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Case Series

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MEK Inhibitor-Associated Ocular Hypertension

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Ocular hypertension · Oncology · Drug toxicity

Abstract
Introduction: Mitogen-activated protein kinase kinase (MEK) inhibitors are targeted anticancer agents that are prescribed to treat a broad range of cancers. Despite their strong efficacy profile, MEK inhibitors have been associated with ocular toxicities, most notably, self-limited serous detachments of the neurosensory retina. In this report, we outline 3 cases of a rarely documented toxicity, MEK inhibitor-associated ocular hypertension. ***Case Presentations:*** In the first case, a 69-year-old female with metastatic cholangiocarcinoma presented with an intraocular pressure (IOP) of 25 mm Hg right eye (OD) and 27 mm Hg left eye (OS) 2 months after starting trametinib therapy. Similarly, in the second case, a 26-year-old female with Langerhans cell histiocytosis presented with an elevated IOP of 24 mm Hg bilaterally (OU) 13 months after beginning treatment with an investigational MEK inhibitor. In the third case, a 46-year-old male with Langerhans cell histiocytosis presented with a new onset of elevated IOP of 24 mm Hg 21 days after initiating treatment with cobimetinib. All 3 patients' IOP returned to normal following dorzolamide/timolol administration and continued their cancer therapy. ***Discussion/Conclusion:*** This report presents 3 cases of elevated IOP in patients taking three distinct MEK inhibitors which would suggest that IOP-elevating effects exist across the class of MEK inhibitors. All 3 patients had a satisfactory response to topical pressure-lowering drops while continuing their life-preserving MEK inhibitor drug dose, indicating that discontinuation of therapy may not be necessary. Due to the increasing use of MEK inhibitors, it is important that ophthalmologists familiarize themselves with the broad range of potential adverse ocular effects of MEK inhibitors.

Introduction

Mitogen-activated protein kinase kinase (MEK) inhibitors are a class of targeted anticancer agents. They are administered orally and work by blocking the mitogen-activated protein kinase (MAPK) pathway that becomes dysregulated in more than one-third of all malignancies [1]. MEK inhibitors are indicated for a variety of neoplasms including melanoma, non-small-cell lung cancer, and colorectal cancer. Despite their strong efficacy profile and convenient route of administration, MEK inhibitors have long been associated with retinal toxicities, especially self-limited serous detachments of the neurosensory

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Table 1. Description of which MEK inhibitor each patient was prescribed, date of treatment relative to initiation of therapy, time of IOP check, and IOP values at all visits

	MEK inhibitor	Visit date relative to initiation of therapy	Time of IOP check	IOP OD, mm Hg	IOP OS, mm Hg	Description
Case 1	Trametinib	+58 days	4:00 p.m.	**25**	**27**	First visit following trametinib initiation
		+78 days	1:10 p.m.	12	13	On dorzolamide/timolol
Case 2	Mirdametinib	0 days	11:20 a.m.	17	16	Start of mirdametinib
		+35 days	1:45 p.m.	16	17	
		+273 days	1:45 p.m.	20	19	
		+392 days	12:00 p.m.	**24**	**24**	
		+574 days	2:00 p.m.	15	15	On dorzolamide/timolol
Case 3	Cobimetinib	−960 days	10:35 a.m.	20	16	
		−915 days	9:30 a.m.	20	17	
		−846 days	8:20 a.m.	19	17	
		+28 days	11:35 a.m.	**24**	**24**	First visit following cobimetinib initiation
		+42 days	10:50 a.m.	16	12	On dorzolamide/timolol

(+) values indicate a visit after and (−) values indicate a visit before initiation of the MEK inhibitor. Highest IOP values for each patient are bolded. Baseline IOP values were not available for case 1. IOP values recorded by applanation. IOP, intraocular pressure; MEK, mitogen-activated protein kinase kinase.

retina which is known as MEK inhibitor-associated retinopathy [2]. Furthermore, retinal vein occlusions, blurry vision, diplopia, dry eye, and eyelid edema have also been associated with MEK inhibitors [3]. This report discusses 3 cases of a rarely reported toxicity, ocular hypertension. Due to the increasing use of MEK inhibitors, it is important that ophthalmologists familiarize themselves with the broad range of potential adverse ocular effects of MEK inhibitors.

Case Series

Case 1

This study was waived by the Institutional Review Board of the Memorial Sloan Kettering Cancer Center. A waiver of informed consent was received from each patient. Patients selected for this case series were identified by searching electronic health records for individuals who presented with ocular hypertension and who were concurrently on MEK inhibitor therapy. The first patient is a 69-year-old female with metastatic cholangiocarcinoma, who was referred for blepharitis 2 months after beginning trametinib treatment (2 mg PO QD). She was found to have an intraocular pressure (IOP) of 25 mm Hg right eye (OD) and 27 mm Hg left eye (OS) (Table 1). Optic discs were pink with sharp margins and a cup-to-disc ratio of 0.2 bilaterally (OU). She had bilateral vitelliform subretinal fluid foci and a skin irritation which was believed to be caused by trametinib. Upon treatment with topical dorzolamide/timolol (2.23–0.68%, 1 drop BID), the patient's IOP was lowered to 12 mm Hg OD and 13 mm Hg OS 3 weeks later, while on continued trametinib. The patient was concurrently treated with the anti-PD-1 immune checkpoint inhibitor pembrolizumab, which has the potential to cause inflammation-induced IOP elevations [4]. However, this case had no evidence of ocular inflammation, arguing against an immune checkpoint inhibitor-associated mechanism.

Case 2

The second instance of ocular hypertension occurred in a 26-year-old female with Langerhans cell histiocytosis. The patient was prescribed mirdametinib, an investigational MEK inhibitor (4 mg tablets PO BID), made available through a compassionate use program and referred for routine MEK inhibitor toxicity monitoring. At baseline, prior to drug initiation, the patient's IOP was 17 mm Hg OD and 16 mm Hg OS. Both optic discs were pink with sharp margins with a cup-to-disc ratio of 0.3 OU. The patient's IOP remained normotensive at 1 month and at 8 months after continued treatment. However, at 13 months, the patient's IOP was elevated to 24 mm Hg OU, and she was asymptomatic with no changes in her optic nerve from baseline. Consequently, she continued the drug, was prescribed dorzolamide/timolol (2.23–0.68%, 1 drop BID) while continuing treatment with mirdametinib, and the pressures lowered to 15 mm Hg OU at 6-month follow-up. Of note, at 8 months after initial baseline visit when IOP was normotensive, optical coherence tomography of the macula showed a separation between the ellipsoid zone and interdigitation zone bilaterally (a common MEK inhibitor-associated finding), which demonstrated resolution at the 13-month ocular assessment.

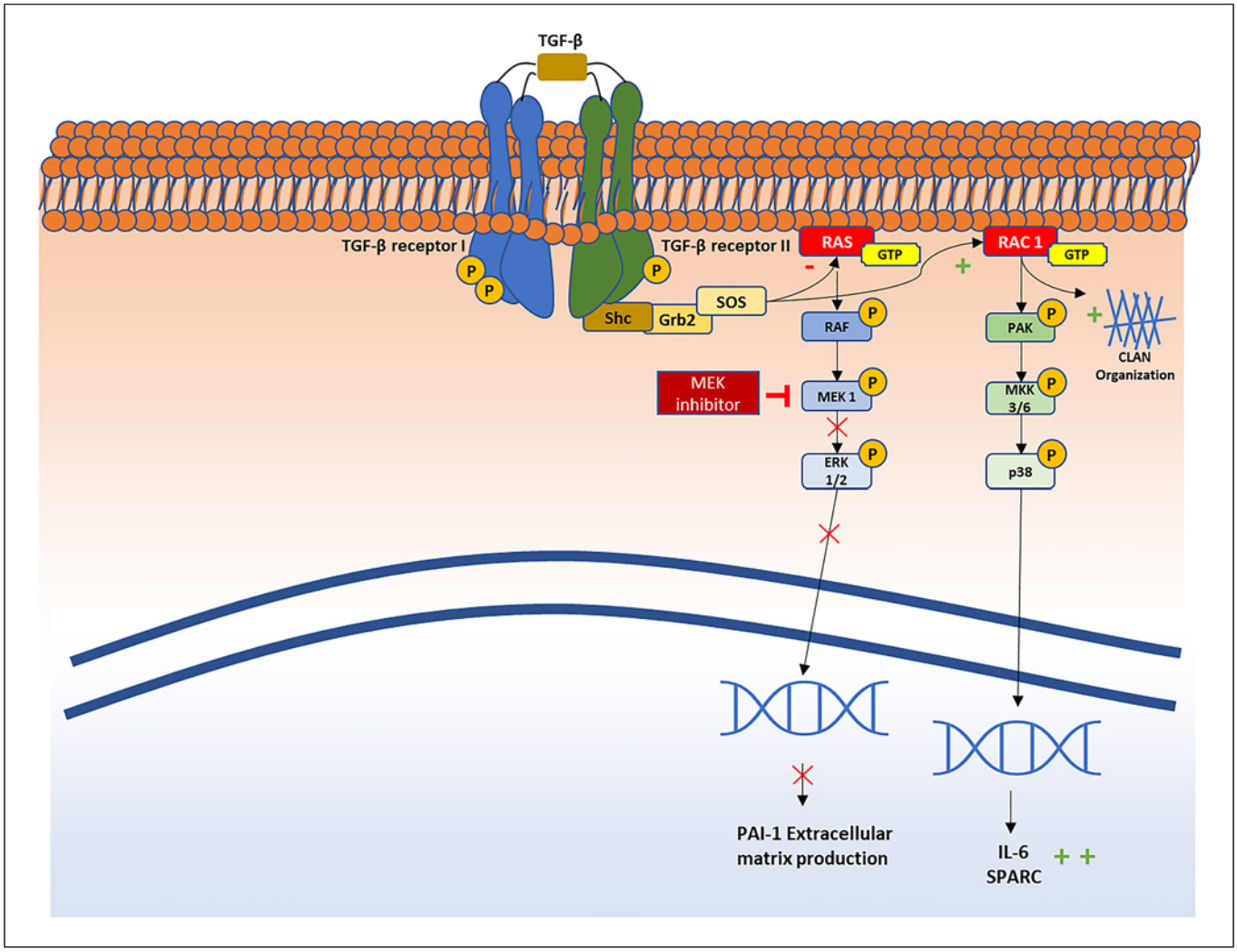

Fig. 1. MEK inhibitor effect on transforming growth factor-β (TGF-β) signaling pathways. TGF-β binds to its TGF-β receptors, triggering autophosphorylation of the tyrosine residue in the TGF-β receptor II. In turn, Src homology domain 2-containing protein (Shc), growth factor receptor-binding protein 2 (Grb2), and SOS are recruited. SOS, a GEF, then activates RAS and RAC1. RAS can activate RAF which triggers the activation of MEK 1 and subsequently ERK 1/2. During MEK inhibition, MEK 1 will not activate ERK 1/2, leading to the inactivation of the RAS/RAF/MEK/ERK pathway and inhibition of expression of plasminogen activator inhibitor-1 (PAI-1). RAC1, however, can still activate CLAN as well as p21-activated kinase (PAK), MAP kinase kinase (MKK) 3/6, and P38. This pathway may be upregulated. P38 crosses the nucleus and induces the expression of IL-6 and SPARC. CLAN, cross-linked actin network.

Case 3

A third instance occurred in a 46-year-old male with Langerhans cell histiocytosis. The patient was prescribed cobimetinib (40 mg PO QD on 21 days and off 7 days). At a previous visit several years prior to MEK inhibitor therapy, his IOPs were normotensive in both eyes (Table 1). Twenty-eight days following cobimetinib treatment, IOPs were noted to be 24 mm Hg OU on the follow-up exam. Optic discs were pink with sharp margins with a cup-to-disc ratio of 0.3 OU. The patient was prescribed dorzolamide/timolol (2.23–0.68%, 1 drop BID), and the IOP returned to normal at 2 weeks. This patient did not display any additional MEK inhibitor-induced ocular findings.

Discussion

No patient had other structural or inflammatory findings to suggest an alternate explanation for IOP elevations; and no patient was on concomitant steroids. While the previous literature has suggested that environmental factors such as coffee, yoga, tight neckties, weightlifting, and playing a wind instrument can increase IOP, none of these factors were identified among the 3 patients [5]. Epigenetics has also been investigated as a possible cause of increased

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IOP. McDonnell et al. [6] found that DNA methylation, which has been identified as a possible cause of fibrosis in the trabecular meshwork, was significantly higher in the lamina cribrosa of glaucomatous eyes compared to those without glaucoma. However, they found that in glaucomatous eyes, the promoter region of transforming growth factor-β (TGF-β) had more unmethylated DNA, leading to upregulation of this pathway. While it is unclear what role DNA methylation plays in MEK-induced IOP elevation, TGF-β is a cytokine that is important for the activation of the RAS/RAF/MEK/ERK pathway as well as the cross-linked actin network. Our proposed mechanism of MEK-induced IOP elevation is downregulation of the RAS/RAF/MEK/ERK pathway by MEK inhibition that leads to downstream upregulation of cross-linked actin network organization, which is hypothesized to decrease the elasticity of cells in the trabecular meshwork and impair the aqueous humor outflow as shown in Figure 1. Concomitant upregulation of the p38 MAPK pathway leads to proteins that regulate growth factor efficacy and matrix metalloproteinase expression, which may also influence IOP [7].

MEK inhibitor-associated ocular hypertension was reported in early-phase clinical trial data of binimetinib, but specifics are scant [8, 9]. This report presents three cases of elevated IOP in patients taking three distinct MEK inhibitors other than binimetinib, which would suggest that IOP-elevating effects exist across the class of MEK inhibition. As demonstrated by these cases, detection of ocular hypertension can be variable, ranging from 28 days in 1 patient to 13 months of continuous MEK inhibition in another. Two of the 3 patients had posterior segment findings consistent with MEK inhibition, demonstrating concurrent side effects caused by the drug. Finally, all 3 patients had a satisfactory response to topical pressure-lowering drops while continuing their life-preserving MEK inhibitor drug dose, indicating that recognition and treatment of this sight-threatening toxicity may be adequately controlled without compromise to the patient's ability to remain on MEK inhibitor therapy. Further research with a larger sample size and additional follow-up is needed to further corroborate the findings in these three cases.

Statement of Ethics

The case report was performed in compliance with the tenets of the Declaration of Helsinki. Written informed consent was obtained directly from each patient for publication of the details of their medical case and any accompanying images for all participants. No vulnerable patients were included in the study. The study was conducted under Institutional Review Board approval from the Memorial Sloan Kettering Cancer Center with a waiver of informed consent. Written informed consent was obtained directly from each patient for publication of the details of their medical case and any accompanying images for all participants. No vulnerable patients were included in the study.

Conflict of Interest Statement

All the authors report grants from the National Institute of Health, during the conduct of the study in addition to D.A.C.: none; J.C.: none; G.K.A.-A. discloses research support from Arcus, Agios, AstraZeneca, BioNtech, BMS, Celgene, Flatiron, Genentech/Roche, Genoscience, Incyte, Polaris, Puma, QED, Silenseed, and Yiviva, as well as consulting support from Adicet, Alnylam, AstraZeneca, Autem, Bayer, BeiGene, Berry Genomics, Celgene, Cend, CytomX, Eisai, Eli Lilly, Exelixis, Flatiron, Genentech/Roche, Genoscience, Helio, Incyte, Ipsen, Legend Biotech, Merck, Nerviano, QED, Redhill, Rafael, Servier, Silenseed, Sobi, Surface Oncology, Therabionic, Vector, and Yiviva (PCT/US2014/031545 filed on March 24, 2014, and priority application serial no. 61/804,907 filed March 25, 2013); E.L.D. discloses editorial support from Pfizer Inc., outside the submitted work and paid advisory membership with Day One Biopharmaceuticals and Springworks Therapeutics; D.H.A.: none; J.H.F.: none.

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Author Contributions

David A. Collet BS, Julia Canestraro OD, Ghassan K. Abou-Alfa MD, David H. Abramson MD FACS, Eli L. Diamond MD, and Jasmine H. Francis MD FACS all contributed to the research design, data acquisition, data analysis, and manuscript preparation.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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