INTRODUCTION

Radiation retinopathy is seen after irradiation of intraocular, orbital, sinus, brain, and neck cancers (1-6). The first clinical manifestation is radiation vasculopathy characterized by microaneurysms, neovascularization, vascular occlusions, and incompetence (2, 4, 7). Leakage of normal and abnormal appearing retinal blood vessels results in clinically apparent edema, hemorrhages, and exudates (2). Microvascular occlusions are seen as retinal cotton-wool spots and angiographic capillary nonperfusion. However, early vision loss is usually due to vascular incompetence-associated macular edema (2). Late macular vision loss is typically due to ischemia and fibrosis. Left untreated, eyes with radiation retinopathy are also at risk for vitreous hemorrhage, retinal detachment, and neovascular glaucoma (4, 8).

There is no widely established treatment protocol for radiation retinopathy. Past case series have examined the efficacy of hyperbaric oxygen and focal and panretinal laser photocoagulation (9-12). Intravitreal drug therapy has involved the use of triamcinolone acetonide and anti–vascular endothelial growth factor (anti-VEGF) agents (13-17). In 2007, we reported our initial observations that intravitreal injections of anti-VEGF bevacizumab for radiation maculopathy and optic neuropathy were associated with

PURPOSE. To report on intravitreal bevacizumab treatment for external beam radiation therapy (EBRT)-related radiation maculopathy.

METHODS. Three patients (4 eyes) with EBRT-related maculopathy were treated with periodic (4- to 8-week) intravitreal injections of bevacizumab (1.25 mg in 0.05 cc). Outcome measures included best-corrected Early Treatment Diabetic Retinopathy Study visual acuity, retinal examination, fundus photography, fluorescein angiography, and optical coherence tomography.

RESULTS. Patients were diagnosed with Stage 3 radiation maculopathy occurring 12, 19, and 48 months after irradiation. One received 50 Gv of 6-MV photon EBRT for a maxillary carcinoma, the second 30.6 Gv of 6-MV photon EBRT for intraocular lymphoma, and the third 72 Gy proton beam irradiation for adenoid cystic carcinoma of the lacrimal gland. With up to 33 months follow-up, visual acuities improved (8 and 11 letters) in 2 eyes, gained 5 letters in 1 eye and 1 decreased 5 letters from 20/16 to 20/20. All cases demonstrated clinical findings of decreased intraretinal hemorrhages, cotton-wool spots, and retinal edema. There were no significant ocular or systemic side effects.

CONCLUSIONS. Intravitreal anti-VEGF therapy was associated with reductions of EBRT-related retinopathy. No ocular or systemic side effects were noted. Anti-VEGF therapy may be considered radiation maculopathy secondary to EBRT.

KEY WORDS. Anti-VEGF, Avastin, Photon, Proton, Radiation, Retinopathy

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regression of retinal edema, hemorrhages, exudates, and neovascularization (14). Most of these patients were found to have resolution of metamorphopsia and stabilization and/or improvement in visual acuity. Longer-term follow-up showed a trend toward suppression of radiation maculopathy with preservation of vision (15). More recently, a second anti-VEGF drug, ranibizumab (Lucentis, Roche-Genentech, South San Francisco, California, USA), was shown to suppress radiation retinopathy (16). All of the aforementioned cases of radiation maculopathy occurred as a result of ophthalmic plaque radiation therapy.

Many more patients develop radiation retinopathy after external beam radiation therapy (EBRT) for thyroid eye disease, sinus malignancies, and orbital and intracranial tumors (4). In review of the literature, we could only find one recent case report of successful anti-VEGF therapy for radiation maculopathy after external “proton” beam radiation therapy (18). Herein, this study is important because it examines the effect of periodic intravitreal anti-VEGF bevacizumab for a series of patients with radiation maculopathy secondary to EBRT.

RESULTS

Case 1

An 85-year-old woman was referred to The New York Eye Cancer Center due to radiation maculopathy–related decreased visual acuity in her left eye. She was functionally monocular with hand motions vision in the right eye due to an old central retinal vein occlusion, a macular scar, and optic neuropathy. The currently affected left eye was 20/100, with subjectively diminishing vision and ophthalmoscopic evidence of intraretinal microangiopathy, retinal hemorrhages, and macular edema (Fig. 1). Fluorescein angiography revealed hypofluorescence related to retinal hemorrhages and scattered areas of retinal capillary nonperfusion. Late-phase angiographic images revealed severe cystoid macular edema (CME), confirmed by combined scanning laser ophthalmoscopy (SLO)/OCT.

MATERIALS AND METHODS

This study adhered to the tenets of the Declaration of Helsinki of 1975, as revised in 2000, the Health Insurance Portability and Accountability Act of 1996, and was approved by the Institutional Review Board of The New York Eye Cancer Center. Entry criteria included the presence of EBRT-related radiation retinopathy. Patients’ charts were reviewed for the original pathology, radiation treatment details, comorbidities, and clinical history.

A best-corrected visual acuity measurement (Early Treatment Diabetic Retinopathy Study charts with certified examiners), ophthalmoscopy, fundus photography, angiography, and optical coherence tomography (OCT) imaging were obtained to establish baseline characteristics. These examinations were subsequently repeated every 6 to 8 weeks to monitor the safety and efficacy of treatment. Our methods of intravitreal injection (aseptic technique) have been described (3). In brief, bevacizumab (Avastin, Roche-Genentech, South San Francisco, CA, 1.25 mg in 0.05 cc in a tuberculin syringe) was introduced through the pars plana (through a 31-gauge needle). Optic nerve perfusion was assessed by clinical examination with dilated ophthalmoscopy. Both optic nerve perfusion and intraocular pressures were acceptable prior to discharge and the patients subsequently were placed on topical antibiotic therapy for 3 days. Injections were repeated every 4 to 8 weeks based on changes in visual acuity and funduspic appearance.
Fig. 1 - Case 1. (A) Fundus photography taken before the first injection of intravitreal bevacizumab reveals multiple retinal hemorrhages (arrow). (B) Corresponding initial fluorescein angiography shows diffuse bright leakage temporal to the optic nerve (arrows) particularly around the fovea (cystoid macular edema). (C) Fundus photography documents resolution of the retinal hemorrhages (1 year after periodic intravitreal bevacizumab injections). (D) Corresponding fluorescein angiography demonstrates reductions in retinal edema consistent with restoration of the functional anatomy of the macula and improved visual acuity (from an initial 20/100 to 20/63).

Fig. 2 - Case 3. (A) Fundus photography before first injection of intravitreal bevacizumab reveals multiple cotton-wool spots (arrow). (B) Corresponding fluorescein angiography reveals capillary dropout and mild perifoveal edema. As compared to case 1, there is less macular edema and better initial visual acuity (20/20). (C) Fundus photography after 33 months of periodic intravitreal bevacizumab; the cotton-wool spots have disappeared and the patient maintains 20/20 visual acuity. (D) Corresponding fluorescein angiography reveals persistent macular edema (arrow).
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no local or systemic complications related to intravitreal injection of bevacizumab.

Case 2

A 78-year-old woman presented to The New York Eye Cancer Center for management of radiation maculopathy. Six years before, she had been diagnosed with marginal B-cell lymphoma of the spleen and bone marrow. Six months before our examination, she underwent a pars plana vitrectomy that had established the diagnosis of intraocular lymphoma in her left eye. In the context of her systemic disease and ocular involvement, the patient was treated with EBRT. Bilateral orbital radiation was delivered in 17 daily fractions of 180 cGy, for a total 30.6 Gy. A Thiotepa-based systemic chemotherapy regimen was subsequently discontinued due to congestive heart failure. On 12-month follow-up after completion of EBRT, the patient’s visual acuity was 20/30 OD and 20/25 OS. Funduscopic examination revealed dot hemorrhages in her right macula with intraretinal edema (stage 3 radiation retinopathy). Treatment involved 11 intravitreal bevacizumab injections in her right eye from April 2008 to May 2010. One month after the second injection into her right eye, retinal hemorrhages resolved. Later, a cotton-wool spot appeared but also resolved. More recently, she has been noted to develop radiation maculopathy in her left eye and has received 2 monthly intravitreal bevacizumab injections. Her most recent visual acuity was 20/25 OD and 20/20 OS. Ophthalmoscopy, fluorescein angiography, and OCT have revealed resolution of her macular edema in the right eye. No local or systemic complications could be related to anti-VEGF therapy.

Case 3

A 25-year-old man presented to The New York Eye Cancer Center for a management of a left adenoid cystic carcinoma of the lacrimal gland (AJCC T4a). A previous excisional biopsy revealed perineural involvement, focal vascular invasion, and multifocal involvement of the surgical margins. With a preoperative visual acuity of 20/16, a lateral orbitotomy was performed with an extended resection (including bone removal) followed by high-dose, fractionated, proton beam radiation therapy (total dose of 72.0 Gy in 36 200 cGy daily fractions). Nineteen months after irradiation, the patient’s visual acuity was 20/20 in the left eye. However, funduscopic examination revealed intraretinal macular hemorrhages and multiple cotton-wool spots (stage 3 radiation retinopathy). Fundus photography, fluorescein angiography, and OCT revealed evidence of intraretinal edema consistent with radiation maculopathy (Figs. 2 and 3B).

From September 2007 to June 2010, he received 19 intravitreal bevacizumab injections. Due to the combination of dry eye and mechanics of injection, he experienced 2 transient corneal abrasions. There were no systemic complications. At last follow-up, his visual acuity remained at 20/20 OS with noticeable reductions of retinal hemorrhages, cotton-wool spots, and macular edema (Fig. 2). All 3 patients in this series tolerated periodic intravitreal in-
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Injections of anti-VEGF bevacizumab. Findings of decreased retinal hemorrhage, diminished retinal edema, and improvements in visual acuity were associated with treatment. Retinal edema was more persistent and the resultant visual acuity worse in case 1, where treatment was started later than the other cases (Fig. 3). No permanent ocular or systemic side effects were noted during this study.

DISCUSSION

This study demonstrates that periodic intravitreal anti-VEGF bevacizumab injections were associated with decreased leakage of retinal blood vessels, diminished macular edema, and preservation or improvements in visual acuity in treatment of patients with EBRT-related radiation retinopathy. This is important because radiation retinopathy is a common and blinding complication of EBRT. Specifically, the incidence may be as high as 20% for cases of maxillary sinus cancer (as described in case 1). Parsons et al (19) reported that radiation retinopathy was both dose and dose rate dependent. They found it less likely with daily fractions less than 1.9 Gy and at total doses less than 45 Gy. Similarly, plaque-related radiation maculopathy has been found to be dose dependent in multivariate analysis including patient- and tumor-specific factors (2). Several studies suggest that patients with comorbid diabetes and those who receive adjuvant chemotherapy (as described in case 2) are at greater risk (1, 2, 4).

Multiple centers have reported that anti-VEGF therapy can suppress plaque brachytherapy-related radiation retinopathy (14-17, 20, 21). Reports now include the use of both bevacizumab (Avastin) and ranibizumab (Lucentis). In general, these studies have revealed OCT findings of restoration of the functional anatomy of the macular retinal nerve fibers (typically destroyed by persistent edema), decreased vascular permeability with resolution of components, profound changes in retinal blood flow, and preservation of vision. Infectious endophthalmitis continues to be the most concerning risk related to intravitreal anti-VEGF therapy (due to its potential for significant vision loss). Studies of serial intravitreal bevacizumab (for its most common indication, neovascular age-related macular degeneration) revealed less than a 0.07% risk of endophthalmitis with every injection (22, 23). Given the frequency of intraocular injections for radiation retinopathy, there are concerns related to the cumulative risk for a serious infection. Other reported local complications include secondary glaucoma (24).

In consideration of the findings of this study, periodic surveillance of eyes exposed to EBRT is indicated. However, unlike choroidal melanoma (where ocular oncologists and retinal specialists periodically evaluate patients after plaque brachytherapy), patients with orbital and sinus EBRT are less likely to be monitored with periodic dilated ophthalmoscopic examinations. In consideration of the progressive pathophysiology of radiation retinopathy, such delays in diagnosis are likely to result in long-term macular edema leading to ischemia, fibrosis, and irreversible vision loss. For example, this is seen in case 1, where ophthalmologists were involved only after the patient noted a subjective decrease in vision, and when the more longstanding maculopathy was more difficult to remediate. In contrast, in cases 2 and 3 (where ocular oncologists were primarily involved), the maculopathy was treated early and the vision preserved.

Radiation retinopathy and optic neuropathy are leading causes of severe irreversible blindness after radiation therapy for intraocular, head, and neck cancers and certain orbital inflammatory disorders. We have previously reported on our original experience with intravitreal bevacizumab and ranibizumab for the treatment of radiation maculopathy and optic neuropathy related to palladium-103 plaque brachytherapy for choroidal melanoma (14-16, 25, 26). This initial study reports on improvements or stabilization of vision after intravitreal bevacizumab for patients with EBRT-related radiation retinopathy. Further long-term and prospective studies of anti-VEGF treatments for radiation retinopathy are indicated.

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