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, ophthalmic 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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for 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. 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).

Figure 1. Composite of color and fluorescein angiographic images over time. A, Case 1: prior to bevacizumab treatment, the color photograph reveals retinal hemorrhages, exudates, and intraretinal microangiopathy. B, The corresponding early fluorescein angiogram reveals macular edema, capillary nonperfusion, microaneurysms, and focal leakage of neovascular vessels. C, Three months after treatment with intravitreal bevacizumab, a color photograph reveals decreased hemorrhages and exudates. D, The corresponding fluorescein angiogram shows markedly decreased macular edema, decreased intraretinal microangiopathy, and leakage (sharpening of vessel walls).
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 non-perfusion, 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.
However, no patients required anterior chamber para-
centesis or pharmacologic intervention.

No endophthalmitis, retinal detachment, or vitreous hemorrhage occurred. One patient was treated for ocu-
lar pain (systemic antibiotic) and one patient required
cataract surgery (needle injury).

**COMMENT**

Radiation retinopathy is a frequent complication of oph-
thalmic radiation therapy. Specifically, ionizing radia-
tion (used for radiation therapy) damages cellular DNA
and other vital cellular structures leading to either im-
mediate cell death or mutations that can take years to de-
stroy cells. Thus, ophthalmic plaque radiation therapy
induces a progressive closure of tumor and retinal ves-
sels within the targeted zone beneath the plaque. Histo-
pathology of radiation-induced vasculopathy reveals the
destruction of both vascular endothelial cells and peri-
cytes (that maintain blood vessel walls). Clinically, ra-
diation vasculopathy appears as microaneurysms, vas-
cular occlusions, capillary dropout, and leakage
(hemorrhage, exudation, and edema). All these find-
ings 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 pho-
tocoagulation to obliterate the ischemic irradiated zone
created by ophthalmic plaque brachytherapy. While their
findings suggested that laser photoagulation of the ir-
radiated extramacular “target” zone was effective in pre-
venting 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 bevaci-
zumab seems promising in addressing. One might theo-
rize that like laser photocoagulation, 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 (hem-
orhage, exudates, intraretinal microangiopathy, and macu-
lar edema) was noted after treatment with intravitreal be-
vacizumab. There was no apparent effect on capillary
nonperfusion. The most consistent finding was decreased
leakage from both preexisting and neovascular retinal ves-
sels. These findings stand in stark contrast to the natural
course of radiation maculopathy.

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 judg-
ment will also factor in the patient symptoms (eg, meta-

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

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<th>HTN</th>
<th>Tumor Location</th>
<th>Length, mm</th>
<th>Width, mm</th>
<th>Height, mm</th>
<th>Plaque Size, mm</th>
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Abbreviations: DM, diabetes mellitus; E, equator; HTN, hypertension; P, posterior; −, absent; +, present.

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

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<tr>
<th>Patient No.</th>
<th>Pretreatment Visual Acuity*</th>
<th>Posttreatment Visual Acuity*</th>
<th>Macular Edema</th>
<th>Retinal Hemorrhage</th>
<th>Exudate</th>
<th>Cotton-Wool Spots</th>
<th>Microaneurysms</th>
<th>Bevacizumab Injections, No.</th>
<th>First Injection From Plaque, mo</th>
<th>Follow-up Time, mo</th>
<th>Plaque to Radiation Retinopathy, mo</th>
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<td>3</td>
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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