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Serous Retinopathy Associated with Mitogen-Activated Protein Kinase Kinase Inhibition (Binimetinib) for Metastatic Cutaneous and Uveal Melanoma

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Purpose: To analyze the clinical characteristics of a serous retinopathy associated with mitogen-activated protein kinase kinase (MEK) inhibition with binimetinib treatment for metastatic cutaneous melanoma (CM) and uveal melanoma (UM), and to determine possible pathogenetic mechanisms that may lead to this retinopathy.

Design: Prospective observational, cohort-based, cross-sectional study.

Participants: Thirty CM patients and 5 UM patients treated with the MEK inhibitor binimetinib (CM) or a combination of binimetinib and the protein kinase C inhibitor sotrastaurin (UM).

Methods: Extensive ophthalmic examination was performed, including Early Treatment of Diabetic Retinopathy Study best-corrected visual acuity, applanation tonometry, slit-lamp examination, indirect ophthalmoscopy, digital color fundus photography, and optical coherence tomography (OCT). In selected cases, additional examinations were performed, including visual field testing and electro-oculography (EOG). Blood samples were obtained from 3 CM patients and 3 UM patients to analyze the presence of autoantibodies against retinal and retinal pigment epithelium (RPE) proteins.

Main Outcome Measures: Visual symptoms, visual acuity, fundus appearance, characteristics on OCT, fundus autofluorescence (FAF), and EOG.

Results: Six CM patients (20%) and 2 UM patients (40%) reported visual symptoms during the study. The median time to the onset of symptoms, which were all mild and transient, was 3.5 days (range, <1 hour to 3 weeks). On OCT, subretinal fluid (SRF) was detected in 77% of CM patients and 60% of UM patients. In the 26 patients with SRF, the fovea was affected in 85%. After the start of the medication, an EOG was performed in 19 eyes of 11 patients; 16 of these eyes (84%) developed SRF on OCT. Fifteen of these eyes (94%) showed an abnormal Arden ratio (<1.65). A broad pattern of anti-retinal antibodies was found in 3 CM patients and 2 UM patients tested, whereas anti-RPE antibodies were detected in all 6 tested patients.

Conclusions: A time-dependent and reversible serous retinopathy can develop both in patients with metastatic CM and UM treated with binimetinib. A minority of patients develop visual symptoms, which are generally mild and transient. A cause of binimetinib-associated serous retinopathy may be toxicity of medication, but autoantibodies also may be involved. *Ophthalmology 2015;122:1907-1916 © 2015 by the American Academy of Ophthalmology.*

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Cutaneous melanoma (CM) is an increasingly occurring malignant skin tumor. Distant metastases, either via lymphatics or the bloodstream, occur in 15% of patients, with a 5-year survival rate of 15% to 22%.[1] Although CM represents only 4% of skin cancer cases, it causes 65% of skin cancer–related deaths.[2]

Uveal melanoma (UM) is the most common primary intraocular malignancy in adults. Metastasis occurs in 34% of patients within 10 years after diagnosis, and after detection of metastases, the 2-year survival rate is only 8%.[3] Metastasis in UM occurs purely hematogenously, and the liver is involved in 95% of patients. The median survival in these cases is 4 to 6 months, whereas the median survival in cases without liver metastases is 19 to 28 months.[4]

The treatment options for metastatic CM and UM are limited. However, new targeted treatment options include therapies that target the mitogen-activated protein kinase

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(MAPK) signaling pathway. The MAPK pathway plays a crucial role in intracellular signal transduction and induces transcription of genes, encoding several cellular processes, such as growth, differentiation, migration, inflammation, angiogenesis, and cell death.[5,6] The MAPK pathway is regulated by several growth factors, including fibroblast growth factor receptors, which are present on the cell surface. The MAPK cascade can be activated by the rat sarcoma small guanidine phosphatase, which subsequently activates rapidly accelerated fibrosarcoma kinase, enabling the phosphorylation and activation of mitogen-activated protein kinase kinase (MEK) and, finally, extracellular signal-regulated kinase.[7]

Patients with CM or UM can be subdivided on the basis of underlying genetic mutations in the melanoma cells. In 52% to 86% of patients with UM and in more than 66% of patients with CM, uncontrolled activation and aberrant signaling of the MAPK pathway can be detected.[8] In CM, *RAS* and *BRAF* gene mutations may cause activation of the MAPK pathway.[9] In UM, mutually exclusive mutations in *GNAQ* and *GNA11* often can be found. These mutations cause a permanently activated GTP-bound state, leading to the activation of protein kinase C and consequently the MAPK pathway.[8,9]

Several targeted therapies, such as the BRAF inhibitors vemurafenib and dabrafenib, the MEK inhibitors trametinib, selumetinib, and binimetinib (MEK162), and combinations of BRAF and MEK inhibitors, have emerged as novel therapeutic options, especially for patients with metastatic BRAF-mutated CM.[10–12] In patients with NRAS-mutated CM, MEK inhibition by MEK162 has shown clinical activity.[13]

Retinopathy, described as a "central serous chorioretinopathy-like event," an unspecified "chorioretinopathy," or a "bilateral, multifocal, mild and self-limiting retinopathy," was described in association with binimetinib treatment in patients with advanced or metastatic CM in 2% to 65% of patients.[12,14]

Little is known about the clinical characteristics, outcome, and pathogenesis of MEK inhibitor–associated retinopathy. In this study, we analyzed the clinical characteristics of retinopathy associated with MEK inhibition treatment for metastatic CM and UM. In addition, we studied possible pathogenetic mechanisms that may lead to such retinopathy, and we examined a correlation between the development of retinopathy and the tumor response to MEK inhibition treatment in metastatic CM.

Methods

Patient Characteristics

Twenty patients from an academic medical center (Radboud University Medical Center, Nijmegen, The Netherlands) and 10 patients from a comprehensive cancer center (The Netherlands Cancer Institute Antoni van Leeuwenhoek, Amsterdam, The Netherlands, in collaboration with the general hospital Onze Lieve Vrouwe Gasthuis, Amsterdam, The Netherlands) were included. These patients had a histologically confirmed, locally advanced, and unresectable or metastatic CM harboring *BRAF* V600E or *NRAS* mutations, confirmed by a central laboratory.[12] From another academic medical center (Leiden University Medical Center, The Netherlands), 5 patients with liver biopsy-confirmed metastatic UM were included.

The local ethics committee approved the study. Each patient signed informed consent, and the studies were performed in accordance with the Declaration of Helsinki. The clinical trials were registered in the Clinical Trial Registration as numbers NCT01320085 (Nijmegen and Amsterdam) and NCT01801358 (Leiden). Within these trials, patients were included from July 2011 to April 2014.

Treatment

In patients with metastatic CM, the MEK inhibitor binimetinib was administered in a phase II trial setting. Patients received 45 mg of binimetinib orally twice per day, continuously for 28 days (defined as a 1-treatment cycle, for scheduling purposes). The patients with metastatic UM received a combination of binimetinib and the protein kinase C inhibitor sotrastaurin (AEB071) in a phase Ib/II trial setting. Patients with metastatic UM started with continuous dosing of binimetinib 30 or 45 mg twice daily for 28 days. They also received sotrastaurin twice daily. Patients continued with the study medication until the development of disease progression or unacceptable toxicity.

Ophthalmic Examinations

All patients received a complete ophthalmic examination, including Early Treatment of Diabetic Retinopathy Study (ETDRS) best-corrected visual acuity (BCVA), applanation tonometry, slit-lamp examination, and indirect ophthalmoscopy. When ETDRS BCVA was not available (in 10 patients), Snellen BCVA was determined and a previously established conversion method was used to achieve ETDRS values.[15]

Dilation of pupils was achieved by topical administration of 1% tropicamide and 5% phenylephrine drops. Optical coherence tomography (OCT), using spectral-domain OCT (Spectralis HRA+OCT; Heidelberg Engineering, Heidelberg, Germany) or the Cirrus OCT device (Carl Zeiss Meditec, Dublin, CA), and digital color fundus photography (Topcon Corp., Tokyo, Japan) were performed at baseline, at day 15 of treatment cycle 1 (CM) or at day 8 and day 22 of treatment cycle 1 (UM), day 2 of each treatment cycle from cycle 2, and at the end of treatment (within 14 days after discontinuation of treatment). In selected cases, enhanced-depth imaging OCT, fundus autofluorescence (FAF), and fluorescein angiography (FA) were performed with spectral-domain OCT. In addition, electro-oculography (EOG) and electroretinography (ERG) were performed according to the guidelines of the International Society for Clinical Electrophysiology of Vision in selected cases, as well as color vision testing using the Desaturated Panel D-15 test.[16–18]

In 25 patients (20 with CM and 5 with UM), central visual analysis was performed (Humphrey Field Analyzer, Carl Zeiss Meditec; 24-2 or 30-2 SITA Standard Algorithm). One patient underwent microperimetry using the MAIA microperimeter (CenterVue, SpA, Padova, Italy), examining an area covering the central 15°.

Patients who reported new or worsened visual symptoms received an additional ophthalmic examination at their earliest convenience. Additional ophthalmic examinations were performed as clinically indicated. When signs of ocular toxicity occurred, patients received weekly ophthalmologic examinations until the symptoms resolved or stabilized after at least 6 months of follow-up.

In this study, serous retinopathy was defined as retinal lesions on ophthalmoscopy corresponding to a localized separation of the neuroretina and retinal pigment epithelium (RPE) on OCT.