Vismodegib for Periocular and Orbital Basal Cell Carcinoma

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IMPORTANCE Basal cell carcinoma (BCC) represents 90% of malignant eyelid tumors and is locally invasive and destructive, if left untreated.

OBJECTIVE To assess the feasibility of using vismodegib for periocular and orbital BCC based on its efficacy and tolerability.

DESIGN, SETTING, AND PARTICIPANTS In this prospective observational case series, consecutive patients with periocular or orbital BCC who met criteria for treatment with vismodegib were recruited prospectively during an 8-month period from February through September 2012 from 2 academic hospitals. Seven patients received oral vismodegib, 150 mg daily, until maximum clinical response was achieved, the tumor progressed, or the patient could no longer tolerate adverse effects. Clinical response and adverse effects related to treatment were recorded. The primary endpoint was reduction in lesion size, measured as percentage change in the externally visible dimension.

EXPOSURE Oral vismodegib.

RESULTS All 7 patients had locally advanced, biopsy-proven, infiltrative BCC that was not amenable to surgical resection or radiation. No patients had metastatic disease at presentation. The mean patient age was 71 years (range, 43-100 years), and 4 patients (57%) had secondary orbital involvement. The mean lesion size was 3.4 cm (range, 1.0-6.0 cm), and all 7 cases (100%) represented recurrent tumors excised previously with controlled margins by frozen section or Mohs micrographic surgery. The mean treatment duration was 11 weeks (range, 4-16 weeks), and the mean duration of follow-up was 7.3 months (range, 5-10 months). Two patients (29%) demonstrated complete clinical regression, 2 (29%) demonstrated greater than 80% partial clinical regression, 2 (29%) demonstrated less than 35% partial clinical regression, and 1 (14%) progressed. Adverse reactions occurred in 6 patients (86%) and included alopecia (29%), dysgeusia (29%), muscle cramps (29%), and anorexia (14%). Two patients (29%) developed new squamous cell carcinomas (well-differentiated, keratoacanthoma type) at uninvolved sites including the eyebrow and forearm.

CONCLUSIONS AND RELEVANCE Vismodegib seems to be well-tolerated and effective for treating periorcular and orbital BCC in about half of all cases. Patients receiving treatment should be monitored for new squamous cell carcinomas at uninvolved sites.
Basal cell carcinoma (BCC) represents 90% of malignant eyelid tumors. Left untreated, BCC is locally invasive and destructive. Periocular lesions are typically managed surgically with margin control using Mohs micrographic surgery or frozen section analysis. Surgical resection with these approaches is curative for more than 90% of cases. However, patients with metastatic BCC or locally advanced disease that has recurred after surgery or who are not candidates for surgery or radiation pose a therapeutic challenge. In January 2012, the US Food and Drug Administration approved vismodegib (Erivedge TM, GDC-0449, Genentech) for these indications. Approval was based on the results of a nonrandomized phase 2 parallel cohort study of 99 patients with advanced BCC. Vismodegib is the first molecularly targeted therapy for BCC. The agent is orally bioavailable and selectively and potently inhibits the Hedgehog signaling pathway. Although this pathway is crucial for cellular differentiation during fetal development, its subsequent activity in the body is limited and tightly controlled. Most patients with BCC have dysregulated, abnormal Hedgehog signaling in isolated tumors and as part of the basal cell nevus syndrome. The purpose of our pilot study was to determine the tumor response rate and tolerability of vismodegib for periocular and orbital BCC. To our knowledge, this is the first report of vismodegib used in this patient population.

Methods

The study was performed in accordance with the Declaration of Helsinki. Written informed consent from patients was obtained; no specific institutional review board approval was obtained because these few cases were pooled from multiple institutions. Patients were recruited from the practices of 2 oculofacial surgeons and 2 dermatologists. All consecutive patients who met the Food and Drug Administration criteria for treatment with vismodegib (metastatic or locally advanced BCC not amenable to other treatment) were invited to participate and recruited prospectively during an 8-month period from February through September 2012. Recruited patients could not be treated surgically (by a large resection or orbital exenteration) owing to systemic comorbidities. Radiation treatment was not an option for recruited patients because of the cumulative dose required, patient preference, or a combination thereof. Exclusion criteria included major organ dysfunction, pregnancy or lactation, life expectancy less than 3 months, uncontrolled medical illness, and an inability to swallow capsules. Seven patients with locally advanced, recurrent, periorcular BCC were prospectively enrolled in the study. Patients were followed up weekly over the treatment period and then at variable intervals ranging from 2 to 4 weeks. Each patient received oral vismodegib, 150 mg daily, until the maximum clinical response was achieved, the tumor progressed, or the patient elected to stop treatment for any reason (ie, adverse effects). Patient demographics and medical history, lesion size at presentation and last follow-up, orbital involvement, duration of treatment and follow-up, and adverse drug reactions were recorded. The clinical response was presented as the percentage change in the longest dimension of the externally visible lesion. The presence of ulceration pretreatment and posttreatment was noted separately. A complete response was defined as no clinical evidence of a lesion after treatment. Partial responses were quantified based on the percentage change from baseline at last follow-up. Progression was defined as any increase in lesion size at any point during follow-up.

Results

All 7 patients had biopsy-proven infiltrative BCC of the periorcular region. The lesions represented recurrent, locally advanced cases not amenable to surgical resection or radiation. No patients had evidence of metastatic disease at presentation. The Table summarizes demographic data, treatment response, and adverse reactions. The mean patient age was 71

<table>
<thead>
<tr>
<th>Case</th>
<th>Age, y</th>
<th>Sex</th>
<th>Race/Ethnicity</th>
<th>Site of Involvement</th>
<th>Orbital Extension</th>
<th>Lesion Size Pretreatment, cm</th>
<th>Prior Treatment</th>
<th>Recurrences, No.</th>
<th>Duration of Treatment, wk</th>
<th>Duration of Follow-up, mo</th>
<th>Treatment Response</th>
<th>Adverse Reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>53</td>
<td>Male</td>
<td>White</td>
<td>LUL, brow</td>
<td>No</td>
<td>1.0</td>
<td>4 excisions (with FS)</td>
<td>4</td>
<td>7</td>
<td>8</td>
<td>Complete</td>
<td>Developed new SCC</td>
</tr>
<tr>
<td>2a</td>
<td>75</td>
<td>Female</td>
<td>White</td>
<td>LUL, brow</td>
<td>Yes</td>
<td>4.0</td>
<td>1 excision (with MMS)</td>
<td>1</td>
<td>16</td>
<td>8</td>
<td>Progression</td>
<td>Alopecia, dysgeusia, muscle cramps</td>
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<td>3</td>
<td>43</td>
<td>Male</td>
<td>Latino</td>
<td>RLL</td>
<td>No</td>
<td>1.5</td>
<td>3 excisions (with FS)</td>
<td>1</td>
<td>4</td>
<td>10</td>
<td>Complete</td>
<td>Alopecia</td>
</tr>
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<td>4</td>
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<td>Male</td>
<td>White</td>
<td>Left lateral canthus</td>
<td>Yes</td>
<td>2.0</td>
<td>1 excision (with FS)</td>
<td>3</td>
<td>16</td>
<td>8</td>
<td>Partial (-15%)</td>
<td>Dysgeusia, muscle cramps</td>
</tr>
<tr>
<td>5a</td>
<td>101</td>
<td>Female</td>
<td>White</td>
<td>RLL</td>
<td>Yes</td>
<td>5.5</td>
<td>1 excision (with FS)</td>
<td>1</td>
<td>16</td>
<td>5</td>
<td>Partial (-90%)</td>
<td>Developed new SCC</td>
</tr>
<tr>
<td>6</td>
<td>91</td>
<td>Male</td>
<td>White</td>
<td>LLL</td>
<td>Yes</td>
<td>6.0</td>
<td>1 excision (with FS)</td>
<td>1</td>
<td>9</td>
<td>6</td>
<td>Partial (-80%)</td>
<td>None</td>
</tr>
<tr>
<td>7</td>
<td>60</td>
<td>Male</td>
<td>White</td>
<td>LLL</td>
<td>Yes</td>
<td>3.5</td>
<td>1 excision (with FS)</td>
<td>1</td>
<td>10</td>
<td>6</td>
<td>Partial (-35%)</td>
<td>Anorexia</td>
</tr>
</tbody>
</table>

Abbreviations: FS, frozen section; LUL, left upper lid; LLL, left lower lid; MMS, Mohs micrographic surgery; RLL, right lower lid; SCC, squamous cell carcinoma.

*These cases were part of an Expanded Access study sponsored by Genentech (NCT1160250) and were not previously published.
years (range, 43-100 years), and 4 patients (57%) had secondary orbital involvement. The mean lesion size was 3.4 cm (range, 1.0-6.0 cm), and all 7 cases (100%) represented recurrent tumors excised previously with controlled margins by frozen section or Mohs micrographic surgery. The mean treatment duration was 11 weeks (range, 4-16 weeks), and the mean duration of follow-up was 7.3 months (range, 5-10 months). During follow-up, 2 patients (29%) demonstrated complete clinical regression, 2 (29%) demonstrated greater than 80% partial clinical regression, 2 (29%) demonstrated less than 35% partial clinical regression, and 1 (14%) progressed. Of the 4 cases with orbital extension, 3 demonstrated a partial response to treatment. Each of these cases exhibited significant tumor shrinkage on neuroimaging. All 7 patients had evidence of ulceration prior to treatment, which resolved in all except 2 patients (cases 2 and 4). The response to treatment was maintained during follow-up for all cases. The Figure illustrates the treatment effect in 1 patient (case 5). Adverse reactions occurred in 6 patients (86%) and included alopecia (29%), dysgeusia (29%), muscle cramps (29%), and anorexia (14%). Two patients (29%) developed new squamous cell carcinomas (well-differentiated, keratoacanthoma type) at uninvolved sites including the eyebrow and forearm. During follow-up, there were no cases of disease-related or treatment-related mortality.

Discussion

Surgical resection of BCC is usually curative, although no effective treatment exists for locally advanced or metastatic disease. Large or infiltrative lesions are associated with high rates of recurrence and can result in significant disfigurement, loss of vision, and mortality. Vismodegib offers a novel therapeutic alternative in advanced presentations of BCC. Molecular and genetic studies have shown that abnormal signaling of the Hedgehog pathway results in uncontrollable proliferation of basal cells.9 This pathway is normally inhibited by patched homologue 1 (PTCH1).10 However, when PTCH1 is deficient, a transmembrane protein called Smoothened (SMO) activates the Hedgehog pathway through downstream activation of GLI1.9 The clinical manifestations of PTCH1 loss of function and increased Hedgehog signaling are development and progression of BCC. Vismodegib selectively binds to the extracellular domain of SMO, thereby preventing downstream signaling. In 2000, cyclopamine was reported as the first small molecular inhibitor of the Hedgehog pathway.11 Subsequent research focused on developing derivatives of this naturally occurring compound. Vismodegib is structurally unrelated to cyclopamine but binds SMO with high affinity. The oral dosing regimen of 150 mg daily was based on pharmacokinetic properties.12 Our prospective case series of 7 patients with periocular BCC treated with vismodegib resulted in greater than 80% tumor shrinkage in 5 patients (71%) that was maintained during a mean follow-up of 7.3 months. There were 2 cases with 100% clinical response, 1 case of tumor progression, and 5 cases with a variable partial response to treatment. Although the 1 case that progressed presented with orbital involvement, the other 3 orbital cases had a partial response rate varying between 15% and 90%, suggesting that orbital involvement does not seem to predict treatment effect.

An important limitation of our study was that patients with orbital involvement did not undergo a standardized volumetric analysis of the orbital component of the lesion from neuroimaging before and after treatment. This was because of the variability in imaging modalities used between patients because some presented with scans from outside hospitals and did not wish to undergo reimaging. However, after reviewing the posttreatment images, the orbital tumor size seemed to correlate directly with a decrease in proportion to the externally visible lesion. A second limitation of our study was that treated lesions were not rebiopsied for histological correlation with the clinical response. Adverse reactions occurred in 86% of patients, but these were tolerable and no patients elected to stop therapy prematurely. Interestingly, 2 patients (29%) developed new lesions during treatment that were squamous cell carcinoma (keratoacanthoma-type) at uninvolved sites (one affecting the noncontiguous eyebrow and the other the fore-
arm). These cases were published in a separate report.\textsuperscript{23} We found no prior reports of vismodegib association with squamous cell cancers. However, the occurrence of precancerous or malignant skin tumors, such as keratoacanthoma or keratoacanthoma-like squamous cell carcinomas, has been reported with anticancer agents, such as sorafenib, possibly via activation of the MAP-kinase pathway within the skin.\textsuperscript{14} A clear biological explanation is currently unknown. The phase 1 trial of vismodegib for 33 patients with advanced BCC resulted in a 58% response rate over 12.8 months.\textsuperscript{15} The phase 2 trial (Erivance BCC) was an international, multicenter, 2-cohort, non-comparative study in which patients with locally advanced (\(n = 63\)) or metastatic (\(n = 33\)) BCC had a median duration of response of 7.6 months and median progression-free survival of 9.5 months.\textsuperscript{8} The response rate in the locally advanced disease cohort was 43% (95% CI, 31-56; \(P < .001\)), with complete responses in 13 patients (21%). The response rate in the metastatic BCC cohort was 30% (95% CI, 16-48; \(P = .001\)).

Adverse reactions to vismodegib occurred in 30% of patients and included muscle spasms, alopecia, dysgeusia, weight loss, and fatigue. The median duration of treatment was 10 months in both cohorts, and 12% of patients had an adverse reaction leading to discontinuation (muscle spasms were the most common). Seven deaths occurred during follow-up but were not believed to be drug related. Tang et al\textsuperscript{16} performed a randomized, double-blind, placebo-controlled trial in patients with basal cell nevus syndrome treated by vismodegib and the primary end point was reduction in the incidence of new BCCs that required surgical resection. Basal cell nevus syndrome is caused by a germline inactivating mutation of 1 copy of the \(PTCH1\) gene and, if the second allele is inactivated, tumorogenesis occurs. They found that vismodegib reduced the incidence of new lesions but that more than half of all patients discontinued treatment owing to intolerable adverse effects.

We found that vismodegib offers a relatively safe therapeutic alternative for patients with locally advanced periorbital BCC that is not amenable to surgery or radiation. More than half of all patients demonstrate a significant clinical response, which is sustained for at least 6 months. There are growing concerns of acquired resistance to vismodegib secondary to tumor-specific mutations,\textsuperscript{17} so long-term follow-up studies are necessary. In this new era of molecular medicine, vismodegib offers a promising alternative to destructive surgery or radiation for aggressive BCCs of the periorbital region. Patients in our study were not required to pay for treatment. The average cost may be in the range of $7500 per month or $75 000 for a typical 10-month treatment course, according to Genentech. However, the cost of the medication has been heavily subsidized by Genentech.

In conclusion, vismodegib seems to be well-tolerated and effective for treating periorbital and orbital BCC in about half of all cases. Patients receiving treatment should be counseled about common adverse reactions and monitored for new squamous cell carcinomas at uninvolved sites.