Transient MEK inhibitor-associated retinopathy in metastatic melanoma


1Private Ophthalmic Practice in Cooperation with the Skin Cancer Unit, University Hospital of Zurich, Zurich; 2Institute of Physiology and Zurich Center for Integrative Human Physiology, University of Zurich, Zurich; 3Department of Dermatology, University Hospital of Zurich, Zurich; 4Novartis Pharma AG, Basel, Switzerland

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Background: Melanoma is one of the most aggressive skin cancers. Recently, selective MEK inhibitors have shown efficacy in patients with advanced BRAF- and NRAS-mutant melanoma. Soon after the initiation of clinical oncology trials with MEK inhibitors, it was observed that some participants developed an eye condition resembling central serous choriretinopathy. The present article addresses the clinical features and management of these MEK inhibitor-associated retinal syndromes.

Patients and methods: Thirty-two patients with advanced cutaneous melanoma were treated with the selective MEK inhibitor binimetinib (MEK162) in three different Phase 1b or 2 clinical trials. Twenty patients on binimetinib monotherapy and 12 on binimetinib plus RAF inhibitor [pan-kinase RAF inhibitor RAF265 (n = 7) or selective BRAF inhibitor encorafenib (LGX818) (n = 5)] combination therapy underwent ophthalmological examinations at regular intervals, including determination of best corrected visual acuity, perimetry, colour vision testing, dilated fundus examination, and multimodal imaging.

Results: Grade 1–2 bilateral retinopathies with multiple lesions were observed in 13 of 20 patients on binimetinib monotherapy, 4 of 7 patients on binimetinib plus RAF265 combination therapy, and 2 of 5 patients on binimetinib plus encorafenib combination therapy. In this study population, the rate ranged from 40% to 65%. Retinopathy events appeared during the first 4 weeks, and in some cases, during the first few days of treatment. Patients reported mild and only short-lived visual symptoms. Optical coherence tomography revealed neuroretinal elevations. Central retinal thickness and volume showed dose-dependent increases after the start of treatment, followed by a marked decrease despite continued treatment, which was associated with symptom resolution. No vascular abnormalities were found with fluorescein and indocyanine green angiography.

Conclusions: Treatment with the selective MEK inhibitor binimetinib as a single agent or in combination with RAF inhibitors induced transient retinopathy with multiple bilateral lesions in some patients. Binimetinib-induced retinopathy was usually mild, self-limiting, and tolerable as visual function was not seriously impaired.

Key words: melanoma, MEK inhibition, neuroretinal detachment, visual disturbance, optical coherence tomography

Introduction

The treatment of advanced cutaneous melanoma has recently entered a new era. As a result of intensive research efforts, novel effective approaches with immunomodulation [1–3] and targeted blockades in regulatory growth signalling pathways [4, 5] have been introduced. Significant discoveries related to melanoma carcinogenesis, especially an understanding of the role of activating mutations in the mitogen-activated protein kinase (MAPK) signalling pathway, have been fundamental in the development of new drugs for cutaneous melanoma, as well as various other cancers. Melanoma subtypes differ in their development, clinical features, and response to treatment due to differences in mutations [6]. Many selective MEK and BRAF inhibitors and combinations of these two classes of agents have already been evaluated in clinical trials [7–11]. Trametinib (Mekinist®, GlaxoSmithKline) is the only FDA-approved selective MEK inhibitor to date. Binimetinib (MEK162) and selumetinib are other selective MEK1/2 inhibitors in development that have shown promising results in BRAF- and NRAS-mutant cutaneous melanoma and uveal melanoma, respectively [12]. The use of novel BRAF and MEK inhibitors in melanoma is limited by short-lived responses due to acquired resistance [13, 14] and associated adverse events [15, 16]. Along with skin-related
toxicities (e.g. dermatitis aciform) and gastrointestinal disorders (e.g. diarrhoea, nausea), MEK inhibitors are associated with ocular events [11, 17].

Retinal vein occlusion, optic neuropathy, and reversible visual disturbances with MEK inhibition have been previously reported in preclinical studies and Phase 1 trials [17-19]. As such, particular attention has been given to potential occurrences of ocular toxicities in subsequent studies with MEK inhibitors, including incorporation of appropriate exclusion criteria for ocular risk factors in trial protocols. Currently, only individual reports have described ophthalmological findings resembling central serous chorioretinopathy (CSR) related to MEK inhibitor administration [20, 21]. The present article addresses the clinical features and management of MEK inhibitor-associated retinal syndromes.

patients and methods

ethics statement. The study protocols were approved by the Hospital Ethics Committee (No. 2011-0105, NCT01320085; No. 2011-0217, NCT01352273; No. 2013-0018, NCT01543698).

subjects and methods. Patients with advanced BRAF- and NRAS-mutant cutaneous melanoma were recruited in the Department of Dermatology, University of Zurich. Patients participated in three different clinical trials with the active substance binimetinib as monotherapy (NCT01320085), in combination with the pan-inhibitor RAF265 (NCT01352273), or in combination with the selective BRAF inhibitor encorafenib (LGX818) (NCT01543698). During these prospective clinical studies, patients underwent ophthalmological examinations at regular intervals, in accordance with each trial protocol.

ophthalmological examination. Patients were evaluated by ophthalmological examinations at screening, at day 15 after treatment initiation and the first day of each subsequent treatment cycle (i.e. every 21 or 28 days), and 4 weeks after discontinuing treatment. Examinations included a detailed assessment of ophthalmological history, determination of best corrected visual acuity, static or kinetic perimetry, colour vision testing, slit-lamp examination, applanation tonometry, dilated fundoscopy, and optical coherence tomography (OCT). When specifically indicated, digital colour fundus imaging, and fluorescein/indocyanine green angiographies were carried out. Detailed descriptions of ophthalmological examinations are included within the supplementary material, available at Annals of Oncology online.

statistical analysis. All statistical analyses were carried out using OriginPro 8G (Origin Laboratory, Northampton, MA) and SPSS Version 20 (SPSS Inc., Chicago, IL). Linear regression was used to assess influences on central retinal and retinal volume as dependent variables. The dose of binimetinib, treatment duration, and patient age were included as continuous independent variables in the regression model. The mode of treatment (combination therapy versus monotherapy) was addressed using a binary predictor. Baseline values (before the start of treatment) were used as the reference category in the regression model. If not otherwise indicated, figures show mean ± standard deviation. P-values of <0.05 were considered to be statistically significant.

results

patient characteristics

Thirty-two patients enrolled between June 2011 and September 2013. Twenty patients treated with binimetinib monotherapy, 7 with binimetinib plus RAF265 combination therapy, and 5 with binimetinib plus encorafenib combination therapy were analysed for MEK inhibitor-associated ocular adverse events. Grade 1–2 retinopathy was detected in 19 of 32 patients. The incidence of retinopathy was similar in men (12/20; 60%) and women (7/12; 58%). Treatment group characteristics and the duration of follow-up (from initial screening to last visit), are provided in supplementary Table S1, available at Annals of Oncology online. Reasons for stopping treatment (i.e. progression of disease, occurrence of adverse events, or study withdrawal) will be reported elsewhere. The mean age of the patients was 55 (range 34–85) years. The mean age of patients with NRAS-mutant melanoma (n = 12) was 59 (range 34–85) years, with a mean treatment or follow-up period of 92 (range 36–181) days. The mean age of patients with BRAF-mutant melanoma (n = 20) was 52 (range 30–78) years, with a mean treatment period of 117 (range 10–595) days.

visual function

Only 8 of 19 patients with retinopathy described mild visual disturbances, despite the presence of considerable ocular changes observed by ophthalmoscopy. The maximum reduction in vision was by 0.4 decimal points, usually manifesting only as a reduced reading velocity. Four patients were assessed earlier than on planned visit day 15 because of marked metamorphopsia and glare. Four patients reported visual disturbances without any ophthalmoscopic evidence of retinopathy. Refractometer measurements and subjective refraction showed fluctuations in the presence of a subfoveal exudate with a slight hyperopic shift and astigmatic changes. Findings on both perimetry and colour vision testing (n = 8) provided no evidence of significant visual disturbances. In six patients, able to cooperate consistently, visual-field analysis showed no changes over several treatment cycles (>6 static examinations).

slit-lamp findings

There was little complaint about lid oedema and conjunctivitis that can coincide with macular papulopustular skin rash commonly observed with binimetinib monotherapy. Only one patient, with marked generalized oedema, weight gain, and raised blood pressure, repeatedly exhibited slightly raised intraocular pressure of 20–24 mmHg. No signs of anterior or posterior uveitis were observed.

ophthalmoscopic findings and recorded images

Retinopathy in affected patients was always bilateral with focal lesions extending into the mid-periphery (supplementary Figure S1A and B, available at Annals of Oncology online). In some cases, findings were subtle and easily overlooked. Without
exception, patients were very sensitive to light, did not tolerate examination well, and were therefore difficult to examine. Greyish-yellow round or oval lesions were often not very prominent when examined by biomicroscopy. In most patients, a larger foveal lesion and, in particular, multiple small foci could be seen along the temporal vascular arcades. Foveal lesions in combination with foci elsewhere were found in 15 of the 19 cases, with foveal lesions alone in the other 4. When counted, 1–5 extrafoveal lesions per eye were observed in 6 cases; 6–10 in 4 cases, and >10 in 5 cases. In isolated cases, small linear hemorrhages and small cotton-wool-like lesions, but no vascular thrombosis, were seen. There were no abnormalities in fundus autofluorescence (recorded in two patients after 65 and 100 days of treatment).

infrared images and OCT sections
The size and number of foveal lesions were much more easily determined by infrared images and OCT sections than by ophthalmoscope. Some lesions were >1 optic disc in diameter (supplementary Figure S1C–F, available at *Annals of Oncology* online). OCT sections showed multiple serous elevations of the neurosensory retina and thickening of the outer retinal layers in some areas. When symptoms were reported early, after only 1–3 doses of the study drug, a bullous subfoveal elevation was observed (supplementary Figure S2, available at *Annals of Oncology* online), with development of a narrow cleft between the pigment epithelium and the neuroretina at various excipient sites (supplementary Video S1, available at *Annals of Oncology* online). Small cysts formed in the inner retinal layers (supplementary Figure S2B, available at *Annals of Oncology* online). Some patients reported fluctuating visual acuity, particularly in the first 2–4 h after taking binimetinib tablets, within the same timeframe that an increase in retinal thickness and exudates was noted (supplementary Figures S3 and S4, available at *Annals of Oncology* online).

fluorescein and simultaneous indocyanine green angiography
Two patients (one each on binimetinib monotherapy and binimetinib plus RAF265 combination therapy) showed no vascular abnormalities or leakage (supplementary Figure S5A and B, available at *Annals of Oncology* online). Only dye pooling was observed at sites where OCT analysis revealed elevations of the neurosensory retina.

quantitative evaluations
Central retinal thickness and volume in a total of 178 scans (right and left eyes of 16 patients) showed a dose-dependent increase after the start of the treatment, followed by a decrease with continued treatment (supplementary Figure S6A and B and supplementary Table S2, available at *Annals of Oncology* online). No difference in the incidence of retinopathy was found when patients were treated with binimetinib as monotherapy or in combination with RAF inhibitors RAF265 or encorafenib (supplementary Figure S6C, available at *Annals of Oncology* online). However, central retinal volume and maximal thickness were significantly lower in patients treated with a combined therapy (supplementary Table S2, available at *Annals of Oncology* online).

dose-dependence of binimetinib-associated retinopathy
An increased incidence of retinopathy was observed even shortly after starting study-drug treatment with binimetinib at 60 mg twice-daily (BID) doses in seven of eight patients (88%) (supplementary Figure S6C, available at *Annals of Oncology* online). As other adverse events were also common at this dose (e.g. skin rashes, cardiomyopathy, elevated creatine kinase), in all cases, the study drug was reduced to 45 mg BID, interrupted, or, in three cases, discontinued entirely. All patients enrolled later in the binimetinib studies were given an initial dose of binimetinib at 45 mg BID. At this dose, retinopathy was seen much less often (10 of 19 patients, 53%). The dose of 45 mg BID was left unchanged in 11 patients, including 4 with retinopathy who had spontaneous remission. According to the trial protocols, a further dose reduction to binimetinib 30 mg BID was required if no improvement was seen after monitoring at shorter intervals (9 patients). Extensive retinal findings with >10 lesions per eye were observed four times at the 60 mg BID dose but only once at 45 mg BID.

evolution of the lesions
Even with very pronounced retinopathy, symptoms disappeared in all patients, and visual acuity returned to baseline values. Marked resolution (8 patients) or a complete return to normal of the changes in the fundus, retinal thickness, and volume (9 patients) were seen after 2–6 weeks with ongoing therapy or discontinuation of treatment. Some patients had continuing small daily fluctuations of retinal thickness until treatment discontinuation (supplementary Figure S7A, available at *Annals of Oncology* online). Extrafoveal lesions took more time to resolve.

discussion
This article describes the clinical characteristics of MEK inhibitor-associated retinopathy that was observed in some patients during clinical studies with the selective MEK inhibitor binimetinib (MEK162) alone or in combination with RAF inhibitors. In our study population, MEK inhibitor-associated retinopathy based on biomicroscopic findings were found in 19 of 32 patients (59%). Only 8 of these 19 patients described mild visual symptoms (25% of the total population). Retinopathy events were dose- and time-dependent, and fully reversible even with continued drug exposure. The symptoms experienced by the patients with retinopathy were usually mild. The addition of a RAF inhibitor to binimetinib treatment had no influence on the incidence of retinopathy; however, the increase in retinal thickness and volume was lower in patients undergoing combined treatment. Retinal changes may be less extensive with combined therapy due to the use of lower binimetinib doses when combined with a RAF inhibitor. Based on clinical experience, the likelihood of making a diagnosis of retinopathy depends very much on the timing of examination and the diagnostic method used. As many patients did not complain of visual disturbances...
(42% in this patient population), there is no need for a full ophthalmological workup in patients receiving binimetinib. OCT and scanning laser ophthalmoscopy were a great help in diagnosing and monitoring the course of binimetinib-induced retinopathy. Tracking the fluctuations in the height of the neuroretinal elevation showed that they ran parallel to the increase in binimetinib blood concentrations (peak $T_{\text{max}}$ after 1.18 h; personal communication from Novartis, 6 November 2013) and the resolution of an acute exude was equally rapid. Retinal changes were completely reversible upon binimetinib discontinuation and did not require additional treatment. Recurrence after reinitiating treatment was often less pronounced than the initial findings. The fact that retinal changes in the studies described here resolved spontaneously despite the continuation of treatment argues for extremely effective and adaptive mechanisms in the retina. Although functional investigations such as colour vision testing and perimetry did not contribute greatly to the diagnosis of retinal disease, their stability over several treatment cycles suggests that there was no damage to other ocular tissues.

**CSR and binimetinib-associated retinal findings**

There were similarities between the MEK inhibitor-associated retinal changes and CSR [22], whose pathogenesis has not yet been fully explained. However, the clinical features of MEK inhibitor-induced retinopathy in this patient population could be clearly distinguished by the close temporal relationship with binimetinib dosing, together with simultaneous bilateral appearance. In classic CSR, major symptoms such as blurred vision are usually monocular, with bilateral retinal findings reported in only 40% of cases. CSR affects predominantly middle-aged men (up to 88%) and is a frequently associated with several risk factors (including psychological stress, Type A personality, and elevated serum cortisol levels). CSR is characterized by a specific pattern of leakage on fluorescein angiography and by disturbances in choroidal blood flow [22, 23]. This is in contrast to MEK inhibitor-associated retinopathy, where no vascular abnormalities have been found on fluorescein and indocyanine green angiography. In patients treated with binimetinib, dye pooling was only observed in the serous exudates, indicating decomposition of the outer blood–retinal barrier in the pigment epithelium [24]. An immunological or allergic trigger for the retinopathy events described here seems unlikely, as the changes were dose-dependent and rapidly regressed with a reduction in binimetinib dose or ongoing treatment. Incipient age-related macular degeneration may also occasionally show similar ophthalmoscopic features compared with binimetinib-induced retinal events, with the presence of large drusen and possibly associated elevation of the pigment epithelium; however, if this were the case, pathological changes due to age-related macular degeneration would already have been present before treatment started.

**cancer-related eye conditions**

During screening of melanoma patients for study enrolment, we observed orbital metastasis with papilloedema, but never found a choroidal dissemination. Despite its excellent blood supply, metastasis to the uvea is rare with cutaneous melanomas, which metastasize to many different organs, including the brain [25]. Also noteworthy are the equally rare eye conditions associated with metastatic disease: cancer-associated retinopathy and melanoma-associated retinopathy [26, 27]. In contrast to the MEK inhibitor-associated retinopathy, both syndromes cause marked visual symptoms and later permanent functional deficits.

**management of binimetinib-associated retinopathy**

Application of topical non-steroidal anti-inflammatory drugs has long been established for preventing and treating retinal disease due to inflammation or trauma [29, 30]. Likewise, carbonic anhydrase inhibitors have been evaluated favourably in different clinical situations involving macular oedema [31, 32], including CSR [33], taxane-induced maculopathies, and in hereditary degenerative conditions such as retinitis pigmentosa and X-linked retinoschisis [34–36]. There are still controversial reports about the efficacy of these drugs. In situations in which visual disturbances distress the patient, it seems important to propose some form of countermeasure. Good patient experiences have been observed with topical nepafenac TID and/or dorzolamide TID. Overall, clinical experience with these drugs offers a sufficient rationale for their use in selected cases with MEK inhibitor-associated retinopathy, as no other treatment exists.

**conclusions**

This investigation illustrates for the first time the clinical features and course of binimetinib-associated retinopathy in a sizeable number of patients with advanced melanoma. It is important for ophthalmologists and oncologists to be aware of the course and the management of this generally mild and self-limiting condition. In patients with persistent visual impairment (20/30 or less), an interruption of treatment or dose reduction might be considered. However, due to its transient features, binimetinib-induced retinopathy should not in any way be a reason for discontinuing treatment if ophthalmological monitoring is provided.

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disclosures
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references