The role that vismodegib will play in advanced periocular basal cell carcinoma depends on its postmarketing results.

Role of Vismodegib in the Management of Advanced Periocular Basal Cell Carcinoma

Kyle F. Cox, MD, and Curtis E. Margo, MD

Background: Vismodegib is the first selective hedgehog pathway inhibitor approved to treat locally advanced and metastatic basal cell carcinoma (BCC). Limited information is available concerning its role in managing advanced BCC around the eye.

Methods: The medical literature was searched for cases of nonsyndromic periocular BCC treated with vismodegib. Clinical information was abstracted and analyzed. In addition, a review of the pharmacology of vismodegib, including general effectiveness and safety, was conducted.

Results: Thirty study patients with nonsyndromic periocular BCC treated with vismodegib were found in the literature. Vismodegib was used in 3 ways: medical therapy, adjuvant therapy prior to surgery or radiotherapy, and treatment of positive surgical margins. Complete regression was reported in 9 study patients (30%), with follow-up visits after therapy averaging fewer than 5 months. Four study participants developed squamous cell carcinoma while receiving treatment.

Conclusions: Too few cases exist to draw any conclusions on the role that vismodegib might play in the management of periocular BCC. In addition, long-term follow-up data are not yet available. Although the objective response rate of advanced BCC is impressive in study patients receiving vismodegib, well-controlled clinical studies are needed to determine whether vismodegib has any impact on survival or quality of life.

Introduction

In general, periocular basal cell carcinoma (BCC) is usually treated with surgical excision and, when indicated, microscopic control of margins. Typically, recurrence rates are low and functional outcomes are good; however, some tumors because of their size, location, or lack of therapeutic response are inoperable.1 In such cases, the rates of continued morbidity are high and the rates of cure are low.1

Vismodegib is a selective hedgehog pathway inhibitor. It was approved by the US Food and Drug Administration (FDA) in 2012 and the European Medicines Agency in 2013 for the treatment of locally advanced and metastatic types of BCC.2-4 Given the rarity of these conditions and lack of treatment options, approval was based on noncomparative clinical series of study participants. Phase 1/2 trials showed favorable primary end point responses for both locally advanced and metastatic BCC.5 In a phase 2 study, 43% of patients with locally advanced BCC showed partial or complete responses, whereas 30% of those with metastatic tumor responded to treatment.6

From the Departments of Ophthalmology (KFC, CEM) and Pathology and Cell Biology (CEM), University of South Florida Morsani College of Medicine, Tampa, Florida.

Address correspondence to Kyle F. Cox, MD, Department of Ophthalmology, Morsani College of Medicine, MDC Box 21, 12901 Bruce B. Downs Boulevard, Tampa, FL 33612. E-mail: kfcx02@health.usf.edu

Submitted July 13, 2015; accepted January 5, 2016.

No significant relationships exist between the authors and the companies/organizations whose products or services may be referenced in this article.
Since the US and European approvals of vismodegib,\textsuperscript{2-4} case reports and small clinical series have appeared in the literature reflecting how the therapy is used in clinical practice. Some of these reports involve periorcular (or ocular adnexal) BCC.\textsuperscript{7,13} Use of vismodegib for BCC around the eye poses unique challenges and opportunities because conjunctival and orbital involvement may result in blindness and death.\textsuperscript{1}

**Hedgehog Pathway**

The hedgehog pathway is a signaling system that helps regulate cell growth and development. Initially described in *Drosophila*, the hedgehog pathway controls a range of cellular activities in invertebrates and vertebrates, starting during embryogenesis. Among vertebrates, the hedgehog genes encode polypeptides that, after modification by cholesterol, attach to cell surfaces where they affect signaling. The functional receptors for hedgehog are 2 transmembrane proteins called patched 1 and smoothened. The discovery that aberrant activity of the pathway was linked to several human tumors spurred investigation into drugs that could alter various components of the signaling sequence.\textsuperscript{14} Interest into the therapeutic potential of hedgehog pathway inhibitors was stimulated further when researchers tied the signaling system to diverse functions such as angiogenesis and potentially metastatic spread.\textsuperscript{15}

BCC is driven by mutations in 1 or more hedgehog genes.\textsuperscript{16} Typically, these alterations take the form of a loss-of-function mutation in *PTCH1* or an activating mutation in *SMO*. Nevoid basal cell carcinoma syndrome (also called Gorlin–Goltz syndrome) is caused by a germline mutation in *PTCH1*. The mechanism or mechanisms by which *PTCH1* mutations eventually alter downstream transcription factors is an area of active investigation.\textsuperscript{16}

**Pharmacology**

Vismodegib is the first hedgehog inhibitor approved for the treatment of BCC.\textsuperscript{17} It appears to exert its clinical effect by binding to the smoothened receptor protein, preventing nuclear localization of transcription factors that target gene induction.\textsuperscript{14,18} This in turn can promote cellular proliferation, inhibit apoptosis, and further prolong cell survival through mechanisms such as angiogenesis. Compared with other small molecules capable of blocking this receptor, the pharmacokinetic profile of vismodegib was considered better suited for human use.\textsuperscript{19} Approximately one-third of a 150-mg oral dose of vismodegib (the recommended daily dose) is absorbed; more than 99% is bound to plasma proteins (mostly albumin).\textsuperscript{20} Vismodegib is synthetically derived and not extensively metabolized; more than 80% is excreted in feces.\textsuperscript{20,21} Metabolic oxidation in the liver is incompletely understood.\textsuperscript{20}

After continuous daily dosing, the elimination half-life of vismodegib is 4 days, although the half-life of a single dose can be up to 12 days.\textsuperscript{20-22} Its bioavailability is nonlinear, decreasing with increasing strength and frequency of administration.\textsuperscript{20,23}

**Studies**

**Phase 1**

Although no dose-limiting toxicities were found among an initial cohort of patients enrolled in an open-label phase 1 trial, daily doses higher than 150 mg demonstrated no substantially greater steady-state plasma concentration.\textsuperscript{24} Once the maximum tolerated dose was determined to be 150 mg/day, enrollment of the phase 1 study expanded to include 68 patients with advanced/metastatic BCC and other solid tumors.\textsuperscript{25} In this study, tumor response was only seen among participants with BCC and medulloblastoma.\textsuperscript{25} Six participants (9%) experienced life-threatening or disabling adverse events and 20 participants (28%) experienced severe adverse events; however, the majority of adverse events experienced were mild to moderate in nature (eg, muscles spasms, fatigue, alopecia, dysgenesia, diminished appetite).\textsuperscript{25} Those with BCC had an overall response rate of 55%, stable disease was seen in 33%, and the median duration of response was 12.8 months (range, 3.7–26.4 months).\textsuperscript{25} Five deaths (7%) were reported.\textsuperscript{25}

**Phase 2**

Two phase 2 clinical trials followed, one of which was a dual-cohort study of 96 volunteers with locally advanced/metastatic BCC; the other was a randomized trial involving 41 study patients with nevoid basal cell carcinoma syndrome.\textsuperscript{6,26} The objective response rate for 63 study patients with locally advanced disease was 43%; of those participants, 13 (21%) had a complete response.\textsuperscript{6} The median duration of response was 7.6 months (range, 1–12.9 months), and 34 of the 63 specimens (54%) obtained via biopsy showed no residual tumor.\textsuperscript{6} The median duration of drug exposure was approximately 10 months.\textsuperscript{6} Anatomical locations of individual tumors were not available, so analysis of advanced periorcular BCC could not be performed.

Each study patient in the dual cohort trial experienced 1 or more adverse event, and 12% of those resulted in treatment discontinuation.\textsuperscript{6} Serious adverse events occurred in 26 study patients (27%); of those, 7 (7%) of those events were grade 5 and fatal.\textsuperscript{6} The clinical context of the fatalities were incompletely presented, but the authors found no drug-related culpability because all 7 volunteers had preexisting comorbidities.\textsuperscript{6}

Vismodegib displayed similar rates of effectiveness in reducing BCC in persons with nevoid basal cell car-
cinoma syndrome. Objective tumor shrinkage was seen in 65% of treated study patients compared with 11% in those receiving placebo (P = .005), but the rate of adverse events led to treatment discontinuation in more than 50% of volunteers (14/26).

A 12-month update of a phase 2 trial found a 4.7% increase in objective response rate for study patients with advanced BCC (from 42.9% to 47.6%). The median duration of response in these patients also increased from 7.7 to 9.5 months, and no new safety concerns were reported.

An interim analysis of an international, open-label trial with safety as its primary end point used data from 499 study volunteers with advanced/metastatic BCC. Treatment was discontinued in 400 volunteers (80%), 180 (36%) experienced adverse events, 70 (14%) had disease progression, and 51 (10%) requested treatment be stopped. Overall response rate for those with advanced BCC was 66.7% (302/453); of the 302 cases of clinical responses, 153 of those were complete responses. Deaths were reported in 31 study volunteers, 21 of which were considered to be due to a treatment-related adverse event.

An expanded access, open-label multicenter study of 150 mg vismodegib daily in 119 participants with advanced BCC demonstrated an objective response rate of 46% in those with locally advanced disease and 31% in those with metastatic BCC. Inclusion criteria was a tumor diameter of at least 1 cm and either confirmation of an inoperable tumor or a contraindication to surgery. Study patients were followed for 6.5 months; during that time, the rate of adverse events paralleled those previously reported. Four grade 4 treatment-emergent adverse events and 2 treatment-related deaths were reported.

**Treatment Results**

The outcomes of periocular tumors are difficult to identify because site-specific characteristics are not always available in postmarketing clinical series of BCC. In cases that can be identified as periocular, vismodegib has been used as neoadjuvant therapy prior to surgery and radiotherapy and as treatment for positive surgical margins. We were able to find 30 patients for whom sufficient clinical information could be abstracted for analysis (Table 1).

Vismodegib was reasonably effective in a series of 7 study patients with advanced periocular BCC not amenable to surgery or radiotherapy whose largest tumor, on average, was 3.4 cm in size. None had metastatic disease, but 4 study patients had orbital involvement. All study patients had BCC that had previously failed controlled surgical resection. The average duration of treatment with vismodegib was 11 weeks (range, 4–16 weeks), and the mean duration of follow-up was 7.3 months (range, 5–10 months). Two study patients (29%) demonstrated complete regression, 2 (29%) had more than 50% regression, 2 (29%) had less than 50% regression, and 1 (14%) had disease progression. Six (86%) reported experiencing adverse events similar to those previously documented (eg, alopecia, muscle cramps). Two study patients also developed squamous cell carcinoma (SCC).

Demirci et al described the results of a study involving 8 patients with periocular and orbital BCC, one of whom had nevoid basal cell carcinoma syndrome. Of the 7 nonsyndromic study patients, 5 received vismodegib alone for treatment. Four obtained partial response, and, at the time of publication, all 4 were still taking vismodegib. One study patient with complete response was followed for 3 months. In another study patient, vismodegib was used as adjuvant therapy for involved surgical margins following surgery and in another study patient as neoadjuvant therapy prior to surgery. In both of these roles, tumor response was deemed to be complete during observation periods of 11 and 16 months, respectively. Adverse events were characterized as comparable in severity and frequency as those seen in earlier studies. Data from 1 patient in this series were also published in a separate report.

In a series of 13 study patients with high-risk BCC for whom vismodegib was used as neoadjuvant therapy prior to surgery, 2 tumors were located around the eye. One tumor with a surface area of 2.8 cm² had an 86% reduction in its size prior to surgery, and the resected tissue showed histological cure. The second tumor with a surface area of 2.0 cm² regressed 5% and, when resected, it was still histologically present.

Vismodegib has also been used as adjuvant therapy prior to radiotherapy in a man with recurrent BCC of the medial canthus and lower eyelid. After receiving 150 mg/day vismodegib for 2 months, cross-sectional measurements of his tumor decreased from 6.5 × 7.4 mm to 6.3 × 5.6 mm prior to radiotherapy. Following radiotherapy, he was deemed to be disease free at 12 months by magnetic resonance imaging.

Two other cases of periocular BCC treated with vismodegib have been reported because the study patients developed SCC (keratoacanthoma types) within 2 and 7 weeks of starting therapy. Both secondary cancers arose in previously documented normal skin. Meaningful clinical follow-up beyond the context of the new tumors was not provided.

A man aged 84 years with left upper eyelid and orbital BCC was treated with vismodegib and had complete response in 3 months; however, the tumor recurred and progressed after 9 months. Vismodegib was stopped at 18 months and orbital exenteration was performed the next month. The case was published as an example of secondary resistance.

A retrospective, interventional case series includ-
ed 10 study patients with locally advanced BCC, 4 of whom had metastatic disease. Of the 6 study patients without metastasis, 2 had a complete response. Five would have needed exenteration but instead avoided surgery with vismodegib treatment, although, at the time of reporting, the follow-up period was short (or none at all) after stopping vismodegib. One study patient died of progressive disease. The profile of reported adverse events was similar to that previously described.

It is worth noting that, of the 30 cases of advanced eyelid and periorcular BCC treated with vismodegib to date, the average follow-up period after stopping vismodegib is 4.8 months (see Table 1).
Inoperable and Locally Advanced Disease

The role that vismodegib might play in the clinical treatment of inoperable and locally advanced BCC depends on the perception of what these terms actually mean. Because these conditions have no consensus definition, a panel sponsored by Roche (Basel, Switzerland) of oncologists, dermatologists, and radiation oncologists helped to establish the guidelines for these terms. Although the panel addressed the management of periocular BCC, no member of the group was an ocular oncologist or oculoplastic surgeon.

The proposed guidelines of inoperability for use of vismodegib was based on the tumor, node, and metastasis staging classification of the American Joint Committee of Cancer for eyelid carcinoma (Table 2). Consensus was defined as majority opinion of the 9-member panel. Tumors greater than 2 cm in size that do not invade adjacent ocular or orbital structures (T3a) should be first considered for radiotherapy. The panel also recommended that eyelid tumors of stages T3a (invasive), T3b, and T4 not appropriate for radical local therapy be assessed for possible systemic therapy with vismodegib. The panel also noted that additional factors must be considered in determining the suitability of medical therapy, including general medical health, severe disfigurement, and loss of function. However, the panel’s recommendations were not ideal because guidelines for inoperable tumors defer to a judgment of what constitutes “not appropriate for radical local therapy.”

Any guidelines recommending vismodegib as an alternative therapy to surgery must weigh the limited knowledge of vismodegib against its long-term outcomes. For example, locally advanced BCC involving the orbit would require surgical exenteration (stage T3b) for cure. In an otherwise healthy patient, this surgery should confer long-term, tumor-free survival, albeit with a significant cosmetic cost. However, medical treatment with vismodegib offers an approximately 30% likelihood of complete response and an unknown risk of recurrence beyond 1 year. In addition, the long-term behavior of regressed BCC once vismodegib is discontinued is unknown.

Other Observations

Four cases of secondary SCC were reported among the 19 patients treated for periocular BCC. Rapidly growing SCC has also been observed in persons receiving treatment with vismodegib for BCC located elsewhere. Some types of BCC do not respond to vismodegib, and some of these failures may reflect mutational resistance, which is a new area of investigation likely to gain momentum during the postmarketing period. At least 1 case of periocular BCC with secondary resistance has been described. Novel compounds that overcome vismodegib resistance in vitro are under development for clinical use.

Information is limited about the drug–drug interactions of vismodegib, and the safety of vismodegib in persons with renal and hepatic dysfunction is unknown. A man aged 72 years treated with vismodegib developed cholestatic hepatic dysfunction 1 month after beginning treatment. The patient self-medicated with aspirin and naproxen because of vismodegib-related myalgias, suggesting a drug interaction may have been involved.

Ventarola and Silverstein searched the FDA Adverse Events Reporting System from January 2012 through January 2013 for cases of vismodegib hepatic toxicity, and they found 65 cases of vismodegib-associated reactions, the most frequent of which was gastrointestinal distress (34%) followed by liver toxicity (23%). In 4 cases, vismodegib was considered the sole agent implicated in the hepatotoxic event. However, Ventarola and Silverstein

---

Table 2. — Tumor Staging for Carcinoma of the Eyelid

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumor cannot be assessed</td>
<td>—</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
<td>—</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor ≤ 5 mm in greatest dimension and Does not invade tarsus or margin of eyelid</td>
<td>Average horizontal length of adult eyelid: ~3 cm</td>
</tr>
<tr>
<td>T2a</td>
<td>Tumor &gt;5 mm but ≤10 mm in greatest dimension or Any tumor than invades tarsus or involves margin of eyelid</td>
<td>Average vertical length of upper tarsus: 10–12 mm Average vertical length of lower tarsus: ~4 mm</td>
</tr>
<tr>
<td>T2b</td>
<td>Tumor &gt;10 mm but ≤20 mm in greatest dimension or Any tumor that involves entire thickness of eyelid</td>
<td>—</td>
</tr>
<tr>
<td>T3a</td>
<td>Tumor &gt;20 mm in greatest dimension or Any tumor than invades adjacent ocular or orbital structures or Any tumor with perineural tumor invasion</td>
<td>Adjacent ocular structures include bulbar conjunctiva Anterior orbit begins at orbital septum</td>
</tr>
<tr>
<td>T3b</td>
<td>Complete resection of tumor requires enucleation, exenteration, or bone resection</td>
<td>Exenteration involves removal of orbital contents, including eye</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor unresectable due to extensive invasion of ocular, orbital, or craniofacial structures or brain</td>
<td>—</td>
</tr>
</tbody>
</table>

Adapted from Edge S, Byrd DR, Compton CC, et al, eds. AJCC Cancer Staging Manual. 7th ed. New York: Springer; 2010. Republished with permission of Springer; permission conveyed through Copyright Clearance Center, Inc.
stressed that inclusion in the FDA database does not mean the relationship is causal.

Cost
The cost of vismodegib will depend on factors such as geographical area and markup of intermediate providers.\(^{39,40}\) When made available, the cost of standard daily treatment in clinical studies has ranged from $7,500 to $9,000 per month.\(^{9,20}\) In a single case series of 12 study patients treated for periocular BCC, 2 (17%) discontinued treatment because of cost.\(^{15}\)

Alternative Therapies
Vismodegib was approved by the FDA and European Medicines Agency for the treatment of locally advanced and metastatic BCC without the benefit of a randomized clinical trial because locally advanced and metastatic BCC are uncommon and evidence of effective alternative therapies is lacking.\(^{2,4}\) Historically, patients may have been treated with agents like cisplatinum, which, although not curative, induce a transient reduction in tumor size.\(^{41,42}\) Some investigators have used cisplatinum as neoadjuvant therapy to reduce the tumor size of periocular BCC prior to surgery,\(^{41}\) whereas others have used cisplatinum/doxorubicin to treat advanced BCC around the eye with only short-term benefit.\(^{42,43}\) However, experience with these chemotherapeutic agents is limited in the setting of periocular BCC, and use of these agents has been associated with serious adverse events.\(^{41-44}\)

Treatment for Operable Disease
Although no study has examined use of vismodegib for operable BCC around eye, a phase 2 multicenter, open-label trial has studied its use at all skin sites.\(^{5}\) This nonrandomized trial studied 74 volunteers but was unable to achieve its predefined primary efficacy end point of histological clearance.\(^{6}\) In addition, of the 37 study patients deemed to have complete clinical regression (clearance), 12 (32%) had histological evidence of residual BCC.\(^{3}\) Thus, these results may influence the design of future clinical trials studying operable and inoperable tumors.

Conclusions
Vismodegib may be an important treatment option to patients with locally advanced basal cell carcinoma (BCC) around the eye. However, the exact role it will play has not been established. The reviewed literature suggests that many patients with locally advanced periocular BCC will completely or partially respond when treated with daily 150 mg vismodegib, but their duration of response is unknown because follow-up times have been for periods less than 10 months.

Use of vismodegib outside of a clinical trial has expanded to include the neoadjuvant settings for surgery and radiotherapy.\(^{7,8,10}\) However, because phase 2 studies of locally advanced and metastatic BCC are not placebo-controlled trials and follow-up has been limited, it is unclear whether vismodegib prolongs survival rates or whether it reduces serious rates of morbidity.\(^{45}\)

Given that most patients with locally advanced periocular BCC developed the condition over 5 to 15 years and that clinical follow-up after treatment is brief, judging the role that vismodegib might play in management may be premature.\(^{1}\) When vismodegib is used to shrink surgical margins, it is uncertain whether these margins will remain tumor free over time, particularly after the medication is discontinued. A report from the US Veterans Affairs concluded in 2013 that the net clinical benefit of vismodegib treatment was minimal and that its use had a low likelihood of benefit as well as a low risk of harm.\(^{4}\)

Vismodegib is not well tolerated in study patients: Approximately 40% are unable to continue therapy due to its adverse events.\(^{4}\) Reports of hepatotoxicity, particularly in persons taking other medications that may interact with vismodegib, have also been reported.\(^{6,37,38}\) More information is also needed on the safety of vismodegib in patients with renal and hepatic impairment. Whether any serious, long-term complications are associated with its use is unknown, and no evidence exists to suggest that vismodegib improves rates of survival.

Ever since vismodegib was first approved for clinical use, case reports and small clinical series have appeared in the literature. These studies suffer from short-term follow-up, lack of control groups, and potentially publication bias, because complications and therapeutic misadventures tend to be under-reported after drugs receive market approval.\(^{46}\) Before the therapeutic potential of vismodegib can be realized, larger studies with appropriate control populations and long-term follow-up periods are necessary.

References


