Original Article

The effect of intravitreal bevacizumab and transpupillary thermotherapy on choroidal metastases and literature review

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Aims: To represent the effects of transpupillary thermotherapy (TTT) and intravitreal bevacizumab on choroidal metastases and review the literature. **Settings and Design**: A retrospective, interventional, noncomparative case series. **Materials and Methods**: A retrospective, interventional, noncomparative case series of five eyes in three patients with choroidal metastases was conducted. Fundus findings of choroidal metastases were divided into two types: Solitary or diffuse type. The size of the tumor was termed small (<10 mm diameter), medium (10–15 mm diameter) or large (>15 mm diameter). All eyes received one session of TTT followed by 3 weekly intravitreal bevacizumab injections as an adjuvant therapy. The parameters of treatment for TTT were 1.2–3 mm spot size, 150–300 mW, 60 s with the whole lesion covered confluently. The changes in preoperative and postoperative best-corrected visual acuity (BCVA) were recorded. Serial color fundus photography and optical coherent tomography were performed to measure the treatment efficacy. **Results**: All eight choroidal metastases were solitary type. The size of six tumors was small, the size of one tumor was medium, and the size of one tumor was large. All five eyes of the three patients had improvement of BCVA after treatment. Fundus photos revealed tumor shrinkage and the mean shrinkage percentage was 61.27 ± 21.71%. Optical coherence tomography revealed complete resolution of serous retinal detachment. There was no recurrence after 6 months follow-up. **Conclusions**: TTT combined with intravitreal bevacizumab injections brought about beneficial effects in reducing tumor size and improving vision in all five eyes of the three patients. Despite the retrospective nature of our study, the absence of control group and the size limitation that, of course, limit the statistical power, TTT combined with intravitreal bevacizumab seems to be efficient in providing another cost-reducing and time-saving treatment option for patients with choroidal metastases. The antineoplastic properties of bevacizumab make it a viable adjunctive therapy. Studies with more cases and a longer follow-up period are warranted.

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The uvea is the most common site for ocular metastases in adults.[1] Aggressive treatment of choroidal metastases would be recommended if the lesion is threatening vision or the globe despite systemic chemotherapy. Although external beam radiation, plaque radiotherapy, and proton beam radiation have been used,[2-5] significant complications do occur.[5,6] Verteporfin photodynamic therapy (PDT) is an effective alternative with the relatively high expense.[2,7] And while transpupillary thermotherapy (TTT, Diode laser, 810 nm; Iris Medical OcuLight SLX) has been reported as an effective treatment method for small and early choroidal metastases,[8-10] it has to be combined with other treatment modalities to achieve tumor shrinking in medium-sized choroidal metastases.[8-10] Intravitreal bevacizumab (Avastin, Genentech, Inc.) seems to be effective for early and small choroidal metastasis but does not work well in cases of larger choroidal tumor with exudative retinal detachment.[11-15]

We, therefore, present five eyes of three cases with metastatic choroidal carcinoma, each receiving combined treatment with TTT and 3 weekly intravitreal bevacizumab injections. Significant subjective and objective improvements were achieved without ocular and systemic complications.

Materials and Methods

The authors conducted a retrospective, interventional, and nonrandomized study of TTT and 3 weekly intravitreal bevacizumab injections on patients suffering choroidal metastases from June 2011 to November 2012. Fundus findings of choroidal metastases were divided into two types: Solitary or diffuse type. The size of the tumor was termed small (<10 mm diameter), medium (10–15 mm diameter) or large (>15 mm diameter) according to the definition of choroidal melanoma. The systemic evaluation including lung computed tomography and brain magnetic resonance imaging had been performed to find the primary malignancy and to rule out central nervous system (CNS) metastases. Patients with CNS metastases at the time of presentation were excluded. The options of treatment such as radiotherapy and PDT were also offered. Patients who chose TTT and intravitreal bevacizumab were included. Written informed consent was obtained from the patients. The study was carried out in accordance with the World Medical Association's Declaration of Helsinki.

The study design consisted of TTT with the whole lesion covered and 3 weekly intravitreal 4 mg/0.16 mL bevacizumab injections in the patients' eyes. The parameters of treatment for TTT were 1.2–3 mm spot size, 150–300 mW, 60 s with the whole lesion covered confluently. In general, for a 3 mm spot size, the initial power level was 300 mW. The area centralis

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lens (Volk Optical Inc., Mentor, Ohio, USA) was used. The retinal color was monitored intermittently so that no visible change or a barely detectable light-grey appearance to the lesion was present at the end of the TTT application. If any retinal whitening was observed or the patient felt discomfort during the treatment, the power of the laser was decreased by 50 mW and the treatment was reinitiated.

Intravitreal injection was performed under topical anesthesia as an official procedure. The pupils were dilated with 0.5% tropicamide/0.5% phenylephrine (Mydrin-P, Santen OY, Finland), and the topical antibiotic levofloxacin (Cravit, Santen Pharmaceutical Co., Osaka, Japan) was applied before the intravitreal injections. Topical anesthesia was achieved using 0.5% proparacain hydrochloride (Alcaine, Alcon Pharmaceuticals, Inc.), given 3 times with 2 min intervals before the surgery. Each eye was prepared in a sterile manner using 5% povidone/iodine. 4 mg/0.16 mL bevacizumab was injected intravitreally via the pars plana. After the injection, intraocular pressure and retinal artery perfusion were checked, and the patients received topical levofloxacin 4 times daily for 7 days. Patients were evaluated with best-corrected visual acuity (BCVA), indirect ophthalmoscopy, color fundus photography and optical coherent tomography (OCT; Stratus OCT™, Carl Zeiss Meditec, Inc., Dublin, CA, USA). All cases had been followed-up at least for 6 months.

Results

From 2011 through 2012, five eyes of three patients (two males and one female) were recorded with the diagnosis of choroidal metastases. The mean age at the time of diagnosis was 40.33 years (range 34–47 years). The primary sites of carcinomas were breasts and lungs. All the patients were on concurrent systemic chemotherapy. In Case 2, choroidal metastases were found during the course of systemic chemotherapy. In Case 1 and 3, choroidal metastases were noted before the diagnosis and staging of the primary malignancy. TTT and the initial intravitreal bevacizumab injection were performed before the systemic chemotherapy. All eight choroidal metastases were solitary type [Fig. 1]. The size of 6 tumors (tumor I, III, IV, V, VI, VII) was small, the size of one tumor (tumor II) was medium, and the size of one tumor (tumor VIII) was large. Fundus photos revealed tumor shrinkage and the mean shrinkage percentage was 61.27 ± 21.71% [Table 1]. OCT revealed complete resolution of serous retinal detachment. No ocular or systemic complications were observed at the end of follow-up.

Table 1: The mean shrinkage percentage of DA of choroidal metastatic tumors after treatment

Case	Eye	Lesion	DA ratio		Shrinkage %
			Pretreatment	Post-treatment	
1	OD	Tumor I	6.12	2.23	63.59
	OS	Tumor II	32.25	13.25	58.91
	OS	Tumor III	9.12	4.40	51.77
2	OD	Tumor IV	10.07	5.39	46.46
	OD	Tumor V	9.29	5.58	39.90
	OS	Tumor VI	2.50	0.13	94.78
	OS	Tumor VII	1.89	0.13	93.09
3	OS	Tumor VIII	51.53	30.08	41.63
				Mean shrinkage	61.27±21.71

DA: Disc area, OD: Right eye, OS: Left eye

Case Reports

Case 1

A 47-year-old male who denied having any systemic diseases but a smoking history presented with blurred vision OD and an elevated solitary type choroidal mass with exudative retinal detachment involving the macula was found [Fig. 1-1a, tumor I]. The OCT showed marked subretinal fluid OD and the central foveal thickness (CFT) was 773 μm [Fig. 2-1a]. One large choroidal mass over the nasal quadrant [Fig. 1-2a, tumor II] and the other smaller solitary choroidal mass above the temporal-superior arcade were noted OS [Fig. 1-2a, tumor III]. His BCVA was 20/30 OD and 20/25 OS. After the survey of the possible original malignancy, stage IV small cell lung carcinoma was diagnosed. He received one session of TTT and 3 times of weekly intravitreal 4 mg/0.16 mL bevacizumab in both eyes. The parameters of treatment for TTT were 1.2–3 mm spot size, 150–300 mW, 60 s with the whole lesion covered. TTT and the initial intravitreal bevacizumab injection were performed before the systemic chemotherapy. The systemic chemotherapeutic regimen was gefitinib 250 mg daily for 3 months. Three months after the combined treatment, his BCVA was improved to 20/20 OU and choroidal masses subsided to residual pigmentary change [Figs. 1-1b and 1-2b]. The OCT also showed the resolution of exudative retinal detachment and the CFT reduced to 252 μm OD [Fig. 2-1b]. There was no recurrence after 6 months follow-up.

Case 2

A 34-year-old female was a case of breast cancer with liver metastasis. She complained of decreased vision OD. Her BCVA was 20/40 OD and 20/20 OS. One choroidal mass in the temporal quadrant OD [Fig. 1-3a, tumor IV] and the other elevated solitary type choroidal mass with exudative retinal detachment [Fig. 1-3a, tumor V] in the upper posterior pole extending beneath the macula were found. The OCT showed massive subretinal fluid and the CFT was 983 μm OD [Fig. 2-2a]. Meanwhile, two small choroidal solitary masses were seen in the nasal [Fig. 1-4a, tumor VI] and inferior [Fig. 1-4a, tumor VII] quadrants OS. She was on systemic chemotherapy with cetuximab, but choroidal metastases still occurred. Radiotherapy or intravitreal bevacizumab combined with TTT was offered; she chose the latter for convenience. One session of TTT and 3 times of weekly intravitreal 4 mg/0.16 mL bevacizumab were performed in both eyes. The parameters of treatment for TTT were 1.2–3 mm spot size, 150–300 mW, 60 s with the whole lesion covered. Three months after the combined treatment, her BCVA improved to 20/20 OU with the tumors showing marked shrinkage [Figs. 1-3b and 1-4b]. The OCT also demonstrated no exudative retinal detachment and the CFT reduced to 224 μm OD [Fig. 2-2b], and the visual field was improved. There was no recurrence after 6 months follow-up.

Case 3

A 40-year-old male who denied having any systemic diseases but a smoking history complained of deterioration of vision OS. His BCVA was 20/20 OD and 20/1000 OS. An elevated

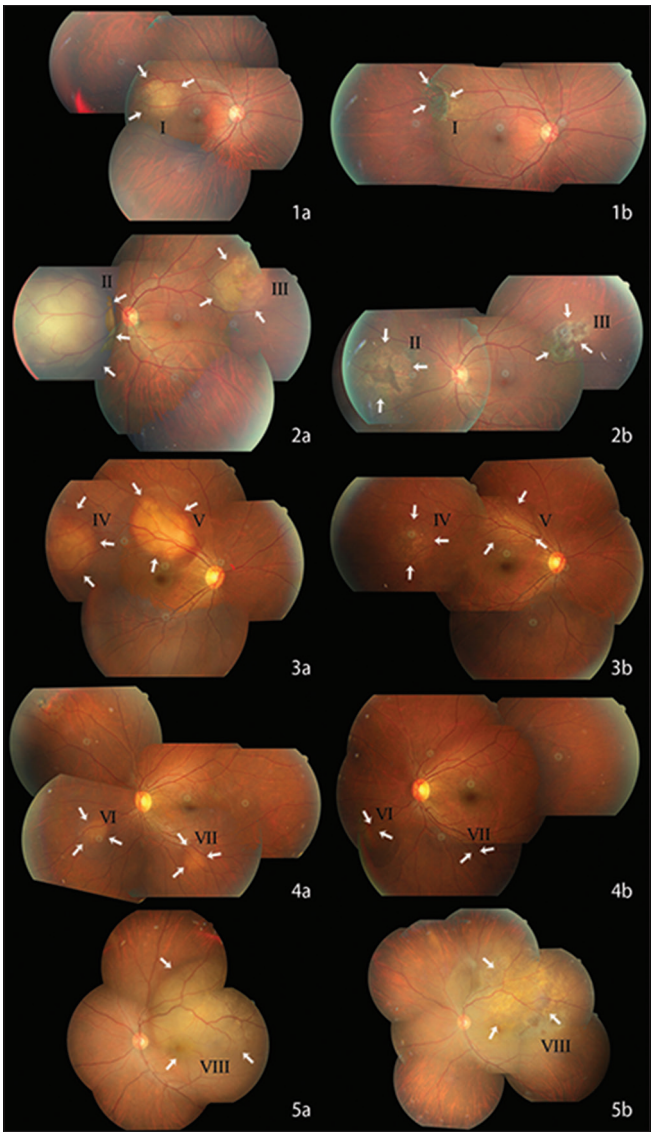

Figure 1: 1(a) A mass (tumor I) OD; 1(b) The mass subsided. 2(a) One large mass over nasal quadrant (tumor II) and one small mass (tumor III) above the temporal-superior arch OS; 2(b) The masses subsided. 3(a) One tumor in the temporal quadrant (tumor IV) and the other with exudative RD (tumor V) in the upper posterior pole extending beneath the macula OD; (b) The tumors shrank. 4(a) Two masses in the nasal (tumor VI) and inferior (tumor VII) quadrants OS; 4(b) The tumors shrank. 5(a) A mass with exudative RD (tumor VIII) in the superior-temporal quadrant involving macula OS; 5(b) The mass shrank

solitary type choroidal mass with exudative retinal detachment was observed in the superior-temporal quadrant with macula involved OS [Fig. 1-5a, tumor VIII]. The OCT revealed an area of choroidal elevation with overlying subretinal fluid and the CFT was 413 µm OS [Fig. 2-3a]. The survey of the possible original malignancy revealed stage IV small cell lung carcinoma with bone metastases. PDT was also offered for the subfoveal lesion, but the patient refused PDT due to the relatively high expense. So he received one session of TTT and 3 times of weekly intravitreal 4 mg/0.16 mL bevacizumab OS. The parameters of treatment for TTT were 1.2–3 mm spot size, 150–300 mW, 60 s with the whole lesion covered. TTT and the initial intravitreal

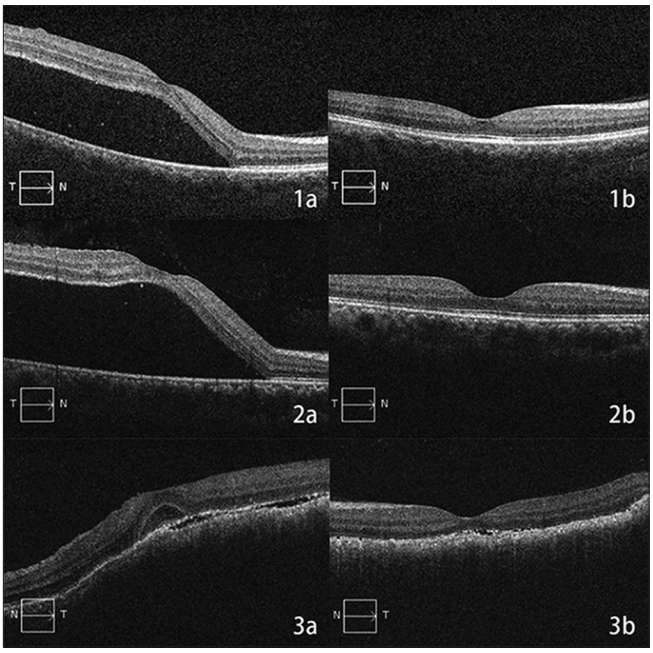

Figure 2: 1(a) The optical coherent tomography (OCT) showed marked subretinal fluid and the central foveal thickness (CFT) was 773 µm OD; 1(b) The OCT showed the resolution of exudative retinal detachment and the CFT reduced to 252 µm OD. 2(a) The OCT showed massive subretinal fluid and the CFT was 983 µm OD; 2(b) The OCT demonstrated no exudative retinal detachment and the CFT reduced to 224 µm OD. 3(a) The OCT revealed an area of choroidal elevation with overlying subretinal fluid and the CFT was 413 µm OS; 3(b) The OCT showed the resolution of choroidal elevation and subretinal fluid OS. The CFT reduced to 235 µm

bevacizumab injection were performed before the systemic chemotherapy. The systemic chemotherapeutic regimen was gefitinib 250 mg daily for 3 months. Three months after the combined treatment, his BCVA was improved to 10/100 OS and the choroidal mass shrank with the subsiding of the exudative retinal detachment [Fig. 1-5b]. The OCT also showed the resolution of choroidal elevation and subretinal fluid OS [Fig. 2-3b]. The CFT reduced to 235 µm. There was no recurrence after 6 months follow-up.

Discussion

Uveal metastasis is the most common intraocular malignancy.[1,2] The most common primary cancer sites for uveal metastases are lung in males and breast in females.[1] The decision of treatment for choroidal metastases is based on the degree of activity and location of the primary tumor. Local treatment is recommended if the metastases threaten vision or destroy the globe despite chemotherapy. External beam radiation, 106Ru plaque radiotherapy, and proton beam radiation have been reported with favorable results.[2-5] Nevertheless, several ocular complications, including cataracts, radiation retinopathy, optic neuropathy, exposure keratopathy and iris neovascularization, do occur and have a significant impact on visual prognosis.[5,6]

Verteporfin PDT is also an effective alternative.[2,7] After PDT, complete control with resolution of subretinal fluid and improvement or stabilization of vision was found to be achieved in the majority of tumors (78%).[7] However, in cases of treatment failure, plaque radiotherapy was still required,

and in the same study, PDT-related complications were found to include intraretinal hemorrhage in one eye The main disadvantage of PDT is that it is relatively expensive and not covered by the national health insurance in Taiwan.

Transpupillary thermotherapy is a technique in which heat is delivered to the choroid and retinal pigment epithelium through the pupil using an 810 nm diode laser. The heating effect on tumor necrosis can be observed within a few days and a significant reduction in tumor volume within a few months after treatment. The proposed mechanism includes vascular thrombosis, thermal inhibition of angiogenesis and induction of fibrosis. TTT has been established as an optional treatment for choroidal melanomas[16] and hemangiomas[17] and was effective in causing the regression of tumors. TTT has also been reported as an effective treatment method for small solitary choroidal metastases with minimal subretinal fluid located in the posterior pole.[8-10] However, in dealing with medium-sized or diffuse type choroidal metastases, TTT still has to be combined with 106Ru brachytherapy,[8] external beam radiotherapy[9] or PDT[10] to achieve tumor shrinkage.

Bevacizumab, a full-length recombinant humanized antibody against all isoforms of vascular endothelium growth factor-A (VEGF-A), is first approved biological therapy of the Food and Drug Administration designed to inhibit tumor angiogenesis. Ranibizumab, an antibody fragment of humanized anti-VEGF monoclonal antibody, was initially designed specifically to treat age-related macular degeneration. The beneficial effects of intravitreal bevacizumab[11-15] or ranibizumab[18] on choroidal metastases have been published. The mechanisms for the response are the antiangiogenic and antipermeability effects of anti-VEFGs agents on new tumor vessels. Although ranibizumab is designed specifically for intravitreal administration and has a possibly higher safety profile, its main disadvantage is that it is much more expensive than bevacizumab.

Electrophysiological and histological studies following intravitreal injection of varying doses of bevacizumab in rabbits indicated that bevacizumab did not appear to be toxic to the retina at a concentration of 2.5 mg.[19,20] Given that the rabbit vitreous cavity volume is assumed to be 1.4 mL, and that the average human vitreous cavity volume (4–5 ml) is at least three times larger, the safe use of intravitreal bevacizumab injection is supported at a theoretical dose of 7.5 mg in a human eye.[12] A higher dose of bevacizumab (4 mg) was chosen in this study, which is more than the usual 1.25–2.5 mg recommended for age-related macular degeneration, because of the severity of the disease and the dose – effect relation between bevacizumab and inhibition of angiogenesis and tumor growth.[11,12] Nevertheless, while intravitreal 4 mg bevacizumab alone seems to be effective for early and small choroidal metastasis, it does not work well in cases of larger choroidal tumor with exudative retinal detachment.[11] For this reason, we combined TTT and 3 weekly intravitreal 4 mg bevacizumab injections to optimize the final outcome.

The limitations of this study include its retrospective nature and the lack of a concomitant control group. In fact, this limitation is due to the scarcity of disease. In Cases 1 and 3, choroidal metastases are the presenting manifestations of lung cancer. As such, ophthalmologists may play an important role in the early detection of systemic malignancies and timely consultation of oncologists. TTT combined with intravitreal bevacizumab displayed beneficial effects in reducing tumor size and improving vision in the five eyes of these three cases of choroidal metastases. The antineoplastic properties of bevacizumab make it a viable adjunctive treatment of metastatic choroidal tumors. No ocular or systemic complications were observed at the end of follow-up. Despite the retrospective nature of our study, the absence of control group and the size limitation that of course limit the statistical power, TTT combined with intravitreal bevacizumab seems to be efficient in providing another cost-reducing and time-saving treatment option for patients with choroidal metastases. Studies with more cases and a longer follow-up period are warranted.

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