EDITORIAL

A New Paradigm in the Treatment of Advanced Periocular Basal Cell Carcinoma?

SHELBY P. UNSWORTH, CURTIS J. HEISEL, AND ALON KAHANA

BASAL CELL CARCINOMA (BCC) IS THE MOST COMMON cancer in the western world—more common than all other cancers combined.[1] The incidence of BCC is the United States is >2 million patients per year.[2] Fortunately, BCC is also highly treatable: its extent is usually limited to local invasion and it is highly amenable to surgical excision. On the face, BCC can be treated definitively by Mohs micrographic surgery (MMS) or surgical excision.[3] With MMS, recurrence rates are 2.1% for previously untreated patients and closer to 5% for recurrent tumors.[4]

Despite such a positive prognosis, when tumors occur on the eyelids and canthi (ie, periorbital BCC), recurrence rates are 50% higher compared with other locations on the face, even after MMS.[5] Recurrent (or neglected) periorbital BCC carries the risk of orbital invasion. This is a particularly devastating complication for an otherwise highly treatable cancer, given the risk to the eye and periocular structures. For these patients, achieving tumor-free margins often requires orbital exenteration.[6] Even when globe-sparing surgery is possible, surgical injury to periocular tissues often leads to poor visual outcomes and multiple follow-up surgeries.[7] As ophthalmologists, it is our life's mission to protect vision. We know that our patients value vision and are willing to give up years of life for maintaining good vision.[8,9] Loss of vision causes a dramatic reduction in quality of life,[10] and loss of the eye leads to even greater reduction in functionality and quality of life.[11,12]

Over the past 7 years, the U.S. Food and Drug Administration approved 2 drugs to treat BCC: vismodegib (Genentech, Inc; South San Francisco, California, USA) and sonidegib (Novartis; Basel, Switzerland). Both drugs target hedgehog signaling, which is dysregulated in BCC.[13–15] The U.S. Food and Drug Administration indications for both vismodegib and sonidegib are nearly identical: vismodegib is "indicated for the treatment of adults with metastatic basal cell carcinoma, or with locally advanced basal cell carcinoma that has recurred following surgery or who are not candidates for surgery, and who are not candidates for radiation." Sonidegib is "indicated for the treatment of adult patients with locally advanced basal cell carcinoma that has recurred following surgery or radiation therapy, or those who are not candidates for surgery or radiation therapy." Both vismodegib and sonidegib have the potential to preserve the eye and visual function in orbital BCC patients. However, because these patients are technically candidates for surgery—although it may lead to loss of vision or loss of the eye itself—these drugs are often not used.

In the absence of prospective clinical trials, the art and practice of medicine often rely on case studies—collective experience gained through clinical practice. Beyond informing clinical practice, these studies lay the foundation for expanding indications. The first article on the use of vismodegib for orbital BCC was published in 2013.[16] Since then, additional studies have been published, extending and refining the role of hedgehog inhibitors for treating locally advanced BCC (laBCC). Most recently, Gonzalez and associates[17] reported vismodegib as a neoadjuvant therapy before MMS, suggesting benefits such as decreased defect size and a decrease in the number of Mohs excisions per patient. In this issue of the *American Journal of Ophthalmology*, Eiger-Moscovich and associates[18] report their experience using vismodegib as adjuvant or neoadjuvant therapy to treat a large cohort of patients with laBCC who have failed other treatments. Eiger-Moscovich and associates[18] report on the treatment of 21 patients who met specific criteria for laBCC, using American Joint Committee on Cancer staging. The majority of these patients achieved at least a partial response, and a substantial number appeared to achieve a complete response, although a few recurred after discontinuation of treatment. It is important to note that in this study, Eiger-Moscovich and associates[18] used nontraditional dosing regimens. This included both "drug holidays" and reduced dosage to reduce symptomatic toxicity. Overall, Eiger-Moscovich and associates[18] report that hedgehog inhibition was highly efficacious for advanced tumor, node, metastasis (TNM) stage 3 and 4 periocular BCC. Indeed, patients who would have surely lost their eye and orbit were able to preserve their eye with medical therapy. This is clearly a paradigm shift for the treatment of advanced BCC around the eye.

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From the University of Michigan Kellogg Eye Center (S.P.U., A.K.) and the University of Michigan Medical School (C.J.H.), Ann Arbor, Michigan, USA.

Inquiries to Alon Kahana, University of Michigan Kellogg Eye Center, 1000 Wall Street, Ann Arbor, MI 48105, USA; e-mail: akahana@med.umich.edu

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Eiger-Moscovich and associates[18] raise several important points. Among them, the most important may be that a clear definition of what constitutes "locally advanced" orbital BCC does not yet exist. For tumors around the eye, relying on TNM classifications might not provide sufficient clarity. TNM emphasizes tumor size; however, a small tumor inside the orbit is much more consequential and dangerous to vision than a much larger tumor on the cheek. In addition, as noted in the article, concerns such as avoiding severe deformity should play a role in classifying laBCC. Increased reporting on the use of hedgehog inhibition for periocular BCC will surely provide more data, but a new expert panel may eventually be required to help redefine the meaning of locally advanced in the periocular region.

Two additional points deserve mention: drug cost and duration of treatment. These drugs are expensive (>$7000 USD per month); however, alternative treatment regimens can bring cost down while also reducing toxicity. Eiger-Moscovich and associates[18] describe such modifications when treating laBCC around the eye. In addition, the optimal duration of treatment is not yet known: some tumors might respond completely, allowing for stoppage of treatment, while other tumors may only regress, requiring long-term treatment that is expensive and may also be debilitating to patients. These latter patients may benefit the most from a neoadjuvant usage, while improved understanding of molecular markers may be necessary for generally optimizing the course of treatment. Ultimately, the collective experience of the community and results from prospective clinical trials will provide the desired clarity regarding the use of vismodegib as primary, adjuvant, or neoadjuvant therapy.

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