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Regression of Choroidal Neovascularization in Response to Systemic Chemotherapy for Cancer

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Introduction

The recent introduction of a new class of drugs that inhibit vascular endothelial growth factor (VEGF), a key mediator of choroidal neovascularization (CNV), has revolutionized the management of neovascular age-related macular degeneration (AMD).^{1, 2} Anti-VEGF therapies are now widely used for this purpose.^{1, 3, 4} Despite impressive outcomes, treatment with these agents requires sustained regimens and monthly intravitreal injections. The recent introduction of aflibercept may reduce the frequency of injections in some patients.⁵ However, there remain patients who do not respond (or who have only a partial response) to treatment with anti-VEGF therapies despite monthly intravitreal injections.⁶ This suggests the need for further investigation into additional therapeutic approaches for the treatment of this potentially blinding disease.

Results

A 79 year-old Caucasian gentleman with a history of occult PP CNV in the left eye treated 4 years prior with focal laser photocoagulation was being followed with a recurrence of his CNV with stable vision and interstitial fluid sparing the foveal center (figure 1A and B). This patient underwent diagnostic cystourethroscopy and was diagnosed with T3 transitional

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cell carcinoma (TCC) involving the bladder and urethra and was initiated with chemotherapy, utilizing a combination of cisplatin and gemcitabine.

The patient returned for ophthalmic evaluation two months later, after completing two of three cycles of chemotherapy; he was scheduled to begin his third cycle the following week. Visual acuity and ophthalmoscopy of the left eye were stable. OCT was slightly worse than on his prior visit with modest thickening of the fovea and definite subretinal fluid (figure 1C). In view of the moderate nature of the progression, a decision was made to continue to monitor without ophthalmic therapy. The patient returned for his last visit with the ophthalmology service 10 weeks after completion of the third chemotherapy cycle, and 18 weeks after completion of the first cycle. This document has been retired without provider signature by the Bayview Medical Center Medical Records Department. This document has been retired without provider signature by the Clinical Data and Documentation Committee. Ophthalmoscopy of the left eye demonstrated decreased thickening in the peripapillary region. A fluorescein angiogram of the left eye was unchanged from prior visits with staining of the laser photocoagulation scar (not shown), but the OCT showed a remarkable improvement with flattening of his retina (figure 1D).

The patient was admitted to the hospital the following week with complications from a relapse of his cancer with pulmonary metastasis. He was started on Taxotrene with tentative plans for further chemotherapy and possible radiation. He died three weeks later, one month following his last ophthalmic examination. His eyes were donated by his wife for research purposes and were procured within six hours of his death. Microscopic examination of the left eye showed a normal temporal macula (figure 2A). However, in the region of the nasal macula and papillomacular bundle, fibrocellular material was present on the inner surface of Bruch's membrane (figure 2B) with outer retinal atrophy and degeneration of photoreceptors. The RPE was largely absent in this region, although a few residual RPE cells were entrapped in the fibrous subretinal scar (figure 2B, inset). CNV was encountered extremely rarely on examination of serial H&E stained step-sections (20 microns) through the macular and peripapillary regions (figure 2C). CD31 immunostains of intervening sections highlighted a few more rare foci of CNV (figure 2D and E). However, the majority of endothelial cells present on the inner aspect of Bruch's membrane were within the subretinal scars and formed haphazard groups with no clear lumina (figure 2F).

Discussion

A rationale exists for combination approaches to target different processes in the pathogenesis of CNV; this may maximize clinical benefits through potentially complementary effects in patients with neovascular age-related macular degeneration.^{7,8} However, the additive efficacy of anti-VEGF therapies may be undermined by the redundancy of their target(s). There is, therefore, a need to identify additional therapeutic targets for the treatment of CNV. Our report exposes a novel potential therapeutic alternative for the treatment of CNV: direct chemotherapeutic inhibition of proliferating endothelial cells. Although spontaneous resolution of peripapillary CNV can occur and is well documented, we hypothesize that almost total regression of the long-standing CNV in

the patient described here was a consequence of the systemic chemotherapeutic agents targeting the proliferating endothelial cells within the CNV lesion.

This theory is not without precedent. Although systemic therapy for cancer has been dominated by the use of cytotoxic chemotherapeutics administered in single doses or short courses at the highest doses possible without causing life-threatening levels of toxicity (referred to as the maximum tolerated dose or MTD), this approach has been under recent reappraisal. More frequent administration of chemotherapeutics at doses significantly below the MTD, with no prolonged drug-free breaks – known as metronomic chemotherapy – may more effectively target the vascular endothelial cells that play an essential role in supplying oxygen and nourishment to the tumor.^{9, 10} Although too low to kill the cancer cells directly, the doses are high enough to arrest capillary growth that would have supplied nutrients to the cancer cells.

Our patient did not get typical metronomic therapy because he had 1-week breaks. Nonetheless, the concept of low dose chemotherapy which targets the endothelial cells rather than the tumor cells (a fundamental component of metronomic chemotherapy) is consistent with the effects we saw with our patient and suggests that such an approach may be effective for patients with CNV. We propose that intrachoroidal concentrations of the chemotherapeutic agents used systemically in our patient may have approached metronomic levels, thereby targeting the proliferating endothelial cells in the small vessels within the choroidal neovascular lesion. We further hypothesize that a local (rather than systemic) approach, using more frequent but lower concentrations (metronomic) of intraocular anti-proliferative (chemotherapeutic) agents may possibly target capillary growth in choroidal neovascularization by similar mechanisms. Administration of anti-proliferative molecules intravitreally (or by other local means), rather than systemically, may provide higher local concentrations with minimal systemic side effects. Further studies examining the safety of intravitreal (or other local) injection of these and other anti-proliferative therapeutic agents would be necessary prior to utilizing these drugs in patients with choroidal neovascularization. More extensive studies of systemic administration of such drugs are also indicated.

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Figure 1.

(A) Fundus photo from OCT reconstruction of the macula demonstrate a chorioretinal scar in the papillomacular bundle of the left eye from prior laser photocoagulation. (B) OCT indicates intact foveal pit, but presence of intraretinal fluid under the papillomacular bundle. Central subfield thickness and volume are 210 and 7.2, respectively. (C) The patient was stable for subsequent follow up visits until 6 months later, when his OCT is slightly worse than on prior visits, showing thickening of the fovea and a small amount of subretinal fluid. (D) Three months later (after 3 cycles of chemotherapy), OCT shows remarkable improvement, with complete flattening of the retina.

Figure 2.

Microscopic Analysis. (A) The temporal macula appears relatively normal (original magnification 400X). (B) A fibrocellular scar on the inner aspect of Bruch's membrane (short arrows) in the peripapillary region contains no patent vessels, but some entrapped RPE cells (inset) are present (original magnification 200x). (C) Recognizable CNV vessels (long arrow) are extremely rare, as are endothelial cell nuclei, with only a few foci identified on serial step sections through the entire region (original magnification 400x). (D,E) CD31 immunostains, which mark endothelial cells, also highlighted only a few foci of patent CNV. One such area containing CNV, boxed in panel D, is shown at higher magnification in E (original magnifications 40x and 400x). The vessels (long arrows) are stained brown, and are growing along the inner aspect of Bruch's membrane (short arrows). (F) Most of the subretinal endothelial cells highlighted by CD31 immunostains are present in poorly-formed masses (long arrows) which contain no clear vascular lumina (original magnification 400x).