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Ocular toxicities of MEK inhibitors and other targeted therapies

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Many classes of anticancer therapy, including chemotherapeutic agents, hormonal and molecular targeted treatments, can produce ocular toxicity. Novel agents that target different cellular pathways have been related to a wide spectrum of ophthalmologic toxicities that can range from mild to severe, and include conjunctivitis, blurred vision, keratitis and optic neuritis, among others. Special attention has been drawn to the inhibitors of the MEK signaling pathway, due to their *sine qua non* ocular toxicity, defined as MEK retinopathy and described as symmetrical bilateral disease that develops in a time-dependent and dose-dependent manner. In this review, we discuss ophthalmologic toxicities associated with molecular targeted therapies, with particular focus on MEK retinopathy, including its nomenclature, incidence, symptoms and management.

Key words: ocular toxicity, antineoplastic agents, mitogen-activated protein kinase, MEK retinopathy, targeted therapies

introduction

Although not traditionally regarded as a common site of toxicity for anticancer therapies, there is growing awareness that newer molecularly targeted cancer treatments can affect the eye in many different ways [1]. These adverse events (AEs) can be classified according to the mechanism of action of each targeted treatment and their effect on healthy ocular structures. Here, we provide an overview of ocular AEs associated with molecularly targeted anticancer therapies. We group ocular AEs based on their effects on cellular proliferation, their disruption of ocular immune privilege and their direct toxicities to ocular structures. We review in detail a novel class of molecularly targeted agents, known as mitogen-activated protein kinase (MEK) inhibitors, that is associated with a unique and poorly understood spectrum of retinal toxicities.

drugs that affect normal cell proliferation

In the eye, drugs that affect normal proliferation act on cells that divide rapidly, such as the ocular surface, the eyelids and lacrimal glands. The epidermal growth factor receptor (EGFR) signaling pathway, which is frequently dysregulated or mutated in cancer cells, driving tumor development [2], also plays an important role in a variety of ocular tissues [3, 4]. Drugs that target the EGFR pathway, such as EGFR monoclonal antibodies and small-molecule EGFR tyrosine kinase inhibitors (TKIs), can therefore affect ocular structures, such as eye lashes, lacrimal system, conjunctiva and cornea [5].

EGFR monoclonal antibodies. Cetuximab is an EGFR monoclonal antibody used to treat head and neck and advanced colorectal cancer. Multiple different ocular toxicities have been reported with the use of cetuximab, including corneal erosions [6], poliosis [7], eyelash trichomegaly [7–11], punctate keratitis [12], conjunctivitis, eyelid dermatitis and blepharitis [10, 13]. Panitumumab is an EGFR monoclonal antibody used in patients with advanced colorectal cancers. Panitumumab-related ocular toxicities have been observed in 15%–18% of the patients, including conjunctivitis, conjunctival hyperemia, increased lacrimation, eye and eyelid irritation [14, 15].

EGFR tyrosine kinase inhibitors. Erlotinib is the first-generation small-molecule EGFR TKI that is approved for the treatment of metastatic non-small-cell lung cancer (NSCLC) and pancreatic cancers. Rare ocular toxicities, such as early episcleritis [16] and corneal epithelial defects with associated infectious keratitis [17], have been reported. More frequently reported ocular toxicities with erlotinib include conjunctivitis and eyelid changes such as entropion, ectropion and trichomegaly [5]. Gefitinib is another first-generation EGFR TKI, which was described to cause ocular toxicity in preclinical and clinical settings. Gefitinib induced thinning of the corneal epithelium in preclinical animal models, and extensive ophthalmologic monitoring in the early phase clinical trials with gefitinib reported mostly dry eye, blepharitis,

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conjunctivitis, visual disturbances such as hemianopia, blurred vision and photophobia, but also corneal erosions, trichomegaly and mild superficial punctate keratopathy [18].

treatment. The ocular side-effects of EGFR-targeting agents are generally mild in severity, and are usually treated with lubricants, eyelid hygiene and warm compresses. Topical steroids are reserved for the most severe cases that do not respond to the aforementioned treatments. Treatment interruption or permanent discontinuation should also be considered depending on the severity.

drugs that disrupt ocular immune privilege

The eye is an immune privileged organ that limits local immune and inflammatory responses to antigens to preserve vision [19]. Therefore, agents that disrupt homeostatic mechanisms that maintain immune privilege cause a local inflammatory reaction in the form of uveitis, iritis, pars planitis and/or vitritis (intraocular inflammation). Three classes of anticancer agents have been associated with altering ocular immune privilege leading to toxicity: BRAF inhibitors, cytotoxic T-lymphocyte antigen (CLTA)-4 monoclonal antibodies and antiprogrammed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) monoclonal antibodies.

BRAF inhibitors. The BRAF signaling pathway is commonly altered in cancer, and activating somatic mutations of the BRAF gene occur in ~50% of malignant melanomas [20]. The United States Food and Drug Administration (FDA) has approved two BRAF pathway inhibitors for patients with late-stage melanoma: vemurafenib and dabrafenib. Vemurafenib in advanced stage melanoma patients caused ocular AEs in 22% of subjects, including uveitis, dry eyes and conjunctivitis as the most common toxicities [21], whereas retinal vein occlusion (RVO) [22] and iritis [1] were reported less frequently. The anticancer efficacy of dabrafenib in patients with advanced melanoma is similar [21, 23], but with a different spectrum of ocular AEs. The most commonly described was photosensitivity (a symptom frequently associated with intraocular inflammation), with an incidence of 3% with dabrafenib compared with 41% with vemurafenib [24]. Several studies have assessed BRAF inhibitors in combination with MEK pathway inhibitors, such as trametinib or cobimetinib, demonstrating additive or synergistic effects [25, 26] and increased ocular toxicity as will be discussed in the MEK inhibitors section.

CLTA-4 monoclonal antibodies. Ipilimumab is a CLTA-4 monoclonal antibody that prolongs the overall survival in advanced melanoma patients by increasing T-cell-mediated adaptive immunity [23], but also causes numerous autoimmune toxicities, including colitis, thyroid function alteration, hepatitis, vitiligo or hypophysitis [23]. Ocular events reported with ipilimumab include conjunctivitis, scleritis, uveitis and Graves' ophthalmopathy [27]. In addition, there are two reported cases of ipilimumab-induced uveitis that resolved after the administration of corticosteroid eye drops and periocular corticosteroid injections in one case and after intravenous dexamethasone followed by oral prednisone in the other [28].

PD-1/PD-L1 monoclonal antibodies. The PD-1 and PD-L1 monoclonal antibodies are negative regulators of the immune system that block the PD-L1/PD-1 interaction, causing immune tolerance [29]. Anti-PD-1 nivolumab and pembrolizumab have received FDA approval for metastatic melanoma treatment [30, 31], and nivolumab has also received regulatory approval for squamous NSCLC [32]. Further antitumor activity of PD-1/PD-L1 monoclonal antibodies has been demonstrated in numerous tumor types, such as renal, urothelial, head and neck, mismatch-repair deficient colorectal and hepatocellular carcinomas [33–38]. Intraocular inflammation (e.g. uveitis) following treatment with pembrolizumab or nivolumab is a rare, but clinically important event, described in 1% of patients [30, 39, 40]. Other immunotherapy agents that are still being evaluated in early clinical trials, such as anti-PD-L1 antibodies atezolizumab and durvalumab, also have the potential risk of eye toxicity because of their immunostimulatory mechanism. More importantly, oncology drug development is rapidly expanding into immune combination treatments where the risk of eye disorders may be aggravated and the first case of uveitis with the combination of pembrolizumab and ipilimumab has been described recently [41].

treatment. Immunotherapy treatment toxicities, such as photophobia, iritis, uveitis and papillitis, occur as a result of disruption of ocular immune privilege [42]. Special attention should be given to the patients diagnosed with malignant melanoma, which has been described to cause anterior chamber and vitreous metastasis that can appear as uveitis, an entity known as masquerade syndrome [43, 44]. Patients are generally managed by referral to an ophthalmologist followed by the administration of topical/periocular steroids and cycloplegic agents.

drugs that cause direct toxicity

Drugs that cause direct toxicity affect cells that are not dividing, like retinal cells [photoreceptors, retinal pigment epithelium (RPE) etc.] causing conditions such as RPE and photoreceptor dysfunction, toxic retinopathy and night blindness. Numerous agents can cause direct ocular toxicity, including heat shock protein (HSP)90 inhibitors and MEK inhibitors.

HSP90 inhibitors. HSP90 is a constitutively expressed molecular chaperone that plays an important role in stabilizing proteins during protein folding and regulates a variety of cellular processes including apoptosis, proliferation, metastasis and differentiation. In cancer cells, HSP90 is involved in resistance to apoptosis, favoring the progression of the tumor. HSP90 inhibitors have shown signs of activity in gastrointestinal stromal tumor, lung and breast cancers. Interestingly, some HSP90 inhibitors cause ocular toxicity (such as AUY922), whereas others do not (such as tanespimycin) [45, 46]. AUY922 revealed visual AEs in 43% of patients [47], with night blindness occurring in ~20% [45]. One advanced lung adenocarcinoma patient treated with the combination of AUY922 and erlotinib reported night blindness coinciding with retinal changes on the optical coherence tomography (OCT) [48]. Following treatment discontinuation, visual acuity remained abnormal for 8 months and structural changes in the retina persisted after 15 months [48]. Antiretinal antibodies were positive for anti-α-enolase, which, as HSP90, also bind to a

Table 1. Ocular side-effects reported with MEK inhibitors

MEK inhibitor	Reported ocular side effects
CI-1040	Transient blurring, altered light perception and periorbital edema
PD0325901	Optic neuropathy, transient but reversible blurred vision and retinal vein occlusion
Selumetinib (AZD6244, ARRY-142,886)	Blurred vision, diplopia, eyelid edema, subconjunctival hemorrhage, increased lacrimation, retinal pigment and epithelial detachment
Trametinib (GSK1120212, JTP-74057)	Central serous retinopathy, retinal vein occlusion and uveitis
RO5126766 (CH5126766)	Serous retinal detachment and blurred vision
RO4987655 (CH4987655)	Punctate keratitis, photopsia, chorioretinopathy, corneal erosion, blurred vision periorbital edema, dry eyes and retinal vein occlusion
Refametinib (RDEA119, BAY 86-9766)	Chorioretinopathy and retinal vein occlusion
Pimasertib (MSC1936369, AS703026)	Retinal vein occlusion, serous retinal detachment, macular edema and visual disturbances
Cobimetinib (GDC-0973, XL-518, RG7421)	Subfoveal neurosensory retinal detachment
Bimetinib (MEK162, ARRY-438162, ARRY-162)	Subfoveal neurosensory retinal detachment
GDC-0623	Retinal pigment epithelial detachment
TAK-733	None reported

survival regulator AKT, suggesting synergism [49]. An HSP90 inhibitor onalespib reported a variety of grade I visual toxicities, including delayed dark/light adaptation, blurred vision and flashes, with an overall frequency of visual disturbance symptoms of 47% out of the totality of patients enrolled in the trial [50].

treatment. Treatment generally involves interrupting drug treatment, referral to a retinal specialist and permanent cessation of drug treatment or careful reintroduction at a lower dose.

MEK inhibitors

The MEK pathway is an intracellular signal transduction pathway that regulates a number of essential physiological processes, such as gene expression, cell cycle control, cell division and proliferation [49, 51]. Dysregulation of the MEK pathway plays an important role in carcinogenesis and occurs frequently in malignant tumors [52]. Although multiple MEK inhibitors have been evaluated in clinical trials (Table 1), only trametinib is FDA approved for the treatment of advanced melanoma harboring *BRAF* V600 mutation [53]. MEK inhibitors are also active in *NRAS* mutant melanoma [54, 55]. In addition to melanoma, the antitumor activity of MEK inhibitors has been observed in patients with hepatocellular carcinoma, as well as low-grade serous ovarian cancer, NSCLC and biliary cancers [56].

ocular toxicities reported with MEK inhibitors

The most common side-effects reported with the MEK inhibitors are rash, diarrhea, fatigue and elevated lipase, and increased creatinine phosphokinase levels. In addition, several MEK inhibitors have been reported to cause ocular toxicities, such as central serous retinopathy (CSR), RVO or periorbital edema, as summarized in Table 1. These ocular toxicities appear to be a class effect of MEK inhibition. An example of the characteristic retinal alterations caused by MEK inhibitors is shown in Figure 1.

The first MEK inhibitor to enter clinical trials, CI-1040, caused visual disturbances in six of 67 patients (9%), including transient blurring and altered light perception [57] that were reversible. In addition, periorbital edema occurred in nine individuals (13%). Clinical development of CI-1040 was discontinued because of limited antitumor efficacy [57].

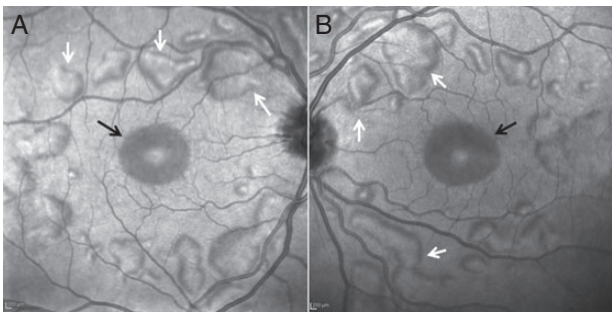

Figure 1. Clinical appearance of MEK retinopathy on infrared image by optical coherence tomography (OCT) in the right eye (A) and the left eye (B). In moderate cases, multifocal serous retinal detachments can be seen involving the fovea (central vision area, black arrow) and peripheral macular area (peripheral vision area, white arrows*). Notice both eyes have a similar appearance, which is characteristic of MEK retinopathy. *Not all serous detachments are marked with arrows.

PD0325901 is a more potent MEK1/2 inhibitor than CI-1040 [58]. In the phase I trial of PD0325901, 1 patient developed optic neuropathy, 7 of 66 patients (11%) experienced transient but reversible blurred vision, and 3 patients were diagnosed with RVO, a serious toxicity that could cause permanent blindness. All cases of RVO occurred in patients who had received low-dose chronic treatment, suggesting that it might be duration- and dose-dependent [59]. All patients with RVO discontinued treatment with PD0325901.

Selumetinib (also known as AZD6244) is an MEK inhibitor with less potency and bioavailability than PD0325901. In a phase I study, 12% of the 57 patients treated reported grade 1 or 2 blurred vision, but there were no cases of RVO [60]. A subsequent open-label phase I study used a hydrogen sulfate salt-based formulation, and reported a variety of ocular toxicities including diplopia, eyelid edema, subconjunctival hemorrhage, blurred vision, increased lacrimation and visual disturbance. Most cases were grade 1, although one patient experienced grade

2 visual disturbances and one patient developed grade 3 blurred vision. Overall, adverse ocular events were observed in nine of 35 patients (26%) treated with maximum tolerated dose of selumetinib at 75 mg twice daily and one of eight patients (13%) treated with selumetinib 100 mg twice daily [61]. Another phase I trial using combination treatment with selumetinib and the AKT inhibitor MK-2206 reported a case of grade 2 serous retinal detachment (SRD) [62].

Trametinib, or GSK1120212, is a potent and selective inhibitor of MEK-1 and MEK-2A. A phase I study reported two cases of dose-limiting toxicity due to CSR and one event of RVO at a daily dose of 2 mg in the seventh cycle of treatment [63]. The clinical trial testing in the combination of trametinib and gemcitabine in advanced solid tumors, which excluded patients with risk factors for RVO and CSR, reported six events of ocular toxicity (19%), including one patient with grade 2, dose-limiting, uveitis accompanied by grade 1 retinopathy, which resolved 33 days after treatment discontinuation. All events were grade 1 or 2, and there were no instances of CSR or RVO [64]. Bilateral grade 1 uveitis was also reported in a patient with stage 3b cutaneous melanoma who was treated with trametinib in combination with dabrafenib, no causality was established to either of the drugs and the authors hypothesized the disorder to be caused by an increased inflammatory response with subsequent breakdown of the blood–retinal barrier [65]. Further ocular toxicity with the combination of dabrafenib and trametinib was reported in two phase III clinical trials, with an incidence of chorioretinopathy of up to 1% [22, 66] and blurred vision in 2% of patients [66].

RO5126766 is dual MEK and RAF inhibitor. The first in-human phase I trial of RO5126766 reported that 50% of patients experienced eye-related adverse effects, including four cases of dose-limiting toxicity: one patient with SRD, and three patients with grade 3 blurred vision [67]. Most toxicities were grade 1, and the most common ocular AEs were blurred vision (22 patients) and SRD (10 patients) [67]. Three cases of grade 3 blurred vision were also reported. No RVO was observed, and all toxicities were reversed either after drug cessation without any intervention [67].

A phase I dose-escalation trial performed with the more selective MEK inhibitor RO4987655 reported that ocular toxicity occurred in 13 of 49 patients (27%), including punctate keratitis, photopsia, chorioretinopathy, corneal erosion, blurred vision periorbital edema, dry eyes and RVO [68]. Two patients experienced grade 3 toxicities (RVO and blurred vision), and one patient reported blurred vision with SRD that was caused by the accumulation of fluid in the subretinal space [68].

Refametinib (also named RDEA119 and BAY 86-9766) is a potent and highly selective allosteric inhibitor of MEK1/2 [69]. In a phase I trial that enrolled 69 patients ocular toxicities were reported in 10%, including grade 1 chorioretinopathy and grade 3 RVO. Both conditions were reversible, and baseline vision was restored in the patient with RVO after treatment with intravitreous bevacizumab [70].

Several other MEK inhibitors have been associated with ocular toxicities. The selective MEK1/2 inhibitor pimasertib (also known as MSC1936369 and AS703026) was associated with ocular dose-limiting toxicities, including grade 2 RVO, and grade 3 SRD and macular edema [71, 72]. One 26-year-old patient was recently reported to have bilateral multifocal SRD, which appeared after 2 days of dosing with pimasertib and spontaneously resolved 3 days after discontinuing [73].

A recent report described the cases of three patients with metastatic tumors who developed subfoveal neurosensory retinal detachment that was associated with the use of MEK inhibitors, including cobimetinib (or XL518/GDC-0973) and binimetinib (or MEK162) [74].

A phase I trial of cobimetinib reported no vision-related dose-limiting toxicities in stage I (intermittent 21/7 dosing schedule), whereas in the stage IA (continuous daily dosing schedule) one dose-limiting toxicity event grade 3 in the form of blurred vision was associated with neurosensory detachment of the retina [75]. In the phase III trial (coBRIM or GO28141) of cobimetinib in combination with vemurafenib versus vemurafenib alone in patients with metastatic melanoma [76], ophthalmologic examinations, including the OCT, were performed at baseline, day 28 and every 3 cycles (84 days) thereafter. The updated ophthalmologic toxicity of the coBRIM trial reported serous retinopathy (SR) more frequently in patients treated with cobimetinib and vemurafenib than placebo and vemurafenib (26% versus 3%). In the cobimetinib and vemurafenib arm, more than 50% of CSRs were grade 1, asymptomatic and identified during surveillance ophthalmic examination, not requiring treatment discontinuation. Forty-nine percent (49%) of patients receiving the combination treatment experienced grade ≥2 SR that occurred before study day 12 in 52% of patients and resolved after dose interruption, reduction or discontinuation of cobimetinib in 75% of the patients at the time of presentation of the results [77].

Binimetinib is another selective MEK1/2 inhibitor that has been associated with transient retinopathy. In the Japanese phase I study of binimetinib, retinal pigment epithelial detachment (RPED) was reported in two patients (10%) [78]. Other clinical trials that tested binimetinib in combination with other anticancer drugs have reported RPED in 28% of patients treated with binimetinib and PIK3CA inhibitor BYL719 [79], whereas the phase Ib/II trial of binimetinib and a BRAF inhibitor encorafenib (LGX818) has reported visual impairment in 20% and blurred vision in 13% of patients treated with the combination [80]. Further analysis of the melanoma patients treated with binimetinib and encorafenib reported retinopathy, chorioretinopathy and RPED in 15%, 5% and 8% of patients, respectively, with 2 patients experiencing grade ≥3 ocular toxicity [81]. Recent review of 32 patients enrolled on the three different clinical trials with binimetinib as monotherapy, in combination with the pan-inhibitor RAF265, or in combination with the selective BRAF inhibitor encorafenib, showed frequent grade 1–2 bilateral retinopathy that ranged from 40% to 65%. Retinopathy events appeared during the first days or weeks of treatment, as mild and transient visual symptoms [82].

MEK retinopathy

Retinal events have been reported for all MEK inhibitors tested in clinical setting and are considered as a class effect. The umbrella term MEK retinopathy is used to describe the dose- and time-dependent retinal side-effects observed with MEK inhibitor therapy. Here, we discuss MEK retinopathy in detail, including its nomenclature, clinical findings incidence, symptoms and classification.

nomenclature. Various terms have been used in the literature to describe the retinal side-effects attributed to MEK inhibitors. These are a combination of clinical findings and nonspecific conditions; they include SR, CSR [83], SRD [67, 84], macular edema [67], visual disturbance [61], retinopathy [82], chorioretinopathy [69, 71, 81, 83] and blurred vision [60, 61, 67, 68]. All of these clinical findings correspond to the same clinical entity. The umbrella term 'MEK retinopathy' has been introduced to clearly identify this unique clinical entity and simplify the nomenclature used to describe MEK inhibitor-related retinal side-effects [85].

incidence. As discussed above, MEK inhibitor clinical trials have reported ocular toxicities in 5%–38% of patients treated [86]. The wide range of incidence may be due to the lack of uniformity in the description, diagnosis and reporting of the same condition. Also, it might be related to differences in potency of MEK inhibition, schedule of administration and the frequency of ophthalmologic assessment across trials.

clinical findings. MEK retinopathy usually presents acutely within the first week of the first dose. The clinical examination of mild presentations is usually characterized by a single SRD that may be accompanied by minimal (Figure 2A) or more substantial (Figure 2B) subretinal fluid as seen on OCT. Moderate cases may develop multifocal SRDs (Figures 1 and 2C). Severe cases may develop intraretinal cysts and a disarrangement of the outer retinal layers (Figure 2D). The clinical presentation is always bilateral and often symmetrical. In cases where only one eye is affected, other diagnoses should be considered.

symptoms. The symptoms of MEK retinopathy vary widely, and many patients with clinical findings of MEK retinopathy are asymptomatic. For example, Urner-Bloch et al. reported that in their study only 8 of 19 patients with MEK retinopathy as demonstrated by OCT reported mild visual disturbances [82]. Symptoms of MEK retinopathy include blurred vision, altered color perception, shadows, light sensitivity, metamorphopsia and glare. Cases are often mild, short-lived, self-limiting, and do not interfere with activities of daily living [82].

pathophysiology

The RPE is an epithelial barrier that maintains the outer blood–retinal barrier and is essential for maintaining neural retinal functions [87, 88]. It is formed of RPE cells, which are highly polarized and function as an active fluid pump. The mitogen-activated protein kinase signaling pathway, including MEK, plays a critical role in maintaining the integrity of the RPE by protecting against various stresses, including oxidative stress, light-induced damage and inflammation [87]. Prior preclinical studies showed that MEK inhibition leads to acute RPE toxicity which results in RPE hyperpermeability and breakdown of the retinal–blood barrier [87, 89].

classification. CTCAE classification: Common Terminology Criteria for Adverse Events (CTCAE) criteria, widely used for AE reporting in oncology studies, include a 4-category grading schema for retinopathy according to symptom severity (Table 2) [90]. This classification has the limitation of being used for all types of retinopathy and is not specific for MEK inhibitor trials. Another limitation of the CTCAE retinopathy classification is that it does not account for baseline visual acuity before starting MEK treatment. Documentation of baseline visual acuity before initiating the MEK treatment may be helpful to determine whether there are changes in visual acuity in the event of MEK retinopathy.

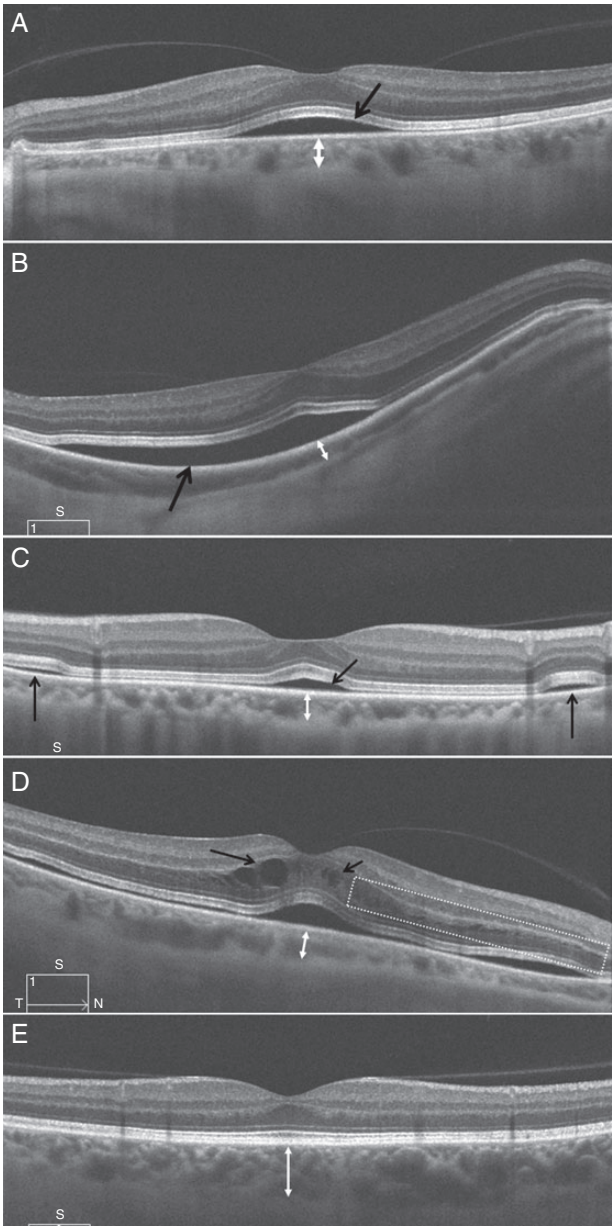

Figure 2. Optical coherence tomography (OCT) findings of MEK retinopathy. (A) Small subretinal detachment (black arrow) in the foveal center. (B) Larger subretinal detachment extending outside the foveal area (black arrow). (C) Multifocal serous detachments (black arrows). (D) More severe cases are characterized by the presence of intraretinal fluid or cysts (black arrows) and/or disarrangement of the outer retinal layers (dotted rectangle). (A–D) A thin choroid has been identified in several patients developing MEK retinopathy (white double-headed arrows indicate the choroidal thickness). (E) Patient with a thick choroid who underwent MEK inhibitor treatment and did not develop MEK retinopathy (double-headed white arrow).

Table 2. The CTCAE criteria for retinopathy

Grade	Findings
1	• Asymptomatic • Clinical or diagnostic observations only
2	• Symptomatic • Moderate decrease in visual acuity (20/40 or better) from baseline • Limiting instrumental activities of daily living
3	• Symptomatic • Marked decrease in visual acuity (worse than 20/40) from baseline • Disabling • Limits self-care-related activities of daily living (ADLs)
4	• Blindness (20/200 or worse) in the affected eye

management. Patients should be proactively informed about the possible ophthalmologic side-effects of the MEK inhibitors, which would allow them to identify symptoms and seek ophthalmologic assessment promptly. Detailed counseling, with an emphasis on the transitory nature of the MEK retinopathy, may help to decrease patients' anxiety.

On the basis of our institutional experience, we recommend the following approach for the management of toxicities based on the CTCAE classification: 'grade 1' and 'grade 2' toxicities should be managed using careful close observation. Patients do not require interruption of dosing with MEK inhibitors, as clinical experience indicates that mild symptoms and OCT abnormalities frequently resolve within days after continued dosing. This suggests that many patients with MEK retinopathy develop tachyphylaxis to continued MEK inhibitor therapy. For 'grade 3' toxicities that are associated with more clinically significant visual symptoms, patients should be instructed to interrupt dosing with MEK inhibitor therapy. When symptoms resolve, patients may be rechallenged at the same dose of MEK inhibitor therapy with close monitoring following re-initiation of treatment. For 'grade 4' toxicities, MEK inhibitor treatment should be discontinued and when symptoms and OCT findings resolve, patients may be rechallenged at a lower dose. If symptoms persist after this initial approach, a complete assessment by an ophthalmologist or retina specialist is warranted.

The management of patients with MEK inhibitor retinopathy requires frequent communication between the patient's oncologist and ophthalmologist and should be individualized considering the patient's disease status and response to therapy. In our experience, MEK retinopathy of any grade did not lead to permanent discontinuation of MEK inhibitor treatment, unless accompanied with severe extra-ocular toxicities. It is noteworthy to mention that there has been not a single case report in current literature of permanent visual impairment secondary to MEK inhibitors use.

imaging

Our clinical experience indicates that fundus imaging and OCT are the most useful tests to establish a diagnosis of MEK retinopathy. Fundus imaging and OCT are known to provide meaningful information in these patients. Fundus imaging allows the fovea, macula and optic disk to be visualized. OCT provides noninvasive real-time visualization that provides histological detail (4- to 10-μm resolution) of the retina and choroid. This makes it the ideal tool to diagnose and follow up patients with MEK retinopathy. The most common clinical presentations are shown in Figure 2. Fluorescein angiogram helps evaluate the retinal circulation and may be considered in patients where the fundus imaging and OCT studies are equivocal or if the clinical symptoms are severe.

anatomical predisposition

Since MEK retinopathy has only recently been described, there are no clinical criteria to indicate potential at-risk patients. On the basis of the clinical findings such as those shown in Figure 2, we hypothesize that a thin choroid may be a predisposing risk factor for the development of MEK retinopathy. This hypothesis should be tested in a clinical trial setting. If confirmed, this could lead to additional studies to better understand the pathophysiology of MEK retinopathy.

conclusions

MEK inhibitors are a novel class of anticancer agents that can cause unique ocular toxicities. MEK retinopathy is a recently described clinical entity characterized bilateral symmetrical disease characterized by single or multiple SRDs that develop in a time-dependent and dose-dependent manner. Although the retinal findings may be dramatic and out of proportion with the clinical symptoms experienced by patients, MEK retinopathy frequently resolves rapidly without treatment interruption or dose modification. This emphasizes the importance of close communication between oncologists and ophthalmologists to ensure the optimal outcome with patients who experience ocular toxicity during anticancer therapy.

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references

1. Singh P, Singh A. Ocular adverse effects of anti-cancer chemotherapy. J Cancer Ther Res 2012; 1: 5.
2. Cui J, Hu YF, Feng XM et al. EGFR inhibitors and autophagy in cancer treatment. Tumour Biol 2014; 35: 11701–11709.
3. Albanell J, Gascon P. Small molecules with EGFR-TK inhibitor activity. Curr Drug Targets 2005; 6: 259–274.
4. Martinelli E, De Palma R, Orditura M et al. Anti-epidermal growth factor receptor monoclonal antibodies in cancer therapy. Clin Exp Immunol 2009; 158: 1–9.

5. Borkar DS, Lacouture ME, Basti S. Spectrum of ocular toxicities from epidermal growth factor receptor inhibitors and their intermediate-term follow-up: a five-year review. Support Care Cancer 2013; 21: 1167–1174.
6. Foerster CG, Cursiefen C, Kruse FE. Persisting corneal erosion under cetuximab (Erbitux) treatment (epidermal growth factor receptor antibody). Cornea 2008; 27: 612–614.
7. Rodriguez NA, Ascaso FJ. Trichomegaly and poliosis of the eyelashes during cetuximab treatment of metastatic colorectal cancer. J Clin Oncol 2011; 29: e532–e533.
8. Bouche O, Brixi-Benmansour H, Bertin A et al. Trichomegaly of the eyelashes following treatment with cetuximab. Ann Oncol 2005; 16: 1711–1712.
9. Cohen PR, Escudier SM, Kurzrock R. Cetuximab-associated elongation of the eyelashes: case report and review of eyelash trichomegaly secondary to epidermal growth factor receptor inhibitors. Am J Clin Dermatol 2011; 12: 63–67.
10. Melichar B, Nemcova I. Eye complications of cetuximab therapy. Eur J Cancer Care (Engl) 2007; 16: 439–443.
11. Vaccaro M, Pollicino A, Barbuzza O, Guarneri B. Trichomegaly of the eyelashes following treatment with cetuximab. Clin Exp Dermatol 2009; 34: 402–403.
12. Specenier P, Koppen C, Vermorken JB. Diffuse punctate keratitis in a patient treated with cetuximab as monotherapy. Ann Oncol 2007; 18: 961–962.
13. Dranko S, Kinney C, Ramanathan RK. Ocular toxicity related to cetuximab monotherapy in patients with colorectal cancer. Clin Colorectal Cancer 2006; 6: 224–225.
14. Giusti RM, Shastri K, Pilaro AM et al. U.S. Food and Drug Administration approval: panitumumab for epidermal growth factor receptor-expressing metastatic colorectal carcinoma with progression following fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens. Clin Cancer Res 2008; 14: 1296–1302.
15. Hecht JR, Patnaik A, Berlin J et al. Panitumumab monotherapy in patients with previously treated metastatic colorectal cancer. Cancer 2007; 110: 980–988.
16. Shahrokni A, Matuszczak J, Rajebi MR, Saif MW. Erlotinib-induced episcleritis in a patient with pancreatic cancer. JOP 2008; 9: 216–219.
17. Johnson KS, Levin F, Chu DS. Persistent corneal epithelial defect associated with erlotinib treatment. Cornea 2009; 28: 706–707.
18. Tullo AB, Esmaeli B, Murray PI et al. Ocular findings in patients with solid tumours treated with the epidermal growth factor receptor tyrosine kinase inhibitor gefitinib ('Iressa', ZD1839) in phase I and II clinical trials. Eye (Lond) 2005; 19: 729–738.
19. Zhou R, Caspi RR. Ocular immune privilege. F1000 Biol Rep 2010; 2.
20. Long GV, Menzies AM, Nagrial AM et al. Prognostic and clinicopathologic associations of oncogenic BRAF in metastatic melanoma. J Clin Oncol 2011; 29: 1239–1246.
21. Choe CH, McArthur GA, Caro I et al. Ocular toxicity in BRAF mutant cutaneous melanoma patients treated with vemurafenib. Am J Ophthalmol 2014; 158: 831–837 e832.
22. Robert C, Karaszewska B, Schachter J et al. Improved overall survival in melanoma with combined dabrafenib and trametinib. N Engl J Med 2015; 372: 30–39.
23. Hodi FS, O'Day SJ, McDermott DF et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 2010; 363: 711–723.
24. Menzies AM, Long GV, Murali R. Dabrafenib and its potential for the treatment of metastatic melanoma. Drug Des Devel Ther 2012; 6: 391–405.
25. Luke JJ, Ott PA. New developments in the treatment of metastatic melanoma—role of dabrafenib-trametinib combination therapy. Drug Healthc Patient Saf 2014; 6: 77–88.
26. Menzies AM, Long GV. Dabrafenib and trametinib, alone and in combination for BRAF-mutant metastatic melanoma. Clin Cancer Res 2014; 20: 2035–2043.
27. Tarhini A. Immune-mediated adverse events associated with ipilimumab ctla-4 blockade therapy: the underlying mechanisms and clinical management. Scientifica (Cairo) 2013; 2013: 857519.
28. Attia P, Phan GQ, Maker AV et al. Autoimmunity correlates with tumor regression in patients with metastatic melanoma treated with anti-cytotoxic T-lymphocyte antigen-4. J Clin Oncol 2005; 23: 6043–6053.
29. Muenst S, Soysal SD, Tzankov A, Hoeller S. The PD-1/PD-L1 pathway: biological background and clinical relevance of an emerging treatment target in immunotherapy. Expert Opin Ther Targets 2015; 19: 201–211.
30. Robert C, Schachter J, Long GV et al. Pembrolizumab versus ipilimumab in advanced melanoma. N Engl J Med 2015; 372: 2521–2532.
31. Weber JS, D'Angelo SP, Minor D et al. Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a randomised, controlled, open-label, phase 3 trial. Lancet Oncol 2015; 16: 375–384.
32. Brahmer J, Reckamp KL, Baas P et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. N Engl J Med 2015; 373: 123–135.
33. Garon EB, Rizvi NA, Hui R et al. Pembrolizumab for the treatment of non-small-cell lung cancer. N Engl J Med 2015; 372: 2018–2028.
34. Le DT, Uram JN, Wang H et al. PD-1 blockade in tumors with mismatch-repair deficiency. N Engl J Med 2015; 372: 2509–2520.
35. Motzer RJ, Rini BI, McDermott DF et al. Nivolumab for metastatic renal cell carcinoma: results of a randomized phase II trial. J Clin Oncol 2015; 33: 1430–1437.
36. Powles T, Eder JP, Fine GD et al. MPDL3280A (anti-PD-L1) treatment leads to clinical activity in metastatic bladder cancer. Nature 2014; 515: 558–562.
37. El-Khoueiry AB, Melero I, Crocenzi TS et al. Phase I/II safety and antitumor activity of nivolumab in patients with advanced hepatocellular carcinoma (HCC): CA209–040. J Clin Oncol 2015; 33(suppl): abstr LBA101.
38. Segal NH, Ou SI, Balmanoukian AS et al. Safety and efficacy of MEDI4736, an anti-PD-L1 antibody, in patients from a squamous cell carcinoma of the head and neck (SCCHN) expansion cohort. J Clin Oncol 2015; 33(suppl): abstr 3011.
39. Ribas A, Hodi FS, Kefford R et al. Efficacy and safety of the anti-PD-1 monoclonal antibody MK-3475 in 411 patients (pts) with melanoma (MEL). J Clin Oncol 2014; 32(5s suppl): abstr LBA9000.
40. Topalian SL, Sznol M, McDermott DF et al. Survival, durable tumor remission, and long-term safety in patients with advanced melanoma receiving nivolumab. J Clin Oncol 2014; 32: 1020–1030.
41. Patnaik A, Socinski MA, Gubens MA et al. Phase 1 study of pembrolizumab (pembro; MK-3475) plus ipilimumab (IPI) as second-line therapy for advanced non-small cell lung cancer (NSCLC): KEYNOTE-021 cohort D. J Clin Oncol 2015; 33(suppl): abstr 8011.
42. Renouf DJ, Velazquez-Martin JP, Simpson R et al. Ocular toxicity of targeted therapies. J Clin Oncol 2012; 30: 3277–3286.
43. Jaissle GB, Szurman P, Rohrbach JM et al. A case of cutaneous melanoma metastatic to the vitreous cavity: possible pathomechanism and review of the literature. Graefes Arch Clin Exp Ophthalmol 2007; 245: 733–740.
44. Manusow JS, Khoja L, Pesin N et al. Retinal vasculitis and ocular vitreous metastasis following complete response to PD-1 inhibition in a patient with metastatic cutaneous melanoma. J Immunother Cancer 2014; 2: 41.
45. Doi T, Onozawa Y, Fuse N et al. Phase I dose-escalation study of the HSP90 inhibitor AUY922 in Japanese patients with advanced solid tumors. Cancer Chemother Pharmacol 2014; 74: 629–636.
46. Zhou D, Liu Y, Ye J et al. A rat retinal damage model predicts for potential clinical visual disturbances induced by Hsp90 inhibitors. Toxicol Appl Pharmacol 2013; 273: 401–409.
47. Sessa C, Shapiro GI, Bhalla KN et al. First-in-human phase I dose-escalation study of the HSP90 inhibitor AUY922 in patients with advanced solid tumors. Clin Cancer Res 2013; 19: 3671–3680.
48. Munk MR, Fernandes J, Mets M et al. Reversible nyctalopia and retinopathy in a patient with metastatic cancer treated with anti-heat shock protein 90 therapy. JAMA Ophthalmol 2014; 132: 899–901.
49. Chang L, Karin M. Mammalian MAP kinase signalling cascades. Nature 2001; 410: 37–40 .
50. Shapiro GI, Kwak E, Dezube BJ et al. First-in-human phase I dose escalation study of a second-generation non-ansamycin HSP90 inhibitor, AT13387, in patients with advanced solid tumors. Clin Cancer Res 2015; 21: 87–97.
51. Robinson MJ, Cobb MH. Mitogen-activated protein kinase pathways. Curr Opin Cell Biol 1997; 9: 180–186.
52. Friday BB, Adjei AA. Advances in targeting the Ras/Raf/MEK/Erk mitogen-activated protein kinase cascade with MEK inhibitors for cancer therapy. Clin Cancer Res 2008; 14: 342–346.
53. Flaherty KT, Robert C, Hersey P et al. Improved survival with MEK inhibition in BRAF-mutated melanoma. N Engl J Med 2012; 367: 107–114.
54. Ascierto PA, Schadendorf D, Berking C et al. MEK162 for patients with advanced melanoma harbouring NRAS or Val600 BRAF mutations: a non-randomised, open-label phase 2 study. Lancet Oncol 2013; 14: 249–256.

55. Sosman JA, Kittaneh M, Lolkema MP et al. A phase 1b/2 study of LEE011 in combination with binimetinib (MEK162) in patients with NRAS-mutant melanoma: early encouraging clinical activity. J Clin Oncol 2014; 32: 9009.
56. Zhao Y, Adjei AA. The clinical development of MEK inhibitors. Nat Rev Clin Oncol 2014; 11: 385–400.
57. Rinehart J, Adjei AA, Lorusso PM et al. Multicenter phase II study of the oral MEK inhibitor, CI-1040, in patients with advanced non-small-cell lung, breast, colon, and pancreatic cancer. J Clin Oncol 2004; 22: 4456–4462.
58. Sebolt-Leopold S, Merriman R, Omer C et al. The biological profile of PD 0325901: a second generation analog of CI-1040 with improved pharmaceutical potential. Cancer Res 2004; 45: abstr 925.
59. LoRusso PM, Krishnamurthi SS, Rinehart JJ et al. Phase I pharmacokinetic and pharmacodynamic study of the oral MAPK/ERK kinase inhibitor PD-0325901 in patients with advanced cancers. Clin Cancer Res 2010; 16: 1924–1937.
60. Adjei AA, Cohen RB, Franklin W et al. Phase I pharmacokinetic and pharmacodynamic study of the oral, small-molecule mitogen-activated protein kinase 1/2 inhibitor AZD6244 (ARRY-142886) in patients with advanced cancers. J Clin Oncol 2008; 26: 2139–2146.
61. Banerji U, Camidge DR, Verheul HM et al. The first-in-human study of the hydrogen sulfate (Hyd-sulfate) capsule of the MEK1/2 inhibitor AZD6244 (ARRY-142886): a phase I open-label multicenter trial in patients with advanced cancer. Clin Cancer Res 2010; 16: 1613–1623.
62. Tolcher AW, Bendell JC, Patnaik A et al. A phase Ib study of the MEK inhibitor GSK1120212 combined with gemcitabine in patients with solid tumors: Interim results. J Clin Oncol 2011; 29(suppl 4): abstr 278.
63. Infante JR, Fecher LA, Falchook GS et al. Safety, pharmacokinetic, pharmacodynamic, and efficacy data for the oral MEK inhibitor trametinib: a phase 1 dose-escalation trial. Lancet Oncol 2012; 13: 773–781.
64. Infante JR, Papadopoulos KP, Bendell JC et al. A phase 1b study of trametinib, an oral Mitogen-activated protein kinase (MEK) inhibitor, in combination with gemcitabine in advanced solid tumours. Eur J Cancer 2013; 49: 2077–2085.
65. Joshi L, Karydis A, Gemenetzi M et al. Uveitis as a result of MAP kinase pathway inhibition. Case Rep Ophthalmol 2013; 4: 279–282.
66. Long GV, Stroyakovskiy D, Gogas H et al. Dabrafenib and trametinib versus dabrafenib and placebo for Val600 BRAF-mutant melanoma: a multicentre, double-blind, phase 3 randomised controlled trial. Lancet 2015; 386: 444–451.
67. Martinez-Garcia M, Banerji U, Albanell J et al. First-in-human, phase I dose-escalation study of the safety, pharmacokinetics, and pharmacodynamics of RO5126766, a first-in-class dual MEK/RAF inhibitor in patients with solid tumors. Clin Cancer Res 2012; 18: 4806–4819.
68. Leijen S, Middleton MR, Tresca P et al. Phase I dose-escalation study of the safety, pharmacokinetics, and pharmacodynamics of the MEK inhibitor RO4987655 (CH4987655) in patients with advanced solid tumors. Clin Cancer Res 2012; 18: 4794–4805.
69. Iverson C, Larson G, Lai C et al. RDEA119/BAY 869766: a potent, selective, allosteric inhibitor of MEK1/2 for the treatment of cancer. Cancer Res 2009; 69: 6839–6847.
70. Weekes CD, Von Hoff DD, Adjei AA et al. Multicenter phase I trial of the mitogen-activated protein kinase 1/2 inhibitor BAY 86–9766 in patients with advanced cancer. Clin Cancer Res 2013; 19: 1232–1243.
71. Houede N, Faivre SJ, Awada A et al. Safety and evidence of activity of MSC1936369, an oral MEK1/2 inhibitor, in patients with advanced malignancies. J Clin Oncol 2011; 29(suppl): abstr 3019.
72. Chang-Yew LC, Gerondakis S, Spencer A. MEK inhibitors as a chemotherapeutic intervention in multiple myeloma. Blood Cancer J 2013; 31; e105.
73. AlAli A, Bushehri A, Park JC et al. Pimasertib and serous retinal detachments. Retin Cases Brief Rep 2016; 10: 191–196.
74. McCannel TA, Chmielowski B, Finn RS et al. Bilateral subfoveal neurosensory retinal detachment associated with MEK inhibitor use for metastatic cancer. JAMA Ophthalmol 2014; 132: 1005–1009.
75. Rosen L, LoRusso P, Ma WW et al. A first-in-human phase 1 study to evaluate the MEK1/2 inhibitor GDC-0973 administered daily in patients with advanced solid tumors. Cancer Res 2011; 71: abstr 4716.
76. Larkin J, Ascierto PA, Dreno B et al. Combined vemurafenib and cobimetinib in BRAF-mutated melanoma. N Engl J Med 2014; 371: 1867–1876.
77. De La Cruz-Merino L, Di Guardo L, Grob JJ et al. Clinical features of cobimetinib (COBI)-associated serous retinopathy (SR) in BRAF-mutated melanoma patients (pts) treated in the coBRIM study. J Clin Oncol 2015; 33(suppl): abstr 9033.
78. Shimokata T, Watanabe K, Shibata T et al. Results of a phase 1 study of MEK162, an oral MEK inhibitor, in Japanese patients with advanced solid tumors. Presented at the 38th ESMO Annual Meeting; 27 September–1 October, 2013; Amsterdam, Netherlands.
79. Juric D, Soria JC, Sharma S et al. A phase 1b dose-escalation study of BYL719 plus binimetinib (MEK162) in patients with selected advanced solid tumors. J Clin Oncol 2014; 32, 5(suppl): abstr 9051.
80. Kefford R, Miller WH, Tan D et al. Preliminary results from a phase Ib/II, open-label, dose-escalation study of the oral BRAF inhibitor LGX818 in combination with the oral MEK1/2 inhibitor MEK162 in BRAF V600-dependent advanced solid tumors. J Clin Oncol 2013; 31(suppl): abstr 9029.
81. Sullivan RJ, Weber JS, Patel SP et al. A phase Ib/II study of BRAF inhibitor (BRAFi) encorafenib (ENCO) plus MEK inhibitor (MEKi) binimetinib (BINI) in cutaneous melanoma patients naive to BRAFi treatment. J Clin Oncol 2015; 33(suppl): abstr 9007.
82. Urner-Bloch U, Urner M, Stieger P et al. Transient MEK inhibitor-associated retinopathy in metastatic melanoma. Ann Oncol 2014; 25: 1437–1441.
83. Schoenberger SD, Kim SJ. Bilateral multifocal central serous-like chorioretinopathy due to MEK inhibition for metastatic cutaneous melanoma. Case Rep Ophthalmol Med 2013; 2013: 673796.
84. Balagula Y, Barth Huston K, Busam KJ et al. Dermatologic side effects associated with the MEK 1/2 inhibitor selumetinib (AZD6244, ARRY-142886). Invest New Drugs 2011; 29: 1114–1121.
85. Velez-Montoya R, Olson J, Petrash M et al. Acute onset central serous retinopathy in association with Mek inhibitor use for metastatic cancer. Invest Ophthalmol Vis Sci 2011; 52: 21153.
86. van der Noll R, Leijen S, Neuteboom GH et al. Effect of inhibition of the FGFR-MAPK signaling pathway on the development of ocular toxicities. Cancer Treat Rev 2013; 39: 664–672.
87. Jiang Q, Cao C, Lu S et al. MEK/ERK pathway mediates UVB-induced AQP1 downregulation and water permeability impairment in human retinal pigment epithelial cells. Int J Mol Med 2009; 23: 771–777.
88. Kuznetsova AV, Kurinov AM, Aleksandrova MA. Cell models to study regulation of cell transformation in pathologies of retinal pigment epithelium. J Ophthalmol 2014; 2014: 801787.
89. Huang W, Yang AH, Matsumoto D et al. PD0325901, a mitogen-activated protein kinase kinase inhibitor, produces ocular toxicity in a rabbit animal model of retinal vein occlusion. J Ocul Pharmacol Ther 2009; 25: 519–530.
90. National_Cancer_Institute. Common Terminology Criteria for Adverse Events v4.0. NCI, NIH, DHHS. NIH publication # 09-7473, 29 May 2009.