Pharmacotherapy for Radiation Retinopathy

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Almost a decade ago, the Collaborative Ocular Melanoma Study (COMS) produced data showing no statistically significant difference in survival rates between patients with medium choroidal melanoma treated with either enucleation or plaque brachytherapy.[1] Thus, the primary treatment for medium-sized choroidal melanomas now utilizes a globe-salvaging approach.[2] Various radioisotopes are employed, including 192Ir, 125I, 106Ru, 103Pd, and 60Co. Retinal tolerances to the effects of radiation usually are far inferior to the therapeutic doses for tumor treatment.[3] As a result, retinopathy secondary to radiation has been found to vary from 10% to 62.8%,[4-12] with mean time to onset of 25.6 months (range, 8 to 74.9).[13] These data correspond to the COMS study finding that 55% of patients treated with radiation had evidence of radiation retinopathy.[14] Higher frequencies of radiation retinopathy have been correlated with increased tumor height, basal diameter, and thickness; higher radiation doses; and closer distance to the macula and fovea.[5,15-17]

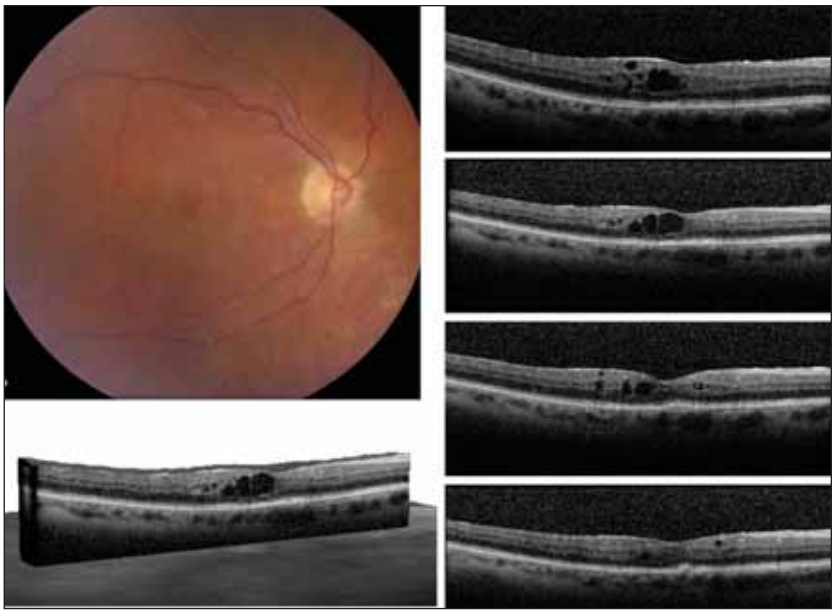

Figure 1. Post-plaque brachytherapy for choroidal melanoma shows radiation-associated macular edema (fundus photo – top left) and intraretinal edema with cysts (OCT, right; 3-D OCT construction, bottom left).

Radiation retinopathy manifests clinically similarly to diabetic retinopathy, with vascular changes including microaneurysms, retinal hemorrhages, exudates, telangiectatic vessels, cotton-wool spots from nerve fiber layer infarcts, as well as capillary nonperfusion and neovascularization.[18] The earliest sign of radiation effects, however, is macular edema, which was found to have a mean time of onset of 12-months based on optical coherence tomography (OCT), with some patients manifesting edema as early as 4 months. Additionally, at 2 years' follow-up, 70% of 135 patients were found to have macular edema by OCT, whereas only 38% were found to have clinical changes consistent with radiation retinopathy. Visual acuity can be variable at presentation, but median visual acuity at the onset of macular edema determined by OCT has been shown to be 20/40.[17]

CLASSIFICATION

The basis for classification of radiation retinopathy has progressed over the years, from clinical findings to fluorescein angiography, and recently to OCT. Early studies established fluorescein angiography as the gold standard for dividing retinopathy into ischemic or nonischemic. Macular edema was classified based on patterns of fluorescein leakage.[19,20] Others have classified radiation retinopathy based on the Early Treatment Diabetic Retinopathy Study (ETDRS),[21] using the ETDRS criteria for clinically significant macular edema (CSME) to apply

to clinically significant radiation macular edema (CSRME).[22,23] Earlier classification schemes were well-suited for use of focal laser photocoagulation as primary treatment. More recently, a staging system was developed to classify radiation retinopathy based on macular and extramacular changes. The system consisted of four stages, with stage 1 indicating extramacular ischemic changes and stage 2 macular ischemic changes. Stage 3 was presence of macular edema and retinal neovascularization, and stage 4 indicated vitreous hemorrhage and extensive retinal ischemia.[17,24] Now, however, with the advent of intravitreal agents, steroids and antiangiogenesis, and the recognition that findings of macular edema may occur as early as 4 months after radiation, a system based on OCT has been developed. Grading of OCT findings was based on a 5-stage scale of worsening macular edema. Grade 1 indicates extrafoveal, non-cystoid edema; grade 2 extrafoveal cystoid edema; grade 3 foveolar, non-cystoid edema; grade 4 mild-moderate foveolar cystoids edema; and grade 5 severe foveolar cystoid edema.[17]

Figure 2. Fundus of same patient after intravitreal bevacizumab shows improvement in intraretinal edema and cysts, with corresponding improvement in visual acuity by 1 line. Montage fundus photo and fundus photo (top and bottom left), with corresponding OCT images through the fovea (right).

PATHOGENESIS

Vascular endothelial growth factor (VEGF) has been shown to be a potent vascular permeability factor[25,26] that is elevated in eyes with ischemia. Studies have shown increased VEGF expression in eyes with choroidal melanoma, with the highest levels found in those receiving radiation treatment.[27,28] Radiation-induced macular edema is secondary to vascular permeability and leakage as seen on fluorescein angiography. VEGF has been postulated to contribute to the pathogenesis of macular edema secondary to radiation.[17] Additionally, other factors and cytokines, including interleukin-1 and -8 (IL-1, IL-8), and intracellular adhesion molecule-1 (ICAM-1), potentially contribute to vascular permeability and the pathogenesis of macular edema.[29] Intravitreal steroids and anti-VEGF agents have been used successfully in the treatment of other retinal diseases, including age-related macular degeneration (AMD),[30] central and branch retinal vein occlusion (CRVO and BRVO), and diabetic macular edema.[31] These findings suggest that the use of intravitreal anti-VEGF agents and triamcinolone may be effective in treating radiation retinopathy-related macular edema.

CORTICOSTEROIDS

Triamcinolone acetonide is a corticosteroid that has been studied for the treatment of macular edema associated with diabetes[32-34] and retinal vein occlusions,[35] with results inferior to focal/grid photocoagulation. Actions of triamcinolone are proposed to be secondary to the effect of decreasing vascular permeability through reductions in VEGF secretion and downregulation of VEGF gene expression and other cytokines, ultimately leading to restoration of the inner blood-retinal barrier.[36-41] Intravitreal triamcinolone has been shown to be effective in case reports, with early demonstration of potential in a patient with radiation retinopathy unresponsive to focal laser therapy.[42] A single intravitreal injection of 4 mg/0.1 mL triamcinolone was shown to improve visual acuity and central macular thickness (CMT) on OCT, with effects persisting for 3 months.[42] Following initial case reports, Shields et al[43] described 31 patients with radiation-associated macular edema who were treated with 4 mg/0.1 mL intravitreal triamcinolone. At 1 month, visual acuity was stabilized or improved in 91% of patients, and at 6 months this dropped to 45%. OCT central macular thickness

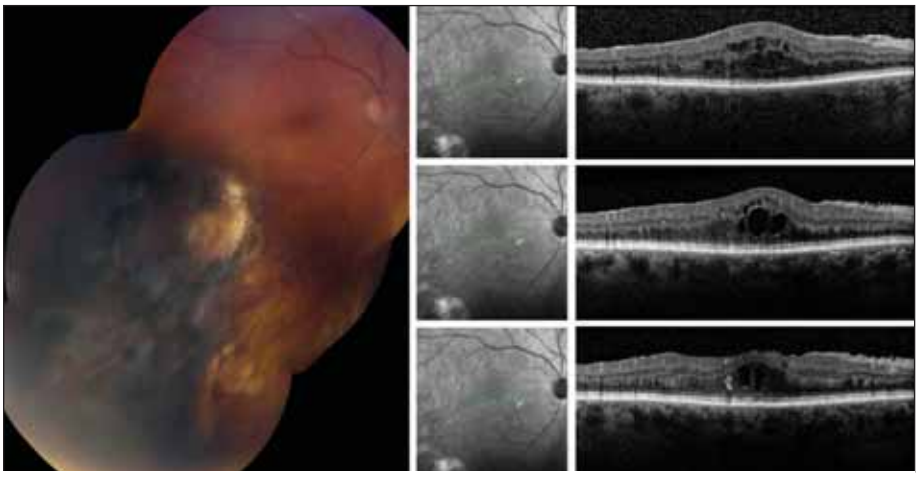

Figure 3. Severe radiation-associated macular edema. Montage photo (left) shows tumor in close proximity to the fovea, increasing likelihood of developing radiation retinopathy. OCT scout images (center) and corresponding OCT images (right) show severe elevation of the fovea with intraretinal fluid and cysts.

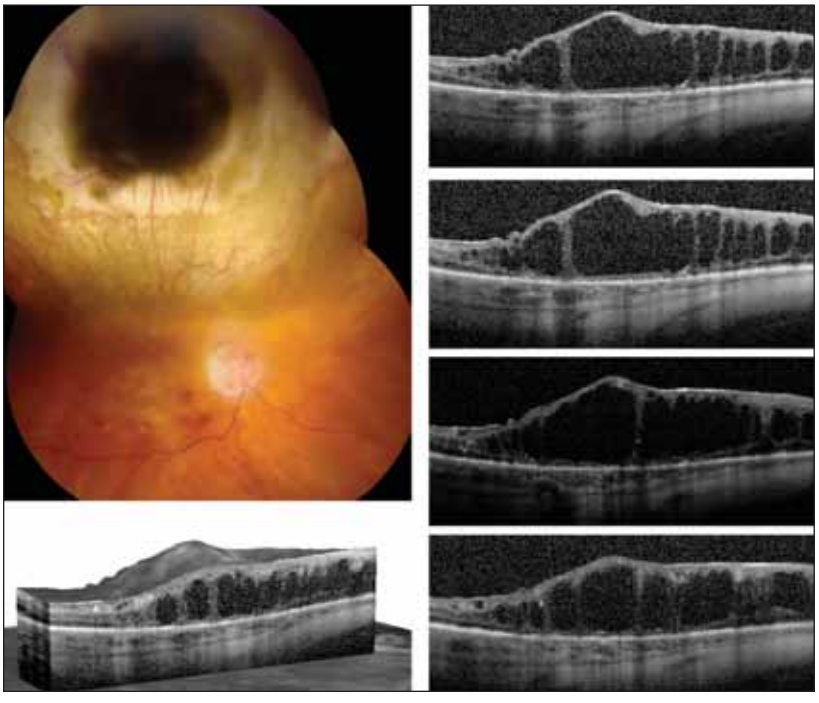

Figure 4. Severe radiation retinopathy (montage photo, top left) develops after plaque brachytherapy for choroidal melanoma. Close proximity to fovea resulted in severe macular edema (OCT, right, and 3-D construction, bottom left).

decreased from 417 µm to 292 µm at 6 months. These initial results show a promising response of edema to triamcinolone that is not sustained, and long-term results are not yet available. Additionally, side effects including cataracts, intraocular pressure (IOP) increases, and risk for infection must be carefully considered.

Periocular delivery of triamcinolone for radiation-associated macular edema has also been investigated. Horgan et al[44] treated 55 patients at the time of plaque radiotherapy, then 4 and 8 months later with 40 mg periocular triamcinolone. Compared with controls, periocular triamcinolone significantly reduced clinical radiation maculopathy from 41% to 16%, thus reducing the risk of developing macular edema (*P*=.002). There was no statistically significant difference, however, at 24 months, regarding rates of moderate to severe vision loss, and side effects included IOP increases in 7% of patients and cataract progression in 45%. Subsequent studies from the same group reported the results of a randomized controlled trial of 108 patients treated with 40 mg of periocular triamcinolone at the same intervals as the prior study. They again found that at 18 months, triamcinolone significantly decreased the risk of macular edema as determined by OCT (*P*=.001), but they also determined that moderate to severe visual loss was significantly reduced at 18 months (31% vs 48%) in patients treated with triamcinolone. Side effects were similar between the groups.[45] These studies, along with earlier studies with prophylactic laser photocoagulation,[24] suggest that early treatment may be beneficial in preventing clinically significant radiation-associated effects.

Finally, a pilot study by Horgan et al compared intravitreal triamcinolone (4mg/0.1 mL) to intravitreal bevacizumab (1.25 mg/0.05 mL) in patients with radiation-associated macular edema. Of 18 patients treated with triamcinolone, 11 (72%) gained one or more lines of Snellen visual acuity, and a reduction in CMT of 172 µm at a mean. In seven patients treated with bevacizumab, only one (14%) had an improvement in visual acuity of one or more lines, and mean CMT increased by 51 µm at a mean of 3 months (Horgan et

al, ISOO meeting Cambridge 2009). The results indicated a significant difference between the two pharmacotherapies; however, sample sizes were small and follow-up short.

ANTI-VEGF

Bevacizumab and ranibizumab are monoclonal antibodies that target VEGF, a key mediator of vascular permeability and angiogenesis in various retinal diseases, including AMD, CRVO, BRVO, diabetes, and retinopathy of prematurity. Bevacizumab and ranibizumab have shown promising results in a number of important clinical trials (MARINA, ANCHOR, BRAVO). Additionally, as the pathogenesis of radiation retinopathy has been shown to involve VEGF, anti-VEGF agents have been investigated for its treatment. Intravitreal bevacizumab has been shown to be effective in improving visual acuity and decreasing macular edema in a number of case reports with short follow-up.[46,47] Several case series have shown mixed results, with patients showing only modest improvements. Mason et al[48] reported that in 10 patients treated with bevacizumab (1.25mg/0.5mL), CMT improved from 482 µm to 284 µm at 6 weeks, regressing to 449 µm at 4 months. Visual acuity improved from 20/100 to 20/86 at 6 weeks, with decrease to 20/95 at 4 months. Finger et al[49] reported on six patients treated with intravitreal bevacizumab (1.25 mg/0.05 mL) every 6 to 8 weeks, with improvement or stabilization of vision in all patients and a reduction in macular edema at a mean follow-up of 4.7 months. Gupta and Muecke[50] investigated intravitreal bevacizumab (1.25 mg/0.05 mL) injected one or two times at 4-week intervals. In the five patients studied, two patients with good visual acuity at baseline had modest 1-line improvements, while three patients remained unchanged. These small studies report mixed results and initial responses that are not sustained with longer follow-up.

Finger et al[51] reported on a larger series of 21 patients in which intravitreal bevacizumab (1.25 mg/0.05 mL) was injected every 6 to 12 weeks. At a mean follow-up of 7.8 months, 18 patients (86%) had improvement or stabilization of visual acuity, and three (14%) improved by two or more lines of vision. The authors also report improvement in vascular leakage as determined by fluorescein angiography. Another report by the same group investigated the use of ranibizumab for radiation retinopathy in five patients. A mean of 8.2 injections of ranibizumab (0.5 mg) was given over a mean follow-up of 8 months. Visual acuity improved by a mean of six letters, with four patients showing a modest improvement on average of 9.5 letters, and one patient losing seven letters. A decrease in vascular leakage and macular edema was seen, and CMT thickness decreased from 416 µm to 270 µm, a 35% reduction. Adverse effects were minimal, including subconjunctival hemorrhage at the injection site and transient post-injection IOP elevations.[52] These studies show that periodic dosing, such as is used in treatment of AMD, may be beneficial in sustaining a treatment effect.

At Bascom Palmer Eye Institute, we have performed a series of 5,496 intravitreal bevacizumab injections for radiation retinopathy.[53] Based on our experience (Figures 1-4), early identification of radiation retinopathy using OCT, followed by early treatment, results in stability and often improvement in visual acuity. Our group has also observed combined efficacy of triamcinolone and bevacizumab in the treatment of radiation-associated macular edema, possibly indicating a synergistic effect of combined therapy. Longer-term follow-up is needed on the efficacy of intravitreal anti-VEGF agents in the treatment of radiation retinopathy, but contrary to prior reports suggesting limited usefulness of anti-VEGF agents in this disease, these preliminary reports and observations warrant further studies to define the role these agents will have in an entity with no proven standard therapy.

CONCLUSION

Despite globe-salvaging treatments for intraocular neoplasms utilizing radiation, the resultant radiation retinopathy proves to be a formidable complication, as no previous therapies have been proven effective. Early studies on intravitreal triamcinolone have been promising in macular edema associated with radiation with improvement in visual acuity and central macular thickness. The current studies and preliminary results emphasize early detection of radiation-associated macular edema with OCT, as well as early treatment to prevent visual loss. Repetitive treatment with anti-VEGF appears to stabilize macular edema and visual loss. Additionally, the use of combined treatment modalities, particularly anti-VEGF and corticosteroids, warrants further study. We anticipate future studies to investigate and compare the efficacy of current pharmacotherapies in a larger cohort of patients, including the Treatment of Radiation Retinopathy (TORR) trial to evaluate the effects of intravitreal bevacizumab and triamcinolone versus sham injections at 1 year. ■

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