Indocyanine Green Mediated Photothrombosis and High Dose Intravitreal Bevacizumab as Adjuvant Therapy for Isolated Choroidal Metastasis from Breast Cancer

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Purpose: To report the effectiveness of indocyanine green mediated photothrombosis (IMP) combined with high dose (4 mg/0.16 ml) intravitreal bevacizumab (IVB) as adjunctive therapy for management of isolated choroidal metastasis from breast cancer.

Methods: This retrospective interventional case report includes three eyes of two patients with choroidal metastasis from breast cancer. Both patients were submitted to one session of IMP combined with high dose IVB as adjuvant local therapy to systemic chemotherapy. Main outcome measures were tumor response, and fluorescein angiography (FA), optical coherence tomography (OCT), and visual acuity (VA) results.

Results: The first patient was a 47-year-old woman who had undergone radical mastectomy, chemotherapy and radiotherapy 7 years earlier and the second patient was a 70-year-old woman managed with chemotherapy and radiotherapy 16 years before presentation. There was no evidence of systemic metastasis in either case and both suffered from gradually blurred vision. The first patient presented with a unilateral choroidal lesion whereas the second case had bilateral unifocal choroidal lesions which was symptomatic in only one eye. Clinical examination, ultrasonography, FA, and OCT revealed accompanying exudative retinal detachment in all three eyes. OCT 3 to 5 weeks after combined therapy demonstrated complete resolution of subretinal fluid and improved VA in two eyes.

Conclusion: Combined IMP and high-dose IVB seems to be an effective adjunctive treatment to systemic chemotherapy for management of isolated choroidal metastasis from breast cancer.

Keywords: Avastin; Bevacizumab; Breast Cancer; Choroidal Metastasis; Indocyanine Green Mediated Photothrombosis
eye. However, bilaterality and multifocality are highly suggestive of the diagnosis. It has been reported that 2-11% of patients are asymptomatic at the time they present to the clinician. In a large series by Shields et al, the most frequent primary site for choroidal metastases was breast (47%), followed by lung (21%) and the gastrointestinal tract (4%). The incidence of ocular metastasis from breast cancer ranges from 9% to 37% which is detected at a median of 3 years after diagnosis of the primary tumor; median survival after the diagnosis of choroidal metastasis is 13.1 months.

Treatment of choroidal metastasis is occasionally indicated to preserve vision and may include laser photocoagulation, cryotherapy, chemotheraphy, radiotherapy, and local surgical resection. Hormonal therapy in choroidal metastasis from primary breast cancer can also result in stabilization or regression of the lesion which is comparable to outcomes of such therapy for other metastatic lesions of breast tumors.

Indocyanine green mediated photothrombosis (IMP) is a noninvasive laser-dye modality used to achieve selective vascular occlusion with minimal or no damage to adjacent structures; the technique has recently been described as an alternative method for choroidal neovascularization. IMP involves intravenous injection of a highly concentrated indocyanine green (ICG) solution followed by focal activation with low irradiance laser with wavelength of 810 nm. This combination produces selective endothelium-bound intraluminal photothrombosis with preservation of the retinal architecture and minimal loss of visual cells. Additionally, IMP has been successfully employed for management of retinal capillary hemangioma. There is only one report on ICG augmented transpupillary thermotherapy (TTT) for choroidal metastasis from breast carcinoma in the literature.

Vascular endothelial growth factor (VEGF) has been demonstrated to be an endothelial cell specific mitogen and angiogenic inducer in a variety of in vitro and in vivo models. The amount of penetration of the full-length anti-VEGF antibody into the human retina is unknown. However, full thickness retinal penetration of intravitreal bevacizumab (Avastin, Genentech Inc., San Francisco, CA, USA) has been observed in an animal model. Additionally, intravitreal bevacizumab (IVB) does not appear to be toxic to the albino rabbit retina up to a dose of 2.5 mg. Considering an average vitreous cavity volume (VCV) of 1.4 ml in rabbits, mean human VCV of 4-5 ml is at least three times that of rabbits. Although it is difficult to extrapolate these results, (IVB) injections may be theoretically safe at doses as high as 7.5 mg in humans. Various reports have demonstrated promising effects from IVB for management of macular edema secondary to central retinal vein occlusion, vascular permeability and fibrovascular proliferation in retinal neovascularization secondary to proliferative diabetic retinopathy (PDR), rubeosis iridis, retinopathy of prematurity, choroidal neovascularization secondary to age-related macular degeneration (AMD), and diabetic macular edema. Recently, Amselem et al described the beneficial effect of a single IVB injection (4 mg) in a patient with choroidal metastasis secondary to breast cancer, three weeks after the injection, visual acuity improved to 20/60. B-mode ultrasonography demonstrated dramatic reduction in tumor size while no ocular or systemic complications were observed at short-term.

The objective of this report is to describe three eyes of two patients treated with IMP combined with high dose (4 mg/0.16 ml) IVB as adjunctive therapy to systemic chemotherapy for management of isolated choroidal metastasis from breast cancer.

METHODS
This is an interventional case report describing three consecutive eyes (two patients) with isolated choroidal metastases and exudative retinal detachment (ERD) treated with IMP combined with high dose (4 mg/0.16 ml) IVB as an adjunct to systemic chemotherapy. The study was approved by the Clinica Oftalmologica Centro Caracas Institutional Review Board. Written informed consent was obtained from...
both patients prior to intervention. Eligibility criteria included previous history of breast cancer together with ophthalmoscopic, ultrasonographic, angiographic, and optical coherence tomography (OCT) findings compatible with choroidal metastasis.

Visual acuity (VA) measurement using the Early Treatment Diabetic Retinopathy Study (ETDRS) chart, color photographs, fluorescein angiography (FA), and OCT (Stratus OCT, Carl Zeiss, Dublin, CA, USA) were performed for both patients at each visit. Each patient made a decision whether or not to undergo treatment, after being informed of the possible advantages and disadvantages of combined IMP and high dose IVB as compared to other available options. The off-label use of the drug and its potential risks and benefits were discussed extensively with all patients. In addition, we adhered with the ethical standards laid down in the Declaration of Helsinki for research involving human subjects.

A modified 810-nm diode laser system (Opto Electronica S.A., Sao Carlos, Brazil) with a slit lamp delivery device was employed. Four mls of ICG aqueous solution (ICV-Indocianina Verde, Ophthalmos Ind, Sao Paulo, Brazil; and IC-Green, Akron Inc., Decatur, IL, USA) at a dose of 2 mg/kg was divided in two equal parts and infused intravenously; the first as a bolus, followed by 5.0 ml saline flush. Thirty minutes later, the second portion of the dose was administered which was similarly followed by 5.0 ml saline flush. Two minutes after the second infusion, a large spot laser light was applied for 100 seconds to the lesion using overlapping multi-spots in two eyes and a single spot in one eye to cover the tumor and an area extending at least 1000 µm beyond its fluorescent border on angiography through a fundus contact lens with 1.5x magnification (Volk QuadrAspheric, Mentor, OH, USA). The laser parameters (irradiance and power) were set according to a protocol based on previous experimental studies at the Federal University of Sao Paulo, Brazil.20,21

Treatment with bevacizumab was delivered on an outpatient basis immediately after IMP. IVB injections were performed in the clinic area under sterile conditions; a 0.25-ml aliquot of commercially available bevacizumab was prepared for each patient and placed in a tuberculin syringe using aseptic techniques. After preparing the eye in a standard fashion using 5% povidone/iodine, the eyelids were stabilized using an eyelid speculum. Finally, injection of 4.0 mg (0.16 ml) of bevacizumab was performed 3.5 mm to 4 mm posterior to the limbus, through the inferotemporal pars plana using a 30-gauge needle under topical anesthesia or subconjunctival lidocaine. After the injection, retinal artery perfusion was checked and patients were instructed to administer topical antibiotics for 7 days.

CASE REPORTS

Case 1

A 47-year-old female patient was referred with a history of radical mastectomy for breast cancer 7 years earlier. She had been treated with radiotherapy and chemotherapy without evidence of systemic metastasis. She presented with progressive decrease in visual acuity in her right eye (OD) for 4 days. Visual acuity was counting fingers OD and 20/25 in the left eye (OS). Intraocular pressure (IOP) was 11 mmHg in both eyes. Anterior segment examination was unremarkable except for the presence of small clumps of pigment deposits on the right corneal endothelium and posterior polymorphous corneal dystrophy in the left eye. Fundus examination revealed an inferior juxtafoveal dome-shaped creamy choroidal tumor associated with perifoveolar serous retinal detachment and retinal pigment epithelium (RPE) clumps of brown pigment on the surface of the tumor; FA demonstrated a filling delay of choroidal vessels with ERD corroborated by B- and A-scan ultrasound evaluation which also showed a choroidal mass with moderate irregular internal reflectivity (Figures 1A, 1B and 1C). Optical coherence tomography revealed highly reflective dots within the neurosensory retina, subretinal fluid and separation of retinal layers (Figures 1D and 1E). Systemic chemotherapy was started but the patient remained unresponsive to treatment. Six months after initiation of
systemic chemotherapy, IMP combined with multi-spot laser applications (Fig. 2) and high dose IVB (4 mg/0.16 ml) were administered; laser light was applied for 100 seconds in each overlapping spot of 8.09 mm, and high dose IVB was injected immediately afterwards.

Three weeks later, significant improvement of VA (20/400) and complete resolution of ERD was observed (Figures 3A and 3B), meanwhile OCT showed no subretinal fluid (Fig. 3C). Four months after combined therapy, visual acuity further improved to 20/100.

Case 2

A 70-year-old woman was referred for progressive decrease in VA together with ERD of 7 months’ duration in her left eye. With a presumptive diagnosis of choroidal metastasis, she had received 10 cycles of systemic chemotherapy for 6 months. Medical history revealed breast cancer 16 years earlier which had been treated with radical mastectomy, chemotherapy and radiotherapy without evidence of metastasis.

Ophthalmic evaluation demonstrated VA of 20/25 in the right eye and hand movements in the left one. IOP was 18 and 17 mmHg in the right and left eyes, respectively. Anterior segment examination showed mild nuclear sclerosis in both eyes.

Fundus examination in the right eye revealed a yellowish, slightly elevated choroidal lesion 3000µ in diameter located temporal to
the macular area (Fig. 4A) and FA showed diffuse early hyperfluorescence and pinpoint areas of fluorescein staining (Fig. 4B). OCT showed elevation of the highly reflective RPE/choriocapillaris complex and subretinal fluid in the same eye (Fig. 4C).

Figure 3. Right eye of case 1, fundus examination (A) revealed complete resolution of exudative retinal detachment with diffuse retinal pigment epithelium (RPE) atrophy and a demarcation line delineating an area of subretinal fibrosis bellow and nasal to the optic nerve. Fluorescein angiography (B) showed an extensive hypofluorescent area which corresponded to hypoperfusion of the choriocapillaris without evidence of subretinal fluid accumulation. Optical coherence tomography (C) demonstrated normalization of the foveal contour with mild irregularity of the RPE, hyperreflectivity of the RPE/choriocapillaris complex and central macular thickness of 236µ.

Figure 4. Fundus appearance (A) of the right eye in case 2, note a yellowish and slightly elevated choroidal lesion 3000µ in diameter temporal to the fovea. Fluorescein angiography of same eye (B) showed a hyperfluorescent pinpoint pattern with retinal folds. Optical coherence tomography (C) revealed subretinal low reflectivity, corresponding to neurosensory detachment and highly reflective deposits (arrow) corresponding to the leopard spots seen clinically.
Fundus examination revealed inferior and temporal ERD with multiple white subretinal lesions and marked RPE changes (Fig. 5). FA in the left eye revealed an elevated, nonpigmented tumor in the posterior pole extending into the inferior and temporal areas; in addition a reticulated pigment pattern on the tumor surface, diffuse early hyperfluorescence and areas of hypofluorescence due to RPE clumping, were also observed (Fig. 5D). B-scan ultrasonography of the left eye showed a choroidal mass with high acoustic solidity and A-scan revealed moderate irregular internal reflectivity (Fig. 5B). The left eye showed low-reflectance elevation in the macular area corresponding to a neurosensory detachment with highly thickened reflective lesion overlying the RPE/choriocapillaris complex (Fig. 5E).

Combined high dose IVB (4 mg/0.16 ml) and IMP was planned for the patient. Laser light was applied for 100 seconds using a single 4.32 mm spot in the right eye and multiple overlapping 4.32 mm spots in the left eye. High-dose IVB was injected immediately after IMP.

Five weeks after treatment, no improvement in VA was noted but a marked decrease in ERD was seen in both eyes by OCT. FA showed an area of RPE atrophy with hypofluorescent regions caused by RPE clumping in the right eye; in the left eye FA revealed complete resolution of ERD with hyper- and hypo-fluorescence areas that corresponded to subretinal fibrosis and RPE clumping, respectively. The optic disc showed early hyperfluorescence (Fig. 6). Seven months after combined therapy, VA improved to counting fingers in the left eye but decreased.

**Figure 5.** B-scan ultrasonography (A) of the left eye in case 2 shows a choroidal mass (black arrows) together with exudative retinal detachment (dB, decibels). A-scan of the same eye (B) showed moderate irregular internal reflectivity. Fundus view of the same eye (C) showed diffuse exudative retinal detachment in the posterior pole with white-creamy subretinal discoloration and retinal pigment epithelial changes. Fluorescein angiography (D) revealed late hyperfluorescence with areas of hypofluorescence. Optical coherence tomography (E) showed subretinal hyporeflectivity corresponding to subretinal fluid accumulation.
to 20/40 in the right eye and there was no sign of active choroidal lesions bilaterally.

DISCUSSION

Treatment of metastatic breast cancer to the eye is usually recommended if the tumor appears active and threatens vision despite concomitant systemic chemotherapy. Demerci et al reported development of ocular metastasis in 141 (53%) patients on systemic chemo- or hormone therapy and concluded that such treatments are not always protective against ocular metastasis.

Treatment options for eye tumors include a combination of laser photocoagulation, cryosurgery, transpupillary thermotherapy, radiation therapy, local resection, and photodynamic therapy (PDT) with verteporfin. In the current report, both patients presented with extensive ERD in one eye, meantime in the second patient an asymptomatic tumor was discovered in the fellow eye. All eyes were treated with a novel combination therapy including IMP and high dose IVB.

Costa et al were the first to report IMP for the treatment of an ocular tumor; in a patient with a retinal capillary hemangioma they effectively restored macular architecture and improved vision by means of substantial occlusion of tumor vasculature and resolution of subretinal fluid. They hypothesized that a mixed type I (heat generation) and type II (singlet oxygen formation) photo-oxidation effect may explain the results of IMP.

Puri et al reported 4 cases with choroidal metastases from breast cancer; all patients presented with gradual regression of the lesion over a mean period of 13.2 months with retention of good VA after receiving ICG augmented TTT. Additionally, there are 3 different reports on single and multispot PDT for choroidal metastases which seems to be a useful palliative procedure to ensure rapid visual improvement and complete resolution of ERD in short term.

Amselem et al reported high dose IVB (4 mg/1.6 ml) as sole therapy for choroidal breast metastasis, revealing a dramatic decrease in tumor size. The anti-permeability effect of anti-angiogenic agents may be beneficial for resolution of ERD usually seen in choroidal metastasis and inhibition of angiogenesis and tumor growth.

Arevalo et al have reported that OCT is useful for evaluating the response of choroidal metastatic tumors to treatment. In addition, they found that OCT allows evaluation of secondary retinal-RPE changes in patients with choroidal

Figure 6. Optical coherence tomography images (A and B) in case 2 showed no subretinal fluid in both eyes and visual acuity improved to counting fingers in the left eye but decreased to 20/40 in the right eye after treatment. Fluorescein angiography in the same patient (C and D) showed an atrophic retinal pigment epithelium (RPE) with hypofluorescent areas caused by RPE clumping in the right eye, and complete resolution of exudative retinal detachment in the left eye which was accompanied by hyperfluorescent and hypofluorescent areas corresponding to subretinal fibrosis and RPE clumping, respectively. The optic disc showed early hyperfluorescence.
metastases. However, OCT imaging is limited by the choroidal location of the metastasis. Enhanced depth imaging (EDI) technique with spectral domain optical coherence tomography (SD-OCT) was not available while this manuscript was being written and was therefore not performed for the patients. In our patients, OCT proved to be useful for visualizing retinal complications and response to treatment in choroidal metastatic tumors. At final follow-up, only one eye demonstrated a decrease in VA, but all cases had complete resolution of ERD 3 to 5 weeks after combined therapy.

In summary, this is the first report of combined high dose IVB and IMP for choroidal metastasis. Such combined therapy may stabilize or improve VA in the short term with complete resolution of subretinal fluid after failed chemotherapy. No ocular or systemic adverse events occurred. This approach may serve as an adjuvant to systemic chemotherapy in choroidal metastasis, however close follow-up after treatment is of utmost importance. Further studies on larger numbers of patients are necessary to define the indications for such therapy.

Conflicts of Interest

None.

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