white lesions in the left retina (Figure 3A). The patient requested a therapy that required less frequent administrations compared with intravitreous methotrexate. After the first injection of intravitreous rituximab, intraocular cell numbers dramatically decreased (Figure 2B), and they completely disappeared after a second injection in both eyes (Figure 2C). The retinal lesion in the left eye also subsided substantially after the first injection (Figure 3B). This shows that...
rituximab can penetrate into the subretinal space. The patient underwent intravitreous injections of rituximab weekly for 4 weeks without complications (the observation period after treatment was 2 months). She has been free of CNS involvement until now.

The recurrences were based on clinical observation (mainly cell infiltration into the eye resistant to corticosteroid treatment), not on biopsy findings. The study protocol was approved by the Osaka University Medical School, Osaka, Japan, ethics committee, and informed consent was obtained from all the patients.

Comment. In these 2 cases, the malignant lymphoma cells disappeared from the eye after 1 intravitreous injection of rituximab, and the ocular lesions associated with CNS lymphoma resolved without significant complications after subsequent weekly injections of the drug for 4 weeks. The standard protocol of intravenous rituximab for B-cell lymphoma is infusion of rituximab at 375 mg/m² once weekly for 4 doses. A previous study indicated that the serum level of rituximab was significantly higher in responders than in nonresponders. The serum level was 71.3 µg/mL in responders 1 week after the first infusion. Kim et al reported that the level of rituximab in the vitreous was 113 µg/mL 1 week after 1 injection of 1 mg of rituximab into the rabbit vitreous. Although differences in anatomical and physiologic characteristics between human and rabbit eyes have to be considered, a 1-mg intravitreous injection into the vitreous once weekly for 4 weeks may be suitable for the initial clinical trial.

Although the mechanism of antitumor activity of rituximab remains debatable, recent studies of animal models and clinical investigations have provided support for apoptosis, complement-mediated cell lysis, and antibody-dependent cellular cytotoxicity. Because we observed a substantial inflammatory reaction in case 1 but not in case 2, we could not reach a conclusion regarding the main mechanism in the rapid clearance of malignant cells in these 2 cases. Further clinical investigations should be performed to clarify this issue.

Recently, intravitreous methotrexate was reported to be an effective local therapy for ocular lesions in CNS lymphoma; however, the effects were obtained after several injections, and ocular complications, including corneal epitheliopathy, developed frequently. Despite the few patients and short follow-up, these case reports suggest that intravitreous injection of rituximab can be an alternative local treatment for ocular lesions in CNS lymphoma.

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