Mitogen-activated protein kinase (MEK) inhibitors are an emerging treatment modality for various metastatic malignancies. Multiple cases of retinal toxicity have been reported in the literature. Furthermore, at the University of Chicago, we have seen several cases of macular neurosensory retinal detachments very soon after the initiation of MEK inhibitors.

Daniel P. Nolan, DO, and Shawn Lewis, MD, will provide an overview of the literature and a case series, as well as summarize current thinking regarding the pathophysiology and management of retinal toxicity from MEK inhibition. The retina specialist needs to be aware of this increasingly common issue, as more than a dozen MEK inhibitors are being developed. Furthermore, we also need to be aware of the management of this condition, since MEK inhibitors seem to be useful to treat metastatic cancers and may be life-saving. Therefore, the eye specialist should take caution before making the recommendation to stop therapy and understand features of retinal toxicity on clinical examination and retinal imaging.

I am certain that the community will value the insights and review of this complex topic provided by Drs. Nolan and Lewis.

Retinal Toxicity Associated With MEK Inhibitor Use for Metastatic Cancer: A Rising Trend in Ophthalmology

by Daniel P. Nolan, DO; Shawn Lewis, MD; Seenu M. Hariprasad, MD

Perhaps there is no field in medicine better versed in clinical trials than oncology. One of the field’s newer agents, mitogen-activated protein kinase (MEK) inhibitors, has been noticed with increasing frequency in the ophthalmology clinics. Its pathway has been well-described in the literature,1 as have its uses for pancreatic and gynecological malignancies,2,3 in addition to various other solid tumors. According to the National Cancer Institute, there are 13 MEK inhibitors currently in various phases of clinical trials:4 AZD8330 (AstraZeneca, Wilmington, DE), binimetinib (Array Biopharma, Boulder, CO), cobimetinib (Genentech, South San Francisco, CA), copanlisib (Bayer, Leverkusen, Germany), GDC-0623 (Genentech, South San Francisco, CA), PD0325901 (Pfizer, New York, NY), pimasertib (Merck, Kenilworth, NJ), refametinib (Ardea Biosciences, San Diego, CA), RO4987655 (Hoffman-La-Roche/Chugai Pharmaceutical), selumetinib (AstraZeneca), trametinib (GlaxoSmithKline, Philadelphia, PA), TAK-733 (Millennium Pharmaceuticals, Cambridge, MA), and WX-554 (WILEX, Munich, Germany). At this time, only trametinib is U.S. Food and Drug Administration (FDA)-approved.

Only within the last few years have MEK inhibitors been brought to light in the ophthalmology literature. Previous reports in the non-ophthalmic literature reported transient, nonspecific, visual symptoms.5,6 These patients reported symptoms such as visual dis-
turbance and glare, but unfortunately authors made no mention of the findings from the ophthalmic examination. The first published report in the ophthalmology literature was described by Schoenberger et al. This patient had acute vision changes after starting therapy and was noted to have bilateral, multifocal, central serous-like retinopathy with nonleaking cystoid macular edema (CME). The medication was discontinued, and vision returned to baseline. Upon retrial, however, the symptoms and signs returned and the medication was ultimately stopped.

McCannel et al. described the next series of patients suffering from MEK inhibitor toxicity. The three patients in this series had subfoveal (but not multifocal) neurosensory retinal detachments without CME. Two of the three also had mild anterior segment inflammation, which resolved with topical corticosteroids. Their patients were all able to continue with the medication and vision returned to baseline within a period of days to weeks.

OUR EXPERIENCE

We had the opportunity to see two patients at the University of Chicago Department of Ophthalmology & Visual Science with MEK inhibitor toxicity. The first such patient was a 70-year-old man who presented in August 2014 with blurred vision 4 days after starting therapy with pimasertib and gemcitabine (Gemzar; Lilly USA, Indianapolis, IN) for metastatic pancreatic cancer. He lost one line of Snellen acuity in each eye, from 20/30 to 20/40 in the right eye and from 20/25 to 20/30 in the left eye. Two weeks prior to initiating therapy, at the request of his oncologist, he had a baseline exam including a normal macular spectral-domain optical coherence tomography (SD-OCT) (Figure 1A). After starting therapy, SD-OCT revealed bilateral CME with neurosensory retinal detachments (Figure 1B). Fluorescein angiography performed the same day revealed nonleaking CME (Figure 2). In discussion with the patient and his oncologist, the medications were discontinued and the patient’s vision and SD-OCT returned to baseline 1 week later (Figure 1C). He resumed chemotherapy with gemcitabine only and at 1 month, vision and SD-OCT were unchanged.

Figure 1. (A) Spectral-domain optical coherence tomographic images of both eyes 2 weeks prior to starting pimasertib, right and left eye. (B) Four days after starting pimasertib, right and left eye. (C) One week after discontinuing pimasertib, right and left eye.
Our second patient was a 58-year-old woman with recurrent ovarian/peritoneal cancer who presented within 24 hours of beginning therapy with pimasertib (with SAR245409, a MTOR inhibitor). She reported her vision changing within 6 hours of her first oral dose of the medication. On exam, best-corrected vision was 20/50 in the right eye and 20/30 in the left. Vision was 20/20 in each eye 10 days prior at her baseline exam, with a normal SD-OCT (Figure 3A). Clinical exam and SD-OCT on the day of acute presentation revealed bilateral multiple neurosensory retinal detachments without CME (Figures 3B and 3C). In discussion with the patient and her oncologist, pimasertib and SAR245409 were discontinued, and 1 week later her vision returned to 20/20 in each eye with a normal macular SD-OCT (Figure 3D).

MORE RECENT PUBLICATIONS

Duncan et al. described two patients with retinal toxicity associated with MEK inhibitors. One of their patients had deep retinal lesions without significant subretinal fluid. The second developed nonleaking CME, similar to our first patient, but again without subretinal fluid. It is interesting to note that the first patient presented within 2 weeks of initiating treatment, whereas the second had a delay of 8 months. Both patients were able to continue treatment with their respective MEK inhibitors.

Three months later, van Dijk et al. reported on MEK inhibition for metastatic skin and uveal melanoma. This is the first prospective report in the ophthalmology literature describing MEK inhibitor toxicity. Excluding those with uveal melanoma, only 20% reported visual symptoms during the study, whereas subretinal fluid was noted in more than 75%. Most of those with subretinal fluid had subfoveal fluid. All of their patients were able to continue with MEK inhibitor therapy with only transient visual symptoms.

Niro et al. later described four cases of ocular toxicity in associated with MEK inhibition for metastatic melanoma. Three of the four patients demonstrated subfoveal neurosensory retinal detachments, whereas the fourth had anterior segment inflammation without posterior findings. All were able to eventually continue with MEK inhibition treatment.

In January 2016 in this journal, Sheyman et al. demonstrated a case of asymptomatic retinal toxicity in association with MEK inhibition. They serially followed a patient over the period of 1 year with multimodal imaging including fundus autofluorescence and OCT angiography. The patient demonstrated multifocal neurosensory detachments without CME. This study is the first to report on MEK inhibition with OCT angiography, one of our newest retinal imaging technologies.

CONCLUSIONS

MEK inhibitor therapy for advanced malignancies is on the rise, and we are likely to see increasingly more patients in our offices with visual disturbances as a result. Although many patients are often asym-
Figure 3. (A) Spectral-domain optical coherence tomographic images of both eyes 9 days prior to starting pimasertib, right and left eye. (B) One day after starting pimasertib, right eye, from left: superior macula, fovea, inferior macula. (C) One day after starting pimasertib, left eye. From left: superior macula, fovea, inferior macula. (D) One week after discontinuing pimasertib, right and left eye.
omatic, others have dramatic presentations within a few days of initiating treatment. Though the exact mechanism of retinal toxicity is unknown, many believe that RPE dysfunction is thought to play a role. Animal models show that MEK inhibition leads to downregulation of aquaporin channels in RPE cells, which leads to breakdown of the blood-retinal barrier and RPE hyperpermeability. This theory is further advanced by Sheyman et al., who demonstrated lack of vascular changes on multimodal imaging and OCT angiography.

MEK inhibitor toxicity is a newly discovered issue in the ophthalmology community, as evidenced by the paucity of reports in the literature. Due to the increasing use of MEK inhibitors, ophthalmologists will find it more important to collaborate with oncology colleagues. Academic centers are more likely to receive such patients during the clinical trial phase of drug development, but private ophthalmologists may start to see these patients more frequently, as MEK inhibitors become FDA-approved and are started to be used more broadly.

REFERENCES


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