Chemoreduction of Orbital Recurrence of Uveal Melanoma by Intra-Arterial Melphalan

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Established Facts

- Orbital recurrence of uveal melanoma may occur in approximately one-quarter of eyes with known extraocular extension on histopathology.
- The treatment of orbital recurrence of uveal melanoma is challenging: exenteration can be disfiguring and does not always control local disease.

Novel Insights

- Intra-arterial melphalan delivered to the orbit can cytoreduce (but not cure) orbital recurrence of uveal melanoma.
- Intra-arterial melphalan delivered to the orbit at doses as high as 30 mg may result in temporary peri-ocular erythema but appears to have limited permanent alterations in cosmesis.

Keywords

Intra-arterial chemotherapy · Neoplasia · Orbit · Orbital tumor · Uveal melanoma

Abstract

Background/Aims: The treatment of orbital melanoma poses a management challenge. This case explores the delivery of high-dose melphalan to an orbital recurrence of uveal melanoma via intra-arterial delivery of melphalan to the or-

bit. A 62-year-old man developed recurrent orbital disease 7 months after enucleation for a large uveal melanoma. He received 6 monthly intra-arterial infusions of melphalan to the orbit, ranging in dose from 20 to 30 mg per infusion. Following the last infusion, mild temporary erythema was noted on the forehead along the distribution of the supratrochlear ar-

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tery. The orbital recurrence was reduced in size by 66% in the longest dimension as measured by magnetic resonance imaging (MRI). However, 9 months following intra-arterial melphalan, tumor regrowth was detected on MRI, and additional treatment options were pursued. **Conclusion:** This case demonstrates that intra-arterial melphalan can result in non-sustained tumor regression of recurrent orbital uveal melanoma. It suggests that local delivery of high-dose melphalan may be helpful as a neoadjuvant treatment for uveal melanoma, and future studies will be useful to confirm the value of this approach in additional cases of recurrent and possibly in primary uveal melanoma.

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Introduction

Primary orbital melanoma is extremely rare [1]. However, orbital melanoma may develop, either from direct extension of an intraocular or surface tumor, or from metastatic disease recurring in this location. Up to 15% of enucleated uveal melanomas are found to have some degree of extraocular extension, which has been associated with increased tumor size and high-risk cytogenetic features [2, 3]. The Collaborative Ocular Melanoma Study (COMS) found that external beam radiotherapy did not affect the rate of metastasis but did reduce the incidence of orbital recurrence [4].

Despite histopathological findings, orbital recurrence occurs in only 3–23% of eyes with known extraocular extension [3]. However, orbital recurrence poses a clinical challenge should it occur. Treatment options are disfiguring, and many tumors will progress despite management with surgery and radiation. This present case is a patient with orbital recurrence of uveal melanoma, who refused exenteration and desired exploration of alternate management options.

This case borrows from the cutaneous melanoma literature and involves localized, high-dose delivery of melphalan to the orbit. Isolated limb perfusion of melphalan was first described as a single case report by Creech et al. [5] in 1957 and is now a well-established technique for inoperable recurrent cutaneous melanoma affecting an extremity [6]. It consists of localized delivery of cytotoxic melphalan to the site of disease, without exposing vital organs to the consequences of these high doses. A similar technique, percutaneous isolated hepatic perfusion, involves a similar technique of melphalan delivery and has established a hepatic control rate for uveal melanoma of 82.4% [7–9]. Our group has extensive experience in ap-

plying this rationale to the treatment of retinoblastoma through the technique of ophthalmic artery chemosurgery [10]. Therefore, we used a similar technique to deliver intra-arterial melphalan to the orbit of a single case with recurrent orbital uveal melanoma; and this report describes the response and outcome.

Case Report

A 62-year-old man weighing 97 kg with melanosis oculi was enucleated for a COMS large ciliochoroidal melanoma [11]. Seven months later, he reported a change in his prosthesis fitting, and magnetic resonance imaging (MRI) revealed a large orbital mass, confirmed as recurrent uveal melanoma on biopsy (Fig. 1). Both the primary and orbital tumors had gene expression profile class IA and disomy 3 [12]. The orbital tumor demonstrated somatic mutations in *GNAQ* and *SF3B1* and an absence of *BAP1* mutation [13]. Imaging revealed no evidence of regional or distant metastases. The accepted treatment options were discussed with the patient (including proton beam radiation and exenteration). He adamantly refused exenteration. An additional meeting was set up in the presence of the patient's family to review the option of exenteration, and still the patient refused. A fully informed consent was obtained outlining the known and potential unknown risks, benefits, and alternatives, and the patient decided to undergo monthly intra-arterial melphalan to the orbital tumor. The initial infusion delivered 3 mg to the anterior deep temporal artery (ADTA) and 7 mg via the ophthalmic artery (OA). A second (4 mg via ADTA and 11 mg via OA) and third (3 mg via ADTA and 12 mg via OA) infusion were given. The fourth infusion delivered 3 mg to the anterior branch of the superficial temporal artery, 5 mg via ADTA and 12 mg via OA. A repeat MRI demonstrated a measurable contraction of the tumor, but with residual tumor in the inferior lateral orbit. For this reason, the infraorbital artery (IOA) was accessed for the final 2 infusions: the fifth infusion delivered 10 mg via IOA, 8 mg via ADTA, and 12 mg via OA. The sixth infusion delivered 7 mg via IOA, 8 mg via ADTA, and 15 mg via OA. Following this, the orbital uveal melanoma demonstrated a dramatic reduction in size with minimal radiographic evidence of residual tumor: specifically, 1.1×1.3 mm to 0.6×0.8 mm (Fig. 1). After the final infusion, the patient reported temporary erythema on his forehead skin along the distribution of the supratrochlear artery, which resolved within 2 weeks and without any permanent sequelae. There was no evidence of hematologic toxicity during the treatment course as measured by complete blood count. The blood count nadir is 7–10 days after chemotherapy: results during this time period revealed a hemoglobin range of 15.2–16.3 g/dL, a platelet count range of $144\text{--}218 \times 10^3/\mu\text{L}$, and absolute neutrophil count of $3.2\text{--}4.2 \times 10^3/\mu\text{L}$. These results are within the normal range.

Nine months following treatment, a repeat MRI demonstrated recurrent disease in the orbit, and the patient received proton beam radiotherapy. Seven months following radiation, recurrence was again noted, and the patient enrolled in 2 experimental trials of systemic therapy (including immunotherapy). Stability was initially noted, but disease again recurred, and the patient eventually agreed to exenteration. He remains free of metastasis at 48 months of follow-up from orbital recurrence.

Fig. 1. **a** T1-weighted fat-saturated magnetic resonance (MR) axial image of the right orbit demonstrating biopsy-proven uveal melanoma surrounding the orbital implant. Arrow demonstrates tumor. **b** T1-weighted fat-saturated MR sagittal image of the right orbit demonstrating biopsy-proven uveal melanoma circumscribing the orbital implant. Arrow demonstrates tumor. **c** T1-weighted fat-saturated MR axial image of the right orbit following 6 infusions of ophthalmic artery chemosurgery (OAC) demonstrating contraction of orbital melanoma. **d** T1-weighted fat-saturated MR sagittal image of the right orbit following 6 infusions of OAC demonstrating contraction of orbital melanoma.

Discussion

The treatment options for orbital melanoma are limited to either radiation or surgical excision, typically by exenteration [14–19], as no chemotherapy, biologic or targeted therapy has been proven to prolong survival. Both options can be disfiguring and are not always effective at preventing progression of disease [15]. Likewise, in this case, the intra-arterial melphalan was not curative of disease, and the tumor recurred at 9 months of follow-up.

The drug choice of melphalan is grounded in clinical responses noted in the treatment of cutaneous melanoma by isolated limb perfusion and liver metastases of

uveal melanoma by isolated hepatic perfusion [5, 6, 9]. Preclinical data support the therapeutic response of human melanoma lines to melphalan and have shown an enhanced response with hyperthermia [20, 21]. However, these studies focus on cutaneous melanoma cell lines, and few have focused on uveal melanoma cell lines. One may question whether other intra-arterial drugs may be useful in this disease. Unfortunately, there is little evidence to suggest that uveal melanoma would respond to the other 2 agents (carboplatin and topotecan), which are routinely delivered via ophthalmic artery chemosurgery. However, there is a possibility that carboplatin, as a platinum-based agent, may radiosensitize uveal melanoma to subsequent radiation [22].

In contrast to the closed circulation of isolated limb perfusion and percutaneous isolated hepatic perfusion involving arterial infusion and venous extraction of the drug, intra-arterial chemotherapy consists solely of drug infusion. This may raise concern for an increased risk of myelosuppression in the latter technique. However, “most” patients treated with isolated limb perfusion received granulocyte colony-stimulating factor [9]. On the contrary, our single patient did not have evidence of myelosuppression. This may be partly attributable to drug dose: in isolated hepatic perfusion, patients receive 3 mg/kg per treatment, and our patient was given between 0.10 and 0.39 mg/kg per infusion.

However, the importance of this case lies in the demonstration that intra-arterial melphalan delivered via ophthalmic artery chemosurgery can dramatically reduce uveal melanoma (by 66% on radiographic imaging) and is well tolerated. For this patient, it effectively resulted in tumor regression with limited transient skin erythema, no systemic toxicity, and with little alteration in cosmesis. Despite being only a single case, it lays the precedent for other possible indications for intra-arterial melphalan in the treatment of ocular melanoma. For instance, intra-arterial melphalan could be used as an adjunct to chemo-reduce orbital uveal melanoma prior to surgical excision or radiation. Or it could be used to reduce large uveal melanomas to a size that could appropriately receive definitive treatment with plaque brachytherapy. In support of this, it is known from the retinoblastoma literature that intra-arterial melphalan results in a substantial dose of drug to the choroid [23]. Or perhaps it could be used in the management of other ocular melanomas, such as refractory conjunctival melanomas with orbital extension. Despite the distinct genetics of conjunctival melanomas (which aligns more with that of cutaneous melanoma), the favorable results of intra-ar-

terial melphalan in cutaneous melanoma suggest that it may be useful in its conjunctival counterpart.

We encourage larger studies to validate these findings and further refine the utility of intra-arterial melphalan in the treatment of ocular melanoma.

Statement of Ethics

The patient provided written informed consent for all treatments, including the use of imaging. This single case study did not require review/approval by the Memorial Sloan Kettering Institutional Review Board.

Disclosure Statement

The relevant financial and commercial conflicts are as follows: Richard Carvajal: AstraZeneca, BMS, Castle Biosciences, Foundation Medicine, Immunocore, Incyte Merck Novartis, Roche/Genentech, Aura Biosciences, Chimeron Rgenix. Paul Chapman: Merck, Cell Medica, Astra Zenica, Takeda, Pfizer, Genentech. Christopher Barker: Bristol Myers Squibb, Merck, Amgen, Pfizer, Novartis. None of the other authors have any financial disclosures or conflicts.

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