Regression of Refractory Intraocular Large B-Cell Lymphoma With Lenalidomide Monotherapy

Case Report

A 59-year-old white woman presented in 2005 with left periorbital swelling, proptosis, and hyposmia. Biopsy of a left paranasal mass revealed sheets of pleomorphic large lymphoid cells, along with scattered mitotic figures (Fig 1). Immunohistochemical stains established a diagnosis of diffuse large B-cell lymphoma. Staging demonstrated disease limited to the left ethmoid sinus. She was treated with six cycles of rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy, plus intrathecal methotrexate as CNS prophylaxis, followed by involved field irradiation.

Six months after completion of treatment, she began to experience the insidious development of bilateral floaters in both eyes, left greater than right. Ultimately, over the course of a year, reading became difficult, and an ophthalmologic examination was performed, which demonstrated a vitreal infiltrate. A vitrectomy was diagnostic of large B-cell lymphoma, as confirmed by flow cytometry, which identified a population of CD19- and CD20-positive B-cells of large size by forward scatter; these were negative for CD5 and CD10 expression. Analysis of light chain expression reproducibly showed a definitive monoclonal, lambda-restricted B-cell population, which was diagnostic for B-cell lymphoma. The surgical pathology report also stated that the histologic type of the vitreal lymphoma cells was compatible with recurrence of the patient's prior large B-cell lymphoma. Restaging could identify only intraocular recurrence. Additional external-beam radiation to the eyes was considered but deferred because of concerns regarding the cumulative effects of irradiation to the left optic nerve as a consequence of prior treatment of the involved field. Instead, the

patient was treated with intravitreal rituximab injections to both eyes, which yielded a partial response, but these were discontinued when repeat brain magnetic resonance imaging (MRI) identified new disease within the left frontal lobe.

She transferred her care to a tertiary care center specializing in CNS lymphoma and was treated with high-dose chemotherapy for recurrent intraocular lymphoma with suspected CNS dissemination. She received 5 months intravenous high-dose methotrexate, in combination with temozolomide plus rituximab. Regression of CNS and intraocular disease was noted by MRI and complete ophthalmologic examination. To consolidate this response, the patient was subsequently treated with infusional etoposide over 96 hours plus high-dose cytarabine 2 gm/m², twice daily, with consideration of autologous stem-cell transplantation.

Within 3 weeks of completion of intensive consolidation, the patient again noted increasing haziness involving the left eye. Recurrent intraocular lymphoma was diagnosed by slit-lamp examination, and restaging MRI again identified a new enhancing lesion, this time within the corpus callosum; large, atypical lymphoid cells were also identified within the CSF (Fig 2). To avoid whole-brain irradiation, the patient elected to participate in a phase I trial of intraventricular rituximab plus methotrexate injections via an Ommaya reservoir. Five weeks of treatments two times per week yielded complete regression of malignant CSF cytology as well as partial regression of the callosal lesion; however, slit-lamp examination documented progression of intraocular lymphoma involving the left eye, prompting discontinuation of intrathecal therapy. Because of the well-circumscribed and solitary nature of her brain parenchymal lymphoma, the enhancing volume was treated with gamma-knife radiosurgery, which on restaging brain MRI resulted in a complete response. However, atypical lymphoid cells were

Fig 1.

Fig 2.

Fig 3.

persistently detected within the CSF, and there was symptomatic progression of intraocular lymphoma.

As a last resort before ocular and whole-brain irradiation, a trial of lenalidomide, starting at 5 mg/d, administered orally, was initiated 2 months after gamma-knife radiosurgery. At this new baseline, funduscopic examination demonstrated vitreal infiltrates involving both eyes. A mild vitreal haze was noted in the right eye temporally, with best corrected visual acuity (BCVA) of 20/40 (Fig 3A). A dense vitreous haze obscured the optic nerve and retinal details in the left eye, with BCVA of 20/70 (Fig 3B, arrow indicates underlying retinal vessels). Within 1 week of daily lenalidomide treatment, the patient noted marked improvement in her vision. At 1 month of lenalidomide monotherapy, marked regression of intraocular lymphoma was confirmed by her ocular oncologist. At 3.5 months of continued treatment with lenalidomide, at modest doses of 5 mg alternating with 10 mg, every other day, further regression of intraocular lymphoma was achieved, and no malignant lymphoid cells within the CSF could be detected. Findings at the 3-month funduscopic examination are shown in Figure 3C, demonstrating clearing vitreous haze temporally in the right eye (BCVA, 20/30) and dramatic regression of the lymphomatous infiltrate in the left eye (BCVA, 20/30; Fig 3D). Of note, the patient did not receive glucocorticoids in the antecedent 6 months or during the intervention with lenalidomide as monotherapy. Thus far, the ocular response with lenalidomide has per-

sisted for at least 4 months, and the intervention has been without significant toxicity.

Discussion

This case illustrates many of the established treatment approaches for ocular lymphoma, some of which have significant limitations. External-beam radiotherapy may still be the most appropriate first-line treatment for primary intraocular lymphoma; however, ocular radiotherapy does not address the risk for brain dissemination in cases of isolated intraocular relapse or in primary intraocular lymphoma, which in 80% of cases ultimately disseminate to the brain.¹ Given that many patients wish to avoid whole-brain irradiation, a rational approach has been to combine high-dose methotrexate with ocular radiotherapy.² The rationale of this approach is underscored by the fact that high-dose methotrexate may yield cytotoxic concentrations (micromolar) in the vitreous and aqueous humor within 4 hours after infusion.³ Other cytotoxic approaches with activity in intraocular lymphoma include trofosfamide (a congener of cyclophosphamide)⁴ as well as high-dose chemotherapy and autologous stem-cell transplantation, including first-line salvage with infusional etoposide plus cytarabine⁵ (a similar regimen was administered to the patient in this report). Direct intravitreal rituximab and methotrexate injections also have significant activity in intraocular lymphoma,⁶⁻¹⁰ but these require repeat administrations and can be associated with serious

complications such as cataracts, corneal epitheliopathy, maculopathy, vitreous hemorrhage, optic atrophy, retinal detachment, and endophthalmitis.¹ There is also preliminary evidence that intravitreal rituximab injections via an Ommaya reservoir may also lead to responses within the intraocular compartment in patients with recurrent/refractory CNS and intraocular lymphomas.¹¹

Here we present the first example, to our knowledge, of a major response to lenalidomide in relapsed/refractory intraocular large B-cell lymphoma. Although lenalidomide has been demonstrated to have immunomodulatory properties, its precise mechanism of action in many contexts is undefined and may also include disruption of tumor-stromal interactions, which promote lymphomagenesis within the ocular or CNS microenvironment.¹²⁻¹⁴ Given the response demonstrated in this patient as well as its potent activity in multiple myeloma and the evidence for its efficacy in other types of non-Hodgkin's lymphomas,¹⁵⁻¹⁷ we believe that the use of lenalidomide in intraocular and CNS lymphomas may warrant additional investigation.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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