American Journal of Ophthalmology Case Reports 26 (2022) 101519

Contents lists available at ScienceDirect

American Journal of Ophthalmology Case Reports

journal homepage: www.ajocasereports.com/

Combination intravitreous melphalan and bevacizumb for cutaneous metastatic melanoma to the vitreous and retina

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ARTICLE INFO

Keywords:
Melphalan
Metastatic melanoma
Bevacizumab
Neovascularization
Vitreous
Retina

ABSTRACT

Purpose: Cutaneous melanoma metastatic to the vitreous/retina is rare but increasingly common. Due to the potential of recurrent disease with current treatment options and the propensity for these eyes to develop neovascularization, these eyes can pose a treatment challenge and novel management strategies are needed. This case series explores the use of combination, sequential intravitreous melphalan and bevacizumab.

Observation: Two eyes of two patients with cutaneous melanoma metastatic to the vitreoretina were eye treated with combination intravitreous melphalan (10-30 mcg) and bevacizumab (1.25 mg) given sequentially during the same office visit, at monthly intervals. Both cases had control of disease at 7- and 12-months follow up. Furthermore, treatment reversed neovascular glaucoma and dramatically improved vision in the eye of one patient; and stabilized vision without the development of neovascularization in the eye of the other patient. There were no ocular adverse events noted in either eye.

Conclusions and Importance: Combination, sequential intravitreous melphalan and bevacizumab is well-tolerated and an attractive approach for treating eyes with intraocular metastatic melanoma.

1. Introduction

In patients with metastatic cutaneous melanoma, immune checkpoint inhibitors and targeted BRAF-MEK inhibitors for BRAF V600 mutant disease have been proven to improve overall survival.[1] Perhaps due to longer survival, there is an increased detection of previously rare sites of metastases, including cutaneous melanoma to the brain, vitreous and retina.[2,3]

Metastases to these intraocular sites pose two potential treatment challenges: 1. Due to the immune privilege status of the eye, they can be a site of uncontrolled disease inaccessible to the immune system, and 2. The pathophysiology of disease results in ocular morbidity characterized by a high propensity for serous retinal detachment and neovascular glaucoma (NVG). Radiation treatment may address the first concern, but recurrence occurs, and radiation toxicity may increase the risk of ocular morbidity.[4] Many eyes will come to enucleation,[5] and improved treatment modality is urgently needed. We describe here two eyes with cutaneous melanoma metastatic to the vitreous and retina treated with combination intravitreous melphalan and bevacizumab.

2. Case descriptions

Case 1: A 65-year-old woman with histopathological metastatic melanoma to the lung and liver developed sites of disease in the brain and left eye. She initially received two cycles of ipilimumab 3mg/Kg and nivolumab 1mg/Kg. Her left intraocular metastatic melanoma presented with blurry vision (Snellen 20/80), iris neovascularization with intraocular pressure (IOP) of 28 mmHg, iris heterochromia, pigmented keratic precipitates, anterior lens capsule and retrolental pigment and vitreous amelanotic/melanotic debris interspersed with hemorrhage (Fig. 1). She was treated with six monthly combination intravitreous melphalan (20mcg x 4 and 30 mcg x 2) and bevacizumab (1.25mg). She received no additional systemic treatment as she developed autoimmune neutropenia. At seven months follow up, her vision improved to 20/25, IOP normalized to 12 mmHg, with resolution of iris neovascularization and intraocular disease; revealing a clear view of her

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https://doi.org/10.1016/j.ajoc.2022.101519
Received 9 February 2021; Received in revised form 25 January 2022; Accepted 3 April 2022
Available online 9 April 2022

fundus (Fig. 1).

Case 2: An 88-year-old man with histopathological metastatic cutaneous melanoma to the lymph nodes and bilateral vitreous cavities received three cycles of nivolumab and external beam radiation (30Gy/10 fractions) to both eyes. Six months later, progression of vitreous disease was noted in the left eye with increased amelanotic vitreous clumping, vision 20/100 and normotensive IOP. Moderate cataracts and Parkinson's-related keratoconjunctivitis sicca contributed to poor vision. The eye received three combination, sequential intravitreous melphalan (10 mcg x 1 and 20mcg x 2) and bevacizumab (1.25mg) injections. At 12-months follow-up, the vitreous disease resolved, no neovascularization was noted, IOP remained normotensive and the retina appeared normal with stable vision. Patient subsequently died from progression of his systemic disease.

3. Discussion

Eyes with intraocular melanoma metastasis are challenging to treat, and the rationale for using combination melphalan and bevacizumab is grounded in the characteristic pathophysiology of the disease. The reasons are two-fold: 1) Treatment strategies for eyes with metastatic cutaneous melanoma include enucleation, which can be morbid, and radiation which can be associated with recurrence.[4] Historically, patients had a poor prognosis, and therefore these two options were permissible. However, thanks to new systemic treatments, patients are living longer[1] and there is a need to better control intraocular sites of disease. Melphalan is cytotoxic to melanoma, as informed by pre-clinical data[6–9] and clinical responses of melanoma from targeted melphalan delivery through isolated limb and hepatic infusion.[10,11] Like these two approaches, intravitreous melphalan injections deliver targeted cytotoxic drug to the isolated site of intraocular disease; as has been demonstrated with uveal melanoma.[12] The dose of intravitreous melphalan was selected based on our prior work relating to severe retinopathy which can occur in retinoblastoma eyes treated with melphalan doses exceeding 30 mcg.[13] 2) It is established that roughly one-third of eyes with intraocular melanoma metastasis will develop neovascularization and neovascular glaucoma,[2] which are two pathological states driven by aberrant vascular endothelial growth factor. This characteristic vasculopathy is perhaps related to the entry of metastatic melanoma through the retinal blood vessels.[2] Intravitreous anti-vascular endothelial growth factor (bevacizumab) is intended to targets this, and either prevent or reverse eyes from developing neovascularization and its sequelae. The present study does not answer whether bevacizumab is prophylactically beneficial to eyes with cutaneous melanoma metastatic to the vitreoretinal in the absence of clinical neovascularization: anti-VEGF injections may be equally beneficial if initiated only at the first detection of neovascularization.

Indeed, in the two eyes presented here, we demonstrate this treatment approach (combination intravitreous anti-VEGF/melphalan given sequentially during the same office visit) is well-tolerated (no evidence of melphalan-related retinopathy[14]) and resulted in resolution of active disease with sustained responses at 7- and 12-months follow up. Treatment reversed NVG, and dramatically improved vision in one eye; and stabilized vision without the development of neovascularization nor serous retinal detachment in the other eye.

4. Conclusions

Given the relatively high propensity for eyes with intraocular metastatic melanoma to develop NVG and the possibility for recurrence with historical treatments, this well-tolerated combination approach is attractive. We hope expansion of this treatment cohort will provide further validation of this management option.

Patient consent

Written consent was obtained by both patients.

Funding

The Fund for Ophthalmic Knowledge, the New York Community Trust and the Cancer Center Support Grant (P30CA008748). The sponsor or funding organization had no role in the design or conduct of this research.

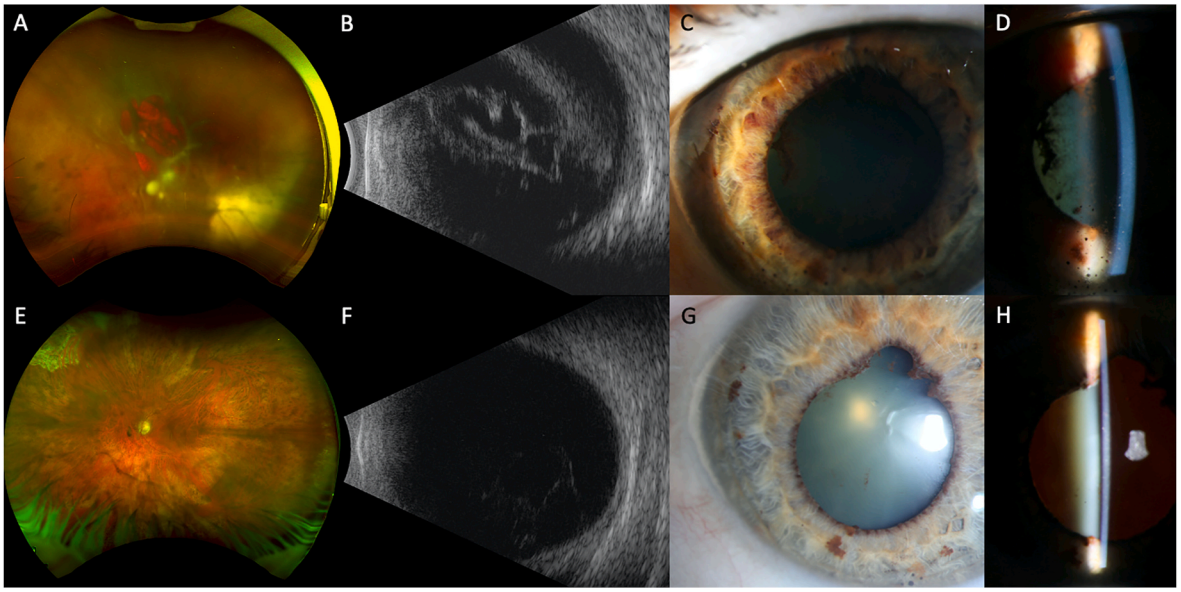

Fig. 1. Case 1 with intraocular metastatic melanoma demonstrated by amelanotic/melanotic vitreous debris and hemorrhage shown on color fundus imaging (A) and ultrasound (B), iris neovascularization, heterochromia, pigmented keratic precipitates, lens pigment shown by slit lamp (C and D). Following 6 monthly combination melphalan and bevacizumab injections, there was a marked improvement in intraocular disease with clearing of the vitreous by fundoscopy (F) and ultrasound (F), and improved anterior segment findings (G and H); accompanied by improved intraocular pressure to 12 mmHg and vision to 20/25. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Other contributions

None.

Declaration of competing interest

MSKCC receives research funding from Amgen, Merck, Alpha Tau Medical for research studies that did not directly support this work. C. A. B. has received honoraria from Regeneron.

A.N.S. declares institutional grant support from Bristol-Myers Squibb, Immunocore, Xcovery, Polaris, and Novartis; Personal fees from Bristol-Myers Squibb, Immunocore, and Castle Biosciences.

All authors attest that they meet the current ICMJE criteria for authorship.

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