Dabrafenib and Trametinib for BRAF-Mutated Conjunctival Melanoma

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Established Facts

- BRAF/MEK targeted therapy is effective in the treatment of cutaneous melanoma with V600 *BRAF* mutation.
- V600 *BRAF* mutation can be seen in conjunctival melanoma in up to half of the cases.
- The efficacy of BRAF/MEK targeted therapy in conjunctival melanoma harboring V600 *BRAF* mutation is unknown.

Novel Insights

- As in cutaneous melanoma, targeted therapy against BRAF/MEK can induce response in a locally advanced conjunctival melanoma with V600 *BRAF* mutation.
- *BRAF* mutation testing should be considered in patients with conjunctival melanoma.

Keywords

Conjunctival melanoma · Targeted therapy · Case report

Abstract

Background: Conjunctival melanoma is a potentially lethal malignancy of the ocular surface. There have been no therapeutic advancements made in the past several decades despite increasing prevalence of the disease. **Methods:** The authors report the case of a 52-year-old Caucasian male with unresectable, recurrent conjunctival melanoma with V600 *BRAF* mutation who was treated with systemic BRAF/MEK inhibition. **Results:** There was complete regression of local disease within the first 9 months. The patient remains without

local recurrence or systemic metastasis at 1 year. **Conclusion:** This is the first reported case of conjunctival melanoma with complete response to BRAF/MEK inhibition. As long as targeted therapy remains an option, patients with conjunctival melanoma should undergo mutational profiling of their tumor.

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Introduction

Conjunctival melanoma (CM) is a rare malignancy of the ocular surface with an incidence of 0.54 per million [1]. The standard of therapy for CM is surgical excision

Fig. 1. Slit-lamp photograph of the conjunctival melanoma before and after treatment with dabrafenib and trametinib. Melanoma is visible on the bulbar conjunctiva (a), inferior limbus (b), and superior tarsal conjunctiva (c) before treatment. Ten months after treatment with dabrafenib and trametinib, there is complete resolution of the multifocal melanoma of the bulbar (d), limbal (e), and tarsal conjunctiva (f).

with cryotherapy. Locally advanced or unresectable CM is treated with exenteration. Despite these interventions, distant metastases arise in 25–30% of CM patients [2, 3]. Tumor-related death occurs in as many as 35% of patients with de novo CM at 10 years [1]. The incidence of CM has increased in recent decades [4], but no new treatment for local or metastatic CM had been introduced for years [5]. Treatment paradigms are shifting as new insights into driver mutations in CM have made clinical benefit from targeted therapies a growing possibility.

Mutation-specific treatments have been successful in patients with metastatic *cutaneous* melanoma. In tumors harboring V600 *BRAF* mutations, comprising an estimated 40% of cutaneous melanomas, targeted therapy using the *BRAF* inhibitor dabrafenib combined with the *MEK* inhibitor trametinib in the phase III COMBI-d trial demonstrated a 3-year overall survival rate of 44% for previously untreated patients [6]. Three-year overall survival was as high as 62% in the subset of patients with normal lactate dehydrogenase and less than 3 organ sites of metastasis [6]. This combination therapy was subsequently studied in the adjuvant setting in patients with completely resected stage III V600 *BRAF*-mutant melanomas in the COMBI-AD trial [7]. Adjuvant dabrafenib plus trametinib compared to placebo improved relapse-free sur-

vival from 39 to 58% [7]. For stage III and stage IV cutaneous melanomas with a V600 *BRAF* mutation, combined *BRAF* and *MEK* inhibition is now the standard of care. Cutaneous melanoma and CM share phenotypic and genotypic characteristics – both harbor *BRAF* mutation in up to 50% of cases [5]. The *BRAF* mutation is hence a reasonable target for CM control. We report a case of recurrent, unresectable, *BRAF*-positive CM with complete response to dabrafenib and trametinib.

Case Report

A 52-year-old Caucasian man presented with a pigmented conjunctival lesion of the right eye. He was initially managed at an outside hospital with incisional biopsy. He was referred for further management upon confirmation of positive margins with CM cells. When he eventually presented to ophthalmic oncology 3 months later, he had multifocal recurrence – both pigmented and amelanotic – involving the corneal limbus, bulbar conjunctiva, and tarsal conjunctiva (Fig. 1a–c). Despite 2 attempts at complete excision, including the “no-touch technique,” alcohol epitheliectomy, and double freeze-thaw cryotherapy, there was residual melanoma (Fig. 2). Rapid local recurrence was noted in the postoperative period. The patient had no lymphadenopathy, and full body PET/CT imaging was negative for metastasis. V600 *BRAF* mutation was identified by polymerase chain reaction single-strand conformation polymorphism of the conjunctival specimen. After discussion of op-

Fig. 2. Microphotograph ($\times 20$) of the conjunctival specimen stained with hematoxylin and eosin (a). The nested epithelioid cells with cytoplasmic clearing indicate conjunctival melanoma, confirmed by S-100 staining (b). The margins were positive.

tions, including topical chemotherapy, radiation, orbital exenteration, immune checkpoint inhibitor therapy, and targeted therapy, the patient elected for systemic targeted therapy. He was started on oral dabrafenib 150 mg twice daily plus trametinib 2 mg daily.

Over the next 10 months, complete resolution of the CM was observed (Fig. 1d–f). He had no significant adverse events from therapy aside from several fevers initially and brief elevation of liver enzyme levels. For the liver enzyme abnormality, temporary dose reduction was instituted for 2 weeks. When the enzyme levels normalized, the initial dosing was reinstated. He remains metastasis free at 15 months since the initiation of systemic therapy. The visual acuity of the involved eye is 20/25. The patient continues treatment with regular surveillance for local recurrence and systemic metastasis by imaging.

Discussion/Conclusion

The role of the *BRAF* oncogene in tumorigenesis is rooted in the mitogen-activated protein kinase (MAPK) pathway. With activation of *BRAF*, *MEK* is also activated, and the downstream effect of this pathway is transcription of cell proliferation signals. A mutation in *BRAF* leads to constitutive activation of the transcriptional pathway that in turn promotes tumor proliferation. While *BRAF* mutation alone may not be sufficient to induce CM as evidenced by the presence of *BRAF* mutation in benign nevi [5, 8], it may work in concert with other mutations that ultimately lead to tumorigenesis and possibly even aggressive phenotype. For example, rates of distant metastasis in 1 report were greater in *BRAF*-mutated CM compared to *BRAF* wild-type CM (31.6 vs. 3.6%, respec-

tively) [4]. Targeting the *BRAF* mutation is, therefore, a logical option for the treatment of unresectable *BRAF*-mutant CM, especially in light of the strong evidence of its success in *BRAF*-positive cutaneous melanoma.

While it is difficult to conduct clinical trials for CM due to its low incidence, a few CM patients have been treated with single-agent targeted therapy with vemurafenib – another *BRAF* inhibitor – with varying results ranging from partial response to recurrence and death [5, 9, 10]. Combination therapy with dabrafenib and trametinib for the treatment of CM was reported in 1 case [11], but with a course complicated by local relapses despite systemic therapy and change from vemurafenib to pembrolizumab – a checkpoint inhibitor that targets programmed cell death protein 1 (PD-1), an entirely different mechanism of action [9]. The case reported herein is the first in the literature to demonstrate a complete response to *BRAF* and *MEK* inhibitor therapy in unresectable CM. This case shows that the combination therapy has the potential to be a globe-sparing treatment option for patients with recurrent and unresectable *BRAF*-mutant CM.

Follow-up of the reported case is needed to study long-term efficacy of treatment and to elucidate the appropriate duration of therapy. Moreover, a larger number of cases is needed to demonstrate reproducibility. As long as targeted therapy remains an option for CM patients, all CMs should undergo mutational profiling. As is the case in cutaneous melanoma, adjuvant therapy after complete surgical excision of CM should be considered for those tumors with V600 *BRAF* mutation.

Statement of Ethics

The study adheres to the guidelines set forth in the Declaration of Helsinki. The patient gave his written informed consent to publish the case and images. The study protocol was approved by the institute's committee on human research.

Disclosure Statement

Sarah Weiss, MD, is a consultant for Array Biopharma. All other authors have no conflicts of interest to declare.

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Author Contributions

Jenna May Kim wrote the manuscript. Sarah Weiss was the primary medical oncologist managing the systemic therapy and monitoring of adverse events. She contributed to the editing of the manuscript. John H. Sinard edited the manuscript and provided the histopathologic diagnosis. Renelle Pointdujour-Lim was the primary ophthalmic oncologist managing the patient since presentation. She also contributed to the editing of the manuscript.

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