Anti–Vascular Endothelial Growth Factor Bevacizumab (Avastin) for Radiation Retinopathy

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Objective: To evaluate intravitreal bevacizumab for radiation retinopathy.

Methods: After plaque radiation therapy, 6 patients developed radiation retinopathy (retinal edema, hemorrhages, microangiopathy, and neovascularization). Intravitreal bevacizumab (1.25 mg in 0.05 mL) was periodically injected (every 6-8 weeks). Ophthalmic evaluations included visual acuity, ophtalmic examination, fundus photography, fluorescein angiography, and optical coherence tomography/scanning laser ophthalmoscopy (OCT/SLO) imaging.

Results: No bevacizumab-related ocular or systemic adverse effects have occurred within the first 8 months of therapy. Progressive reductions in retinal hemorrhages, exudates, cotton-wool spots, and microangiopathy were documented by photography, angiography, and OCT/SLO imaging. Decreased macular edema was the most common finding. Improvement or stabilization of visual acuity was noted in all cases.

Conclusions: Intravitreal bevacizumab was tolerated, improved or maintained vision, and reduced hemorrhage and retinal edema (angiographic leakage). This study should lead to additional and longer-term studies of humanized monoclonal anti–vascular endothelial growth factor antibody therapy for radiation retinopathy.

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Radiation retinopathy is a common sight-limiting complication of ophthalmic radiation therapy. It occurs after irradiation for tumors or inflammations of the choroid, retina, orbit, and paranasal sinuses. The risk of radiation retinopathy is related to effective dose, the presence of systemic disease (eg, diabetes mellitus), and the use of radiation sensitizers (eg, chemotherapy). Although laser photocoagulation can be used to control radiation retinopathy, radiation maculopathy typically results in blindness.

Histopathology of radiation retinopathy reveals an obliterative endarteritis (endothelial cell loss, thickened vessel walls) leading to intraretinal microangiopathy (microaneurysms, arteriovenous shunt vessels, neovascularization). Radiation retinopathy results in both ischemia (capillary dropout) and exudation (retinal hemorrhages, lipids, and edema).

Bevacizumab (Avastin; Genentech, San Francisco, Calif) is a humanized monoclonal antibody to vascular endothelial growth factor (VEGF). Selective antibody blocking (anti-VEGF therapy) inhibits the formation of abnormal blood vessels and decreases vascular permeability. Inhibition of ocular VEGF has been investigated in treatment of exudative macular degeneration, diabetic retinopathy, central retinal vein occlusion, neovascular glaucoma, revision of a filtering bleb, and radiation optic neuropathy.

Systemic bevacizumab has been reported to carry a small albeit significant risk of thromboembolic events (stroke, myocardial infarction). In contrast, intravitreal administration involves a much smaller dose that all but eliminates systemic risks in exchange for ocular risks. This study reports on the short-term effects of intravitreal administration of bevacizumab on radiation retinopathy.

Methods

This study adhered to the tenets of the Declaration of Helsinki, the Health Insurance Portability and Accountability Act of 1996, and the institutional review board of The New York Eye Cancer Center. Entry criteria included the presence of radiation-induced macular edema with secondary vision disturbance or loss of acuity. This report includes the first 6 consecutive patients treated with intravitreal anti-VEGF bevacizumab for radiation retinopathy with maculopathy.

A best-corrected visual acuity measurement (ETDRS [Early Treatment Diabetic Retinopathy Study] chart), ophthalmoscopy, fundus photography, angiography, and optical coherence tomography/scanning laser ophthalmoscopy (OCT/SLO) imaging were used to establish baseline characteristics. These examinations were subsequently repeated every 6 to 8 weeks to moni-
tor the safety and efficacy of treatment. The fluorescein angiogram frames selected for comparison were matched (as close as possible) to each patient’s previous examination (Figures 1, 2, and 3).

Our methods of intravitreal injection (aseptic technique) have been described.16 In brief, bevacizumab (1.25 mg in 0.05 mL in a tuberculin syringe) was introduced through the pars plana (through a 30-gauge needle). All intravitreal injections were performed by one of us (P.T.F.). Following injection, 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 1 week. Injections were repeated every 6 to 8 weeks based on changes in visual acuity and macular edema.

RESULTS

In this series, 6 patients with radiation retinopathy secondary to ophthalmic plaque irradiation for subfoveal or macular choroidal melanomas (not amenable to or uncontrolled by laser photocoagulation) were treated with intravitreal bevacizumab (Table 1). The mean age at time of injection was 56.8 years (range, 34-71 years). There were 5 women, 3 right eyes, and 1 patient with non–insulin-dependent diabetes (Table 1). We report on a mean intravitreal bevacizumab follow-up of 4.7 months (range, 2-8 months).

RADIATION DOSIMETRY

Each patient had been treated with palladium 103 ophthalmic plaque brachytherapy to a mean foveal dose of 77.5 Gy (range, 49-148.1 Gy). Each radiation treatment was delivered over 5 to 7 consecutive days (Table 1). There were no acute complications related to surgery or irradiation. We report on a mean plaque brachytherapy follow-up of 60.7 months (range, 18-187 months).
EXUDATION AND MACULAR EDEMA

The patients in our study had a mean time from plaque brachytherapy to development of radiation retinopathy of 41.5 months (range, 9-159 months). Reduction of macular edema was the most consistent and reproducible finding (Figure 1). Findings of resolution of macular edema were accompanied by improvements in visual acuity (n=2) and reduction in subjective metamorphopsia (n=4) (Table 2). Though less dramatic, there was an overall reduction in the size and distribution of retinal hemorrhages and exudates (Figure 1 and Figure 2). There were no cases of progression of retinal hemorrhages, exudates, or cotton-wool spots.

MICROANGIOPATHY

There was evidence of closure of microaneurysms and intraretinal microangiopathy (Figure 2). The most common finding was decreased vascular permeability, evidenced by sharpening of blood vessel edges on fluorescein angiography (Figure 2). There was no apparent effect on areas of capillary nonperfusion.

OCT/SLO IMAGING WITH PHOTOGRAPHIC CORRELATION

Case 1 pretreatment photographs and fluorescein reveal hemorrhages, cotton-wool spots, capillary nonperfusion, and thickened edematous retina (Figure 3). Imaging with OCT/SLO clearly demonstrates a thickened and hyperreflective nerve fiber layer (between the optic nerve and the fovea) with shadowing of the outer retinal layers and retinal pigment epithelium (Figure 4). The temporal macular retina is attenuated (attributed to high-dose radiation near the tumor). After 2 injection cycles (3-4 months), there was almost complete OCT/SLO resolution of macular edema with restoration of the normal macular contour (Figure 4).

VISUAL ACUITY

Treatment resulted in improvements (n=2) and stability (n=4) in best-corrected visual acuity as well as subjective reports of decreased haze and metamorphopsia (n=4). Overall, no patients lost vision due to radiation retinopathy or bevacizumab during this study (Table 2).
ADVERSE EFFECTS

The most common adverse effects involved subjective reports of seeing “round blue objects” for a day or two after the injection. These were attributed to small air bubbles, though none could be seen with ophthalmoscopy. Optic nerve perfusion was transiently affected by injection (in most cases) as was intraocular pressure.

Figure 3. Composite of color and fluorescein angiographic images over time. A, Prior to bevacizumab treatment, the color photograph reveals retinal hemorrhages, exudates, intraretinal microangiopathy, and cotton-wool spots in the macula. B, The corresponding early fluorescein angiogram reveals mild macular edema, capillary nonperfusion, microaneurysms, and intraretinal hemorrhage between the optic nerve and the fovea. C, Three months after treatment with intravitreal bevacizumab, a color photograph reveals decreased hemorrhages and both increased and decreased retinal exudates. D, The corresponding fluorescein angiogram shows markedly decreased macular hemorrhage exposing additional microangiopathy and capillary nonperfusion. There is overall decreased intraretinal microangiopathy and leakage as evidenced by sharpening of normal and neovascular vessel walls as well as the optical coherence tomography/scanning laser ophthalmoscopy findings in Figure 4.
Radiation retinopathy is a frequent complication of ophthalmic radiation therapy. Specifically, ionizing radiation (used for radiation therapy) damages cellular DNA and other vital cellular structures leading to either immediate cell death or mutations that can take years to destroy cells. Thus, ophthalmic plaque radiation therapy induces a progressive closure of tumor and retinal vessels within the targeted zone beneath the plaque. Histopathology of radiation-induced vasculopathy reveals the destruction of both vascular endothelial cells and pericytes (that maintain blood vessel walls). Clinically, radiation vasculopathy appears as microaneurysms, vascular occlusions, capillary dropout, and leakage (hemorrhage, exudation, and edema). All these findings contribute to tissue ischemia leading to intraocular neovascularization. The use of larger doses (and more rapid dose rates) increases radiation complications and decreases the probability of repair.

Finger and Kurli reported on the use of laser photoacogulation to obliterate the ischemic irradiated zone created by ophthalmic plaque brachytherapy.

While their findings suggested that laser photoacogulation of the irradiated extramacular “target” zone was effective in preventing or regressing radiation retinopathy, they avoided laser to and around melanomas beneath and adjacent to the fovea.

As noted in that series, macular melanomas created a clinical challenge for which treatment with bevacizumab seems promising in addressing. One might theorize that like laser photoacogulation, bevacizumab may decrease the ocular ischemia resulting from plaque radiation or may induce vascular shunting by decreasing vascular permeability in nonvital tissue. Clearly, testing these theories is beyond the scope of this study.

In this series, regression of radiation retinopathy (hemorrhage, exudates, intraretinal microangiopathy, and macular edema) was noted after treatment with intravitreal bevacizumab. There was no apparent effect on capillary nonperfusion. The most consistent finding was decreased leakage from both preexisting and neovascular retinal vessels. These findings stand in stark contrast to the natural course of radiation maculopathy. As noted in that series, macular melanomas created a clinical challenge for which treatment with bevacizumab seems promising in addressing. One might theorize that like laser photoacogulation, bevacizumab may decrease the ocular ischemia resulting from plaque radiation or may induce vascular shunting by decreasing vascular permeability in nonvital tissue. Clearly, testing these theories is beyond the scope of this study.

All visual acuities were either stable or improved during this short-term study. However, we recognize that clinical judgment and prudence will be important in treating patients with 20/20 visual acuity. The risks and benefits must carefully be weighed and explained to each patient. Once diminished from macular edema, visual acuity may never return to 20/20. Clinical judgment will also factor in the patient symptoms (eg, meta-

### Table 1. Patient, Tumor, and Radiation Characteristics Prior to Treatment With Bevacizumab

<table>
<thead>
<tr>
<th>Patient No./Sex/Age, y</th>
<th>Eye</th>
<th>DM</th>
<th>HTN</th>
<th>Tumor Location</th>
<th>Length, mm</th>
<th>Width, mm</th>
<th>Height, mm</th>
<th>Plaque Size, mm</th>
<th>Distance to Fovea, mm</th>
<th>Distance to Optic Nerve, mm</th>
<th>Dose to Fovea, Gy</th>
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<td>10</td>
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<td>4</td>
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<td>2</td>
<td>4</td>
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<tr>
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<td>−</td>
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<td>−</td>
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<td>9.1</td>
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<td>3</td>
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<td>Mean, 56.8</td>
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Abbreviations: DM, diabetes mellitus; E, equator; HTN, hypertension; P, posterior; −, absent; +, present.

### Table 2. Results After Treatment With Intravitreal Bevacizumab

<table>
<thead>
<tr>
<th>Follow-up Time, mo</th>
<th>Plaque to Radiation Retinopathy, mo</th>
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<tbody>
<tr>
<td>Pretreatment Visual Acuity*</td>
<td>Posttreatment Visual Acuity*</td>
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<tr>
<td>Macular Edema</td>
<td>Retinal Hemorrhage</td>
</tr>
<tr>
<td>1 25 25</td>
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</tr>
<tr>
<td>2 320 100</td>
<td>Regression</td>
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<tr>
<td>3 20 20</td>
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<td>6 32 20</td>
<td>Regression</td>
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<td>Mean, 2.8</td>
<td>4.7</td>
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</table>

*Visual acuity is reported as 20/x, the best-corrected visual acuity measured by the ETDRS [Early Treatment Diabetic Retinopathy Study] chart.
Figure 4. Serial optical coherence tomography/scanning laser ophthalmoscopy (OCT/SLO) images were obtained. A, Prior to intravitreal bevacizumab, OCT/SLO imaging revealed the papillomacular nerve fiber layer is thickened (arrowheads) with intraretinal lucencies consistent with edema. The normal foveal contour is slightly flattened. B, Three months later, OCT/SLO imaging reveals persistent albeit decreased macular edema and less intraretinal fluid with some restoration of the normal fovea contour. C, Five months after the first intravitreal bevacizumab injection, as well as 2 additional doses, there is further decrease in papillomacular intraretinal edema with normalization of the macular contour.

morphopsia), the degree to which macular function is threatened, status of the fellow eye, systemic status (eg, metastatic disease, age), and the patient’s ability to return for follow-up visits. This study suggests that larger and longer-term studies of anti-VEGF medications for radiation retinopathy are needed.

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REFERENCES