Hedgehog Pathway Inhibition for Locally Advanced Periocular Basal Cell Carcinoma and Basal Cell Nevus Syndrome

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• PURPOSE: To review our experience treating patients with the Hedgehog pathway inhibitor, vismodegib, in patients with orbital or periocular locally advanced or metastatic basal cell carcinoma (BCC) or basal cell nevus syndrome.

• DESIGN: Retrospective interventional case series.

• METHODS: We reviewed all patients with locally advanced or metastatic orbital or periocular BCC or basal cell nevus syndrome treated with the Hedgehog pathway inhibitor, vismodegib, at a comprehensive cancer center from 2009 through 2015. Reviewed data included age; sex; American Joint Commission on Cancer tumor, node, metastasis staging system designation; type and grade of drug-related side effects; response to treatment; duration of follow-up, and status at last follow-up.

• RESULTS: The study included 10 white men and 2 white women; the median age was 64.5 years. Ten patients had locally advanced BCC; 2 had basal cell nevus syndrome. Among the patients with locally advanced BCC, 5 had T3bN0M0 disease at presentation; 1 each had T3aN0M0, T3bN1M0, T2N1M1, T4N1M1, and T4N2cM1 disease. Overall, 3 patients had a complete response, 6 had a partial response, and 3 had stable disease at last follow-up. Two patients developed progressive disease after a complete response for 38 months and stable disease for 16 months, respectively. All patients developed grade I drug-related adverse effects, most commonly muscle spasms (12 patients), weight loss (10), dysgeusia (9), alopecia (9), decreased appetite (5), and fatigue (4). Five patients developed grade II adverse effects. At last follow-up, none of the 5 patients presenting with T3bN0M0, nor the patient with T3bN1M0 disease, had required orbital exenteration.

• CONCLUSION: Hedgehog pathway inhibition produces a significant clinical response in most patients with locally advanced or metastatic orbital or periocular BCC or basal cell nevus syndrome and can obviate orbital exenteration in some patients. Drug-related adverse effects are manageable in most patients. (Am J Ophthalmol 2015;160(2):220–227. © 2015 by Elsevier Inc. All rights reserved.)

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BASAL CELL CARCINOMA (BCC) IS THE MOST COMmon human malignancy and accounts for 90% of eyelid tumors.[1–3] Fortunately, periocular and facial BCC are typically amenable to local surgical excision, with 5-year recurrence rates of 1%–5.3%.[1,3,4] For advanced periocular BCC—that is, characterized by large tumor size, multiple lesions, or recurrent disease with extension into the orbit or paranasal sinuses—surgical treatment may not be possible without risk of significant ocular morbidity or loss of the eye. A related group of patients who may not be good candidates for surgery are patients with basal cell nevus syndrome (Gorlin syndrome) with numerous BCCs in the periocular region. Additionally, patients with periocular BCC with advanced age or multiple medical comorbidities may not be good candidates for surgery.

The discovery of underlying genetic mutations of the Hedgehog pathway in BCC has allowed for the emergence of targeted medical therapy for advanced, inoperable cases of BCC or in cases that would result in high morbidity with surgery.[5–9] The Hedgehog pathway includes the Patched-1 transmembrane receptor (Ptch-1), a tumor suppressor that normally inhibits the downstream receptor Smoothened (Smo).[7,10,11] A mutation in the Hedgehog pathway may lead to Hedgehog protein binding to Ptch-1 and reversal of the normal inhibition of Smo, leading to cellular proliferation and tumorigenesis, as well as expression of the downstream product GLI1, which is thought to lead to the formation of BCC.[7,12,13] Ptch-1 also plays a role in basal cell nevus syndrome, which is secondary to an autosomal-dominant mutation in the *PTCH1* gene.[9,11,14] Vismodegib (Erivedge; Genentech, South San Francisco, California, USA; GDC-0449) is a selective Hedgehog pathway inhibitor that blocks Hedgehog signaling by binding to Smo, inhibiting downstream activation of Hedgehog target genes.[15,16] Vismodegib was first studied in humans in 2008 and was approved by the US Food and Drug Administration in January 2012 for treatment of

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TABLE 1. Grade Definitions Per the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0,[22] Used to Grade the Severity of Adverse Events in a Series of Patients With Locally Advanced or Metastatic Orbital or Periocular Basal Cell Carcinoma and Basal Cell Nevus Syndrome

Grade	Severity
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death related to adverse effects

TABLE 2. Response Definitions Per the Response Evaluation Criteria in Solid Tumors, Version 1.1,[23] Used to Classify Responses to Vismodegib in a Series of Patients With Locally Advanced or Metastatic Orbital or Periocular Basal Cell Carcinoma and Basal Cell Nevus Syndrome

Response	Definition
Complete response	Disappearance of all target lesions. Any lymph nodes containing disease must have reduction in short axis to <10 mm
Partial response	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters
Progressive disease	At least a 20% increase in the sum of diameters of target lesions with an absolute increase of at least 5 mm, or the appearance of 1 or more new lesions
Stable disease	Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, taking the smallest sum of diameters as reference

metastatic or locally advanced unresectable BCC. Few studies have shown the response to treatment with Hedgehog pathway inhibition with long-term follow-up.

Targeting the Hedgehog pathway in patients with locally advanced periocular and orbital BCC is of particular interest, since successful nonsurgical treatment could mean avoidance of radical and disfiguring surgery in the periorbital region and, in some instances, orbital exenteration. To date, however, reports of Hedgehog pathway inhibition in patients with orbital or periocular lesions have been limited to single case reports or small case series.[7–9,17–20] There is room for reporting of additional experience in this particular patient population. We herein report our clinical experience with Hedgehog pathway inhibition in patients with locally advanced or metastatic orbital or periocular BCC and in patients with basal cell nevus syndrome and significant periocular lesions.

PATIENTS AND METHODS

THE INSTITUTIONAL REVIEW BOARD OF THE UNIVERSITY OF Texas MD Anderson Cancer Center retrospectively approved this study. The study was performed in accordance with HIPAA regulations. For this retrospective interventional case series, we performed a retrospective chart review of all consecutive eligible patients treated for locally advanced or metastatic periocular basal cell carcinoma and basal cell nevus syndrome with Hedgehog pathway inhibition from November 1, 2009 through September 30, 2014. All patients were at least 18 years of age.

Data recorded for this analysis included age; race/ethnicity; sex; site(s) of primary tumor involvement; size of tumor; presence of orbital extension; sites of regional or distant metastasis; tumor, node, metastasis staging system (TNM) designation at presentation according to American Joint Committee on Cancer (AJCC) criteria; type and grade of drug-related adverse effects according to Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 (Table 1); response to treatment according to Response Evaluation Criteria in Solid Tumors (RECIST) (Table 2); duration of follow-up; and status at last follow-up.[21–23]

RESULTS

WE IDENTIFIED 13 PATIENTS WHO MET THE INCLUSION criteria. However, 1 patient with locally advanced BCC was ultimately not included in the data analysis because of a hypersensitivity reaction to vismodegib that led to its discontinuation only 5 days after initiation of treatment. This patient had an orbital exenteration.

The remaining patients, 10 men and 2 women, were included in this study. All patients were white with a median age of 64.5 years (range, 33–86 years). Tumors were staged according to the AJCC, 7th edition TNM criteria using clinical, pathologic, and radiographic data as part of each patient's standard clinical management.[21] In each case, the decision to start treatment with Hedgehog pathway inhibition was made with input from the senior treating oculoplastic surgeon (B.E.) and input from the Radiation Oncology service to ensure that radiation was not an option. Patients with BCC were treated with Hedgehog pathway inhibition only if it was believed that complete surgical excision of the locally advanced