High-Dose (2.5 mg) Intravitreal Bevacizumab as Rescue Therapy for Persistent Postradiation Cystoid Macular Edema

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Keywords

Tumor · Melanoma · Radiotherapy · Cystoid macular edema · Radiation damage · Anti-VEGF

Abstract

Background/Aims: To investigate the efficacy of intravitreal high-dose (2.5 mg/0.1 mL) bevacizumab as rescue therapy for postradiation cystoid macular edema (CME) resistant to standard-dose (1.25 mg/0.05 mL) bevacizumab. **Methods:** Retrospective, interventional case series. **Results:** Fifteen eyes of 15 patients were included. Eyes were treated with a mean of 10 standard-dose (1.25 mg) bevacizumab injections but failed to show CME resolution. Following 3 monthly treatments of high-dose (2.5 mg) bevacizumab, mean central macular thickness (CMT) reduced significantly from 406 ± 100 to $360 \pm 83 \mu\text{m}$ ($p = 0.01$) and mean logMAR visual acuity improved from 0.55 ± 0.17 (Snellen 20/71) to 0.48 ± 0.21 (Snellen 20/60, $p = 0.07$). At the final follow-up of 9 months, CMT was $395 \pm 124 \mu\text{m}$ ($p = 0.67$) and visual acuity was 0.51 ± 0.23 (Snellen 20/65, $p = 0.22$). Five eyes (30%) had a >10% reduction in CMT at the final follow-up. In these eyes, the observed CMT reduction was statistically significant ($p = 0.04$) and logMAR visual acuity was significantly better ($p \leq$

0.01) compared to the remainder of the cohort. **Conclusions:** Overall, the use of high-dose (2.5 mg) bevacizumab did not result in a sustained, significant improvement in CMT and visual acuity outcomes following incomplete response to standard-dose (1.25 mg) bevacizumab. However, a minority of eyes exhibited favorable response with significant CMT reduction.

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Introduction

Cystoid macular edema (CME) is an important cause of vision loss following iodine-125 plaque radiotherapy for uveal melanoma [1, 2], occurring in up to 70% of eyes on optical coherence tomography (OCT) [3]. Following the work of Missotten et al. [4] and Boyd et al. [5] which identified elevated VEGF levels in patients with uveal melanoma and subsequent evidence of increased VEGF drive following plaque radiotherapy, intravitreal anti-VEGF agents have emerged as a first-line therapy for patients with postradiation CME [6]. In a series of 36 eyes, Mashayekhi et al. [7] found that 4 monthly intravitreal injections of 1.25 mg bevacizumab decreased central

macular thickness (CMT) in 56% of eyes and improved visual acuity in 42% of eyes treated for postradiation CME at 4–6 months.

However, treatment guidelines for patients with persistent postradiation CME, despite monthly anti-VEGF therapy, have not been established. In 2013, Finger and Chin [8] described the efficacy of high-dose (2.0 mg) ranibizumab for the treatment of “recalcitrant radiation retinopathy” in eyes previously treated with standard-dose ranibizumab, noting improvement in CMT in 80% at 12 months. Since that time, little information regarding rescue therapies using higher-dose anti-VEGF agents for persistent postradiation CME exists. The purpose of this study was to assess the efficacy of high-dose (2.5 mg/0.1 mL) intravitreal bevacizumab as rescue therapy for persistent postradiation CME resistant to standard-dose (1.25 mg/0.05 mL) bevacizumab.

Methods

Institutional review board approval from Wills Eye Hospital was obtained for this retrospective study. The clinical records of all patients with OCT-evident CME following iodine-125 plaque radiotherapy for uveal melanoma treated with high-dose bevacizumab (2.5 mg in 0.1 mL volume) were reviewed. The use of bevacizumab for postradiation CME is currently off-label. This research adhered to the tenets of the Declaration of Helsinki and was conducted in accordance with regulations set forth by the Health Insurance Portability and Accountability Act. All patients were managed at the Ocular Oncology Service of Wills Eye Hospital, Philadelphia, PA, USA.

Persistent postradiation CME was defined by increased or stable CMT compared to baseline values despite a minimum of 3 monthly treatments of standard-dose (1.25 mg) bevacizumab. Patients who received a minimum of 3 monthly injections of high-dose (2.5 mg) bevacizumab for persistent postradiation CME following failure of standard-dose (1.25 mg) bevacizumab were included. This inclusion criterion of 3 monthly rescue treatments helps to eliminate confounding effects of extending time interval between anti-VEGF treatments and ensures consistency of high-dose therapy. For the purpose of this study, we evaluated CMT and visual acuity following higher-dose (2.5 mg) intravitreal bevacizumab and recorded change in CMT between baseline and follow-up, classified as decreased (>10% decrease in CMT compared to baseline), stable (within 10% of baseline CMT), or increased (>10% increase in CMT compared to baseline). Change in Snellen visual acuity was defined as improved (>1 line gain), stable (within 1 line of baseline), or worsened (>1 line loss).

Patient demographic data including age, gender, and past medical history (including hypertension and diabetes mellitus) were recorded at the time of detection of uveal melanoma. Clinical features at the time of diagnosis, including Snellen visual acuity, past ocular history, and lens status, as well as tumor location, tumor diameter (millimeters measured by indirect ophthalmoscopy), and tumor thickness (millimeters measured by ultrasonography)

Table 1. High-dose (2.5 mg) intravitreal bevacizumab as rescue therapy following standard-dose (1.25 mg) bevacizumab for persistent postradiation cystoid macular edema in 15 cases: patient demographic data

Total number of patients	15
Total number of eyes	15
Mean age, years (median, range)	56 (57, 41–70)
Gender	
Female	10
Male	5
Race	
Caucasian	15
Non-Caucasian	0
Past medical history	
Diabetes mellitus	0
Hypertension	7
Uveitis	0
Cystoid macular edema	0
Epiretinal membrane	0
Symptoms	
None	6
Visual field defect	4
Photopsia	5
Blurred vision	4

were recorded. Information regarding iodine-125 plaque radiotherapy, including total dose (centigray) and dose rate (centigray/hour) to the tumor apex, base, optic disc, and macula, was also recorded.

Details regarding onset and treatment for OCT-evident postradiation CME were given, including the number and timing of standard-dose (1.25 mg) bevacizumab treatments. After initiation of high-dose (2.5 mg) bevacizumab treatment, follow-up examinations with spectral-domain OCT were performed at approximately 4-week intervals for a minimum of 4 months. Snellen visual acuity and CMT in the irradiated and the fellow eye were recorded, with Snellen visual acuities converted to logMAR equivalents for statistical analysis.

Change in CMT and logMAR visual acuity for the full cohort was analyzed using a Student *t* test (GraphPad Software Inc., La Jolla, CA, USA). For eyes that showed CMT reduction (>10% from baseline) at the final follow-up, the nonparametric Wilcoxon signed rank test (IBM SPSS Statistics, IBM Inc., Armonk, NY, USA) was used to determine if this change was significant over the course of treatment. A *p* value <0.05 was considered statistically significant. The primary outcomes measured included change in CMT and visual acuity and following treatment with high-dose (2.5 mg) bevacizumab at 3 months and final follow-up.

Results

Fifteen eyes received a minimum of 3 high-dose (2.5 mg) bevacizumab treatments and were included in the study analysis. Patient demographic data are detailed in

Table 2. High-dose (2.5 mg) intravitreal bevacizumab as rescue therapy following standard-dose (1.25 mg) bevacizumab for persistent postradiation cystoid macular edema in 15 cases: ocular and tumor features

Ocular features, <i>n</i>	
Choroidal melanoma	15
Lens crystalline	15
Epiretinal membrane	0
Fluorescein angiography-evident cystoid macular edema	0
Optical coherence tomography-evident cystoid macular edema	0
Mean visual acuity (median, range)	
Affected eye (logMar)	0.21 (0.18, 0–1.3)
Affected eye (Snellen)	20/32 (20/30, 20/20–20/400)
Mean central macular thickness, μm (median, range)	
Affected eye	323.5 (292, 242–552)
Fellow eye	263 (258, 220–302)
Mean tumor dimensions, mm (median, range)	
Basal diameter	11.3 (11, 6–18)
Thickness	5.0 (4.4, 2.2–10.3)
Distance to foveola	4.7 (3, 0.3–15)
Distance to optic nerve	5.5 (6, 0.5–15)
Anteroposterior location of tumor epicenter, <i>n</i>	
Macula	3
Macula to equator	7
Equator to ora	2
Ciliary body	3
Tumor shape, <i>n</i>	
Dome	14
Mushroom	1
Plateau	0
Subretinal fluid extent, <i>n</i>	
None	2
<3 mm	7
3 mm – 1 quadrant	1
2 quadrants	5

Table 1. All patients were Caucasian with a diagnosis of choroidal melanoma. The mean patient age was 56 years (range 41–70), and 10 patients were female. Mean logMAR visual acuity at the time of melanoma diagnosis was 0.21 ± 0.33 (mean Snellen 20/32) in the affected eye. All patients were phakic throughout the study period.

Baseline tumor features are detailed in Table 2. The mean tumor basal diameter was 11 mm (median 11, range 6–18) and mean tumor thickness was 5.0 mm (median 4.4, range 2.2–10.3). The tumor was located between the macula and equator in 10/15 eyes (67%). Subretinal fluid was present in 13/15 eyes (87%) at the time of diagnosis. Baseline fluorescein angiography and spectral-domain OCT was completed in all eyes at presentation. Angiographic CME, macular ischemia, OCT-evident CME, and epiretinal membrane were not present in any eye at baseline. Mean baseline CMT was $323.5 \pm 99 \mu\text{m}$ in the affected eye and $263 \pm 24 \mu\text{m}$ in the fellow eye. Subclinical

macular edema, defined as a greater than 10- μm difference between the affected and fellow eye [9], was present in 10/15 eyes (67%).

Details of plaque radiotherapy are summarized in Table 3. Iodine-125 plaque radiotherapy was performed with a mean radiation dose to the tumor apex of 7,416 cGy and a mean dose to the foveola of 4,305 cGy (mean dose rate to the foveola of 44 cGy/h). Eleven of 15 eyes received prophylactic therapy for the prevention of post-radiation CME, including standard-dose (1.25 mg) bevacizumab every 4 months in 11 eyes (mean 2.5 injections per eye), sub-Tenon triamcinolone in 5 eyes (mean 1 injection per eye), and panretinal photocoagulation in 4 eyes (mean 1 treatment per eye). OCT-evident postradiation CME occurred in all eyes at a mean of 24.4 months (median 15, range 8–110). Compared to time of initial tumor diagnosis, mean CMT at diagnosis of postradiation CME worsened to $427 \pm 75 \mu\text{m}$ in the affected eye

Table 3. High-dose (2.5 mg) intravitreal bevacizumab as rescue therapy following standard-dose (1.25 mg) bevacizumab for persistent postradiation cystoid macular edema in 15 cases: treatment parameters

Feature	Mean (median, range)
Radiation dose, cGy	
Tumor apex	7,416 (7,000, 7,000–8,200)
Tumor base	19,264 (16,460, 9,840–44,966)
Foveola	4,305 (3,857, 1,581–13,001)
Optic disc	2,936 (2,390, 1,548–5,595)
Radiation rate, cGy/h	
Tumor apex	74.5 (74.6, 59.2–85.9)
Tumor base	189.5 (172.9, 103.8–385)
Foveola	44.0 (40.2, 13.4–138.0)
Optic disc	29.3 (23.8, 14.7–60.1)
Onset of optical coherence tomography-evident cystoid macula edema	
Months after plaque	24.4 (15, 8–110)
logMAR visual acuity, affected eye	0.51 (0.50, 0–1.3)
Mean central macular thickness, affected eye, μm	427 (431, 301–552)
Mean central macular thickness, fellow eye, μm	267 (265, 233–304)
Cystoid macular edema treatment	
Total “standard-dose” (1.25 mg) bevacizumab injections	10 (7, 3–29)
Treatment duration, months	14.6 (9, 3–51)
Interval between last “standard-dose” (1.25 mg) bevacizumab treatment and first “high-dose” (2.5 mg) bevacizumab rescue treatment, days	38 (35, 28–50)

Table 4. High-dose (2.5 mg) intravitreal bevacizumab as rescue therapy following standard-dose (1.25 mg) bevacizumab for persistent postradiation cystoid macular edema in 15 cases: outcomes

	Central macular thickness, μm	<i>p</i> value	logMAR visual acuity	<i>p</i> value	Snellen visual acuity	% change in central macular thickness
Baseline at initiation of high-dose (2.5 mg) bevacizumab therapy		–		–		–
Mean	406		0.55		20/71	
Median	384		0.54		20/70	
Range	283–664		0.30–0.88		20/40–20/150	
Outcomes at 3 months		0.01		0.07		
Mean	360		0.48		20/61	–14.6
Median	344		0.48		20/60	–20
Range	230–544		0.18–0.88		20/30–20/150	–38 to +20
Outcomes at final follow-up (mean 9 months)		0.67		0.22		
Mean	394		0.51		20/45	–8.0
Median	374		0.48		20/43	–2
Range	240–714		0.18–1.0		20/30–20/200	–53 to +20

($p = 0.03$) but was stable at $267 \pm 22 \mu\text{m}$ in the fellow eye ($p = 0.40$). Mean logMAR visual acuity worsened to 0.51 ± 0.34 (Snellen 20/65, $p = 0.02$).

All eyes were initially treated with monthly standard-dose (1.25 mg) bevacizumab but continued to show persistent CME after a mean of 10 injections per eye (median 7, range 3–29) over a mean treatment duration of 14.6

months (median 9, range 4–30). The mean interval between the last standard-dose (1.25 mg) bevacizumab treatment and the first high-dose (2.5 mg) bevacizumab rescue treatment was 38 days (median 35, range 28–50). Treatment outcomes are summarized in Table 4. The mean CMT at the time of the first high-dose (2.5 mg) bevacizumab treatment was $406 \pm 100 \mu\text{m}$ and mean logMAR

Fig. 1. A 70-year-old Caucasian female with choroidal melanoma treated with plaque radiotherapy developed cystoid macular edema 14 months after iodine-125 plaque radiotherapy (**a**). Cystoid macular edema persisted despite 3 (**b**), 5 (**c**), 8 (**d**), and 10 (**e**) standard-dose (1.25 mg) intravitreal injections of bevacizumab. After initiation of monthly high-dose (2.5 mg) bevacizumab therapy, the cystoid macular edema resolved as depicted at 3 (**f**) and 6 (**g**) months. Final visual acuity (VA) was 20/50. CMT, central macular thickness.

visual acuity was 0.55 ± 0.17 (Snellen 20/71). Following treatment with 3 monthly injections of high-dose (2.5 mg) bevacizumab, mean CMT improved to $361 \pm 84 \mu\text{m}$ ($p = 0.013$) and mean logMAR visual acuity improved to 0.48 ± 0.21 (Snellen 20/60, $p = 0.07$). At the final follow-up of 9 months (median 7, range 4–18), logMAR visual acuity was 0.51 ± 0.23 (Snellen 20/65, $p = 0.22$) and CMT was $395 \pm 124 \mu\text{m}$ ($p = 0.67$) after a mean of 7.5 (median 6, range 3–17) high-dose (2.5 mg) bevacizumab injections. All patients were phakic throughout the study. No injection-related, local, or systemic adverse events or safety concerns with use of high-dose bevacizumab were encountered.

Overall, mean percent change in CMT was -14.6% (median -20 , range -38 to $+20$) at 3 months and -8.0% (median -2.0 , range -53 to $+20$) at the final follow-up, with negative change indicating improvement in CMT. A reduction of $>10\%$ in CMT was seen in 9/15 eyes (60%) at 3 months and in 5/15 eyes (30%) at the final follow-up.

In these eyes with $>10\%$ reduction in CMT, the degree of reduction was found to be statistically significant at 3 months ($n = 9$ eyes, mean percent change in CMT of -25% , $p = 0.01$) and final follow-up ($n = 5$ eyes, mean percent change in CMT of -35% , $p = 0.04$). An illustrative case of favorable treatment response is presented in Figure 1. Conversely, 3/15 eyes (20%) had a $>10\%$ increase in CMT at the final follow-up. In these eyes, the increase in CMT was not found to be statistically significant ($p = 0.11$).

When comparing eyes with $>10\%$ reduction in CMT at the final follow-up (5/15 eyes) to the remainder of the cohort (10/15 eyes), there was no difference between groups in regards to CMT at the initial presentation (315 ± 92 vs. $326 \pm 106 \mu\text{m}$, $p = 0.84$), tumor diameter (9.3 ± 2.4 vs. $12.3 \pm 4.2 \text{ mm}$, $p = 0.11$), tumor thickness at presentation (3.6 ± 1.2 vs. $5.7 \pm 3.0 \text{ mm}$, $p = 0.07$), tumor distance to fovea (4.6 ± 4.2 vs. $4.8 \pm 4.7 \text{ mm}$, $p = 0.93$),

CMT at the time of initiation of high-dose (2.5 mg) bevacizumab therapy (455 ± 130 vs. 380 ± 78 μm , $p = 0.29$), or radiation dose to the tumor apex ($7,200 \pm 447$ vs. $7,523 \pm 556$ cGy, $p = 0.25$), base ($15,596 \pm 4,011$ vs. $21,098 \pm 10,093$ cGy, $p = 0.16$), or foveola ($3,246 \pm 1,005$ vs. $4,833 \pm 3,454$ cGy, $p = 0.20$). However, there was a significant difference in regards to tumor thickness following plaque radiotherapy (1.9 ± 0.65 vs. 3.7 ± 1.5 mm, $p \leq 0.01$), with thinner tumors associated with more favorable treatment response.

Overall, 4 eyes (27%) had improvement in Snellen visual acuity (mean 2.5 lines gained, range 2–3), 9 eyes (60%) had stable acuity, and 2 eyes (13%) had worsened acuity (mean 2.5 lines lost, range 2–3) at final follow-up. In the 5/15 eyes with >10% reduction in CMT at final follow-up, logMAR visual acuity was significantly better at 3 months (0.27 ± 0.09 vs. 0.59 ± 0.16 , $p \leq 0.01$) and final follow-up (0.27 ± 0.09 vs. 0.62 ± 0.17 , $p \leq 0.01$) compared to the remainder of the cohort.

Discussion

In 2000, Shields et al. [1] reported visual acuity outcomes of 20/200 or worse in up to 68% of patients treated with plaque radiotherapy for uveal melanoma at 10 years, with many of such outcomes attributed to sequelae of radiation retinopathy including postradiation CME. Multiple treatment modalities, including focal laser [10], photodynamic therapy [11], periocular [12, 13] or intravitreal [14–16] corticosteroids, and intravitreal anti-VEGF agents [6–8, 17], have since been investigated for treatment and prevention of postradiation CME. Currently, intravitreal injection of anti-VEGF agents is the most commonly used method for treatment of postradiation macular edema [6, 7, 16, 17] but, unfortunately, many of the treated eyes do not show a clinically significant reduction in CMT despite treatment. In one study, only 56% of eyes with macular edema following plaque radiotherapy showed a >10% reduction in CMT after 4 monthly intravitreal injections of standard-dose (1.25 mg) bevacizumab, with 14% of eyes exhibiting a >10% increase in CMT [7]. Rescue treatments for patients with persistent edema despite regular treatment have not been well described.

The rationale for the use of “high-dose” anti-VEGF therapy as rescue treatment initially stemmed from the pivotal phase III clinical trials evaluating ranibizumab for neovascular age-related macular degeneration (AMD). In the Minimally Classic/Occult Trial of Anti VEGF Antibody Ranibizumab in the Treatment of Neovascular

AMD (MARINA) study, the use of 0.5 mg ranibizumab dosing resulted in greater visual improvement compared to 0.3 mg [18], suggesting a dose response. In the Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in AMD (ANCHOR) study, while 2.0 mg ranibizumab dosing was not found superior to 0.5 mg dosing in treatment-naïve patients [19], no safety issues with high-dose therapy were encountered [20]. Subsequent studies utilizing high-dose anti-VEGF therapy in patients with persistent disease activity yielded favorable outcomes. Brown et al. [21] evaluated the efficacy of high-dose (2.0 mg) ranibizumab for patients with recalcitrant neovascular AMD in the Super-dose Anti-VEGF (SAVE) Trial, noting statistically significant gains in CMT ($p = 0.01$) and visual acuity ($p = 0.001$) at 3 months which were sustained at 1 year with monthly dosing [22]. Similarly, Finger and Chin [8] described the efficacy of high-dose (2.0 mg) ranibizumab in 10 patients with a clinical diagnosis of radiation retinopathy. In that study, 8 of 10 patients had uveal melanoma treated with palladium-103 plaque radiotherapy. While visual acuity outcomes were stable, 8/10 eyes (80%) had a statistically significant improvement in CMT at 1 year.

In this series of 15 eyes with persistent postradiation CME resistant to standard-dose (1.25 mg) bevacizumab, we found a statistically significant reduction in CMT in 5/15 eyes (30%) treated with high-dose (2.5 mg) bevacizumab at final follow-up ($p = 0.04$). In the whole cohort of 15 eyes, visual acuity improved from 0.55 ± 0.17 (Snellen 20/71) at baseline to 0.48 ± 0.21 (Snellen 20/60) ($p = 0.07$) at 3 months and 0.51 ± 0.23 (Snellen 20/65) at final follow-up ($p = 0.22$). Visual acuity was statistically significantly better in patients with >10% reduction in CME at 3 months (0.36 ± 0.15 vs. 0.67 ± 0.14 , $p \leq 0.01$) and final follow-up (0.27 ± 0.09 vs. 0.62 ± 0.17 , $p \leq 0.01$) compared to the rest of the cohort.

While most eyes with postradiation macular edema will respond to intravitreal bevacizumab at the standard dose [17], our results and those of Finger and Chin suggest that there is a subset of patients that might require higher-dose anti-VEGF blockade for an improved effect. The precise reason why some patients responded well to high-dose (2.5 mg) bevacizumab treatment while others did not is uncertain. Prior work has helped to identify risk factors for radiation retinopathy and poor visual acuity following plaque radiotherapy, including, but not limited to, the presence of subretinal fluid at the time of tumor diagnosis (relative risk, 1.4 [1] or 1.78 [23]) and tumor location <5 mm to the fovea (relative risk, 1.4 [1] or 2.17 [23]). More recently, it was found that eyes with mela-

noma and initial subclinical macular edema (greater than a 10- μ m difference in CMT between the affected and fellow eye) were more likely to develop CME after radiation ($p = 0.005$; hazard ratio 1.77) despite prophylactic anti-VEGF treatment [9]. The eyes in the present series have multiple such risk factors, including an average tumor distance to the fovea of 4.7 mm, 12 of 15 eyes with subretinal fluid, and 10 of 15 eyes with subclinical macular edema at presentation. These risk factors may be indicative of eyes at high risk for CME that may be less responsive to anti-VEGF therapy prior to or following plaque radiotherapy. Furthermore, prior studies have demonstrated variable expression of VEGF and other growth factors amongst uveal melanoma cell lines [24]. Greater production of VEGF, or production of proexudative growth factors other than VEGF, by the individual tumors may also explain variable treatment response to high-dose anti-VEGF therapy in this study.

While no patient had evidence of frank macular ischemia on fluorescein angiography, development or progression of mild macular ischemia in these eyes could also account for lack of improvement in primary outcomes at final follow-up for the full cohort. Subgroup analysis of eyes with >10% reduction in CMT at final follow-up revealed tumors of less thickness at baseline ($p = 0.07$) and following plaque radiotherapy ($p \leq 0.01$). Other factors, such as tumor proximity to the foveola and radiation dose to the foveola, could be features at risk for macula ischemia; however, they were not associated with treatment response. Larger studies would be necessary to confirm and further refine baseline features as possible predictors of treatment response. Lastly, given the mean of 10 standard dose (1.25 mg) bevacizumab treatments prior to the use of high-dose (2.5 mg) bevacizumab, mechanisms of tachyphylaxis and tolerance, including upregulation of VEGF receptors, may have blunted treatment response to high-dose (2.5 mg) bevacizumab.

This study has several limitations, including the retrospective nature and limited case number. Another limitation was the lack of a strict treatment protocol for every patient prior to the initiation of high-dose (2.5 mg) bevacizumab therapy, including nonstandardized use of prophylactic bevacizumab therapy and/or corticosteroids immediately following radiation therapy. In addition, follow-up fluorescein angiography after initiation of high-dose bevacizumab therapy was not available in all patients and thus the presence and effect of macular ischemia on treatment could not be formally addressed. Strengths of the study include the exclusive use of bevacizumab and maintenance of monthly treatment intervals. Further

study in prospective, randomized trials comparing treatment options, including alternate anti-VEGF agents or corticosteroids, would be necessary to clarify best practices. In addition, vitreous fluid proteomic studies to identify additional molecular targets in patients with uveal melanoma would help in the design of combination therapy that may be particularly helpful in patients with recalcitrant disease.

In conclusion, the use of high-dose (2.5 mg) bevacizumab in eyes with persistent postradiation CME resistant to standard-dose (1.25 mg) bevacizumab did not result in significant gains in CMT and visual acuity at final follow-up of 9 months. Treatment with high-dose (2.5 mg) bevacizumab significantly improved CMT in a minority (30%) of eyes, which was associated with better final visual acuity. Our results suggest that high-dose anti-VEGF may be effective in select patients as a rescue therapy for persistent postradiation CME, but additional studies are needed to identify patient, eye, tumor, or radiation factors predictive of treatment response.

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Statement of Ethics

Arman Mashayekhi, MD, has had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Disclosure Statement

The authors do not have any proprietary interests in the materials described in the report. No conflicting relationship exists for any author.

Author Contributions

Author contributions were as follows: design of the study (M.A.K., A.M., C.L.S.), conduct of the study (M.A.K., A.M., K.F., J.A.S., C.L.S.), data collection and analysis (M.A.K., K.F.), interpretation of data (M.A.K., A.M., C.L.S.), and manuscript preparation (M.A.K., A.M., K.F., J.A.S., C.L.S.).

References

- Shields CL, Shields JA, Cater J, Gündüz K, Miyamoto C, Micaily B, et al: Plaque radiotherapy for uveal melanoma: long-term visual outcome in 1,106 consecutive patients. *Arch Ophthalmol* 2000;118:1219–1228.
- Horgan N, Shields CL, Mashayekhi A, Shields JA: Classification and treatment of radiation maculopathy. *Curr Opin Ophthalmol* 2010; 21:233–238.
- Horgan N, Shields CL, Mashayekhi A, Teixeira LF, Materin MA, Shields JA: Early macular morphological changes following plaque radiotherapy for uveal melanoma. *Retina* 2008;28:263–273.
- Missotten GSO, Notting IC, Schlingemann RO, Zijlmans HJ, Lau C, Eilers PHC, et al: Vascular endothelial growth factor in eyes with uveal melanoma. *Arch Ophthalmol* 2006;124:1428–1434.
- Boyd SR, Tan D, Bunce C, Gittos A, Neale MH, Hungerford JL, et al: Vascular endothelial growth factor is elevated in ocular fluids of eyes harbouring uveal melanoma: identification of a potential therapeutic window. *Br J Ophthalmol* 2002;86:448–452.
- Finger PT, Chin KJ: Intravitreal ranibizumab (lucentis) for radiation maculopathy. *Arch Ophthalmol* 2010;128:249–252.
- Mashayekhi A, Rojanaporn D, Al-Dahmash S, Shields CL, Shields JA: Monthly intravitreal bevacizumab for macular edema after iodine-125 plaque radiotherapy of uveal melanoma. *Eur J Ophthalmol* 2014;24:228–234.
- Finger PT, Chin KJ: High-dose (2.0 mg) intravitreal ranibizumab for recalcitrant radiation retinopathy. *Eur J Ophthalmol* 2013;23:850–856.
- Mashayekhi A, Schönbach E, Shields CL, Shields JA: Early subclinical macular edema in eyes with uveal melanoma: association with future cystoid macular edema. *Ophthalmology* 2015;122:1023–1029.
- Hykin PG, Shields CL, Shields JA, Arevalo JF: The efficacy of focal laser therapy in radiation-induced macular edema. *Ophthalmology* 1998;105:1425–1429.
- Bakri SJ, Beer PM: Photodynamic therapy for maculopathy due to radiation retinopathy. *Eye* 2005;19:795–799.
- Horgan N, Shields CL, Mashayekhi A, Teixeira LF, Materin MA, O'Regan M, et al: Periocular triamcinolone for prevention of macular edema after iodine 125 plaque radiotherapy of uveal melanoma. *Retina* 2008;28: 987–995.
- Horgan N, Shields CL, Mashayekhi A, Salazar PF, Materin MA, O'Regan M, et al: Periocular triamcinolone for prevention of macular edema after plaque radiotherapy of uveal melanoma: a randomized controlled trial. *Ophthalmology* 2009;116:1383–1390.
- Sutter FKP, Gillies MC: Intravitreal triamcinolone for radiation-induced macular edema. *Arch Ophthalmol* 2003;121:1491–1493.
- Bui KM, Chow CC, Mieler WF: Treatment of recalcitrant radiation maculopathy using intravitreal dexamethasone (Ozurdex) implant. *Retin Cases Brief Rep* 2014;8:167–170.
- Tarmann L, Langmann G, Mayer C, Weger M, Haas A, Wackernagel W: Ozurdex[®] reduces the retinal thickness in radiation maculopathy refractory to bevacizumab. *Acta Ophthalmol* 2014;92:e694–e696.
- Gupta A, Muecke JS: Treatment of radiation maculopathy with intravitreal injection of bevacizumab (Avastin). *Retina* 2008;28:964–968.
- Rosenfeld PJ, Brown DM, Heier JS, Boyer DS, Kaiser PK, Chung CY, et al: Ranibizumab for neovascular age-related macular degeneration. *N Engl J Med* 2006;355:1419–1431.
- Brown DM, Kaiser PK, Michels M, Soubrane G, Heier JS, Kim RY, et al: Ranibizumab versus verteporfin for neovascular age-related macular degeneration. *N Engl J Med* 2006; 355:1432–1444.
- Ho AC, Busbee BG, Regillo CD, Wieland MR, Van Everen SA, Li Z, et al: Twenty-four-month efficacy and safety of 0.5 mg or 2.0 mg ranibizumab in patients with subfoveal neovascular age-related macular degeneration. *Ophthalmology* 2014;121:2181–2192.
- Brown DM, Chen E, Mariani A, Major JC; SAVE Study Group: Super-dose anti-VEGF (SAVE) trial: 2.0 mg intravitreal ranibizumab for recalcitrant neovascular macular degeneration—primary end point. *Ophthalmology* 2013;120:349–354.
- Wyckoff CC, Brown DM, Chen E, Major JC, Croft DE, Mariani A, et al: SAVE (Super-dose anti-VEGF) trial: 2.0 mg ranibizumab for recalcitrant neovascular age-related macular degeneration: 1-year results. *Ophthalmic Surg Lasers Imaging Retina* 2013;44:121–126.
- Melia BM, Abramson DH, Albert DM, Boldt HC, Earle JD, Hanson WF, et al: Collaborative ocular melanoma study (COMS) randomized trial of I-125 brachytherapy for medium choroidal melanoma. I. Visual acuity after 3 years COMS report No. 16. *Ophthalmology* 2001; 108:348–366.
- Boyd SR, Tan DSW, de Souza L, Neale MH, Myatt NE, Alexander RA, et al: Uveal melanomas express vascular endothelial growth factor and basic fibroblast growth factor and support endothelial cell growth. *Br J Ophthalmol* 2002;86:440–447.