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Efficacy of Vismodegib (Erivedge™) For Basal Cell Carcinoma Involving the Orbit and Periocular Area

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Abstract

Purpose—Evaluate the effectiveness of vismodegib in the management of basal cell carcinoma with orbital extension and/or extensive periocular involvement.

Methods—Retrospective chart review of six consecutive patients with biopsy-proven orbital basal cell carcinoma and two additional patients with extensive periocular basal cell carcinoma who were treated with oral vismodegib (150 mg/day).

Results—Basal cell carcinoma extended into the orbit in 6 of 8 patients (involving orbital bones in 1 patient), and 2 of 8 patients had extensive periocular involvement (one with basal cell nevus syndrome). Vismodegib therapy was the only treatment in 6 patients, off-label neoadjuvant in 1 patient and adjuvant treatment in 1 patient. Orbital tumors in all 4 patients who received vismodegib as sole treatment showed partial response with a mean 83% shrinkage in tumor size after a median of 7 months of therapy. In the 2 patients receiving vismodegib as neo-adjuvant or adjuvant therapies there was complete response after a median of 7 months of therapy and no evidence of clinical recurrence after discontinuing therapy for a median of 15 months. The 2 patients with extensive periocular involvement experienced complete clinical response after a median 14 months of treatment. During treatment, the most common side effect was muscle spasm (75%) followed by alopecia (50%), dysgeusia (25%), dysosmia, and episodes of diarrhea and constipation (13%).

Conclusions—Basal cell carcinoma with orbital extension and extensive periocular involvement responds to vismodegib therapy. The long-term prognosis remains unknown, and additional prospective studies are indicated.

Keywords

Eye; Eyelid; Orbit; Periocular; Cancer; Basal Cell Carcinoma; Vismodegib; Hedgehog; Erivedge; Mohs; adjuvant; neo-adjuvant

INTRODUCTION

Basal cell carcinoma is the most common eyelid tumor. Orbital or extensive periocular involvement occurs in less than 5% of cases in developed countries.^{1,2} However, in developing countries, up to 17% of patients are reported to show orbital involvement.³ Management options for basal cell carcinoma are primarily surgical, including both Mohs micrographic surgery and wide surgical excision with margin control. In the majority of well-localized, periocular tumors, these surgical approaches can eliminate the primary tumor over 95% of cases while achieving good functional and cosmetic outcomes. Surgery for cases with orbital or extensive periocular involvement usually requires large excisions that can deform the face and compromise visual function, occasionally even requiring orbital exenteration. In these cases, adjuvant radiotherapy has been an option, although results are mixed.

Vismodegib (Erivedge™) is a recently FDA-approved, oral Hedgehog signaling pathway inhibitor that provides a new treatment option for locally aggressive or metastatic basal cell carcinoma. In a multicenter, phase II study, Sekulic et al.⁴ reported complete clinical response to vismodegib therapy in 21% and partial response in 22% of 63 locally advanced basal-cell carcinomas and in 30% of 33 metastatic basal cell carcinomas. Among patients with basal cell nevus syndrome, vismodegib significantly reduced the development of new basal cell carcinomas and the size of existing tumors.⁵ In the periocular and orbital area, vismodegib has been used as a medical or adjuvant therapy to decrease the tumor size, in the latter case to render it amenable to globe-sparing excision.⁶⁻⁸ In this report, we analyze our results in using vismodegib for the treatment of basal cell carcinoma with orbital extension and/or extensive periocular involvement.

METHODS

Medical record review was performed for all consecutive patients with basal cell carcinoma with orbital extension and extensive periocular basal cell carcinoma treated with oral vismodegib (Erivedge™) in the Department of Ophthalmology and Visual Sciences at the W.K. Kellogg Eye Center, University of Michigan, from March, 2012 to October, 2013. The Institutional Review Board at the University of Michigan approved this study, and it is in compliance with HIPAA regulations.

The patient data collected at initial evaluation included age, sex and race. All patients underwent detailed external examination, slit lamp bio-microscopy, and fundus examination. Duration (months) and frequency of oral vismodegib therapy were noted. At presentation and each follow-up, the site of periocular involvement (upper eyelid, lower eyelid, medial canthus, lateral canthus, eyebrow, cheek and forehead) was recorded. The orbital involvement was evaluated with either computed tomography (CT) or magnetic resonance imaging (MRI) at presentation and at 3 to 4 months intervals thereafter. Vismodegib treatment was considered if surgical morbidity was considered to be substantial (deformity, vision loss, diplopia, loss of eye/vital orbital structures, etc.). Following an oncologic evaluation, patients were prescribed oral vismodegib 150 mg daily, and followed regularly. The clinical response was evaluated as percent change in the longest dimension for the

periocular tumors and in volume for orbital tumors, calculated using measured dimensions on CT or MRI. Partial clinical response was defined as at least 40% decrease in tumor size on clinical and/or radiological evaluation. Complete clinical response was described as complete regression of basal cell carcinoma on clinical and radiologic evaluation. Stable disease was described as no change in size or less than 40% decrease in tumor size on clinical and radiologic evaluation.

RESULTS

Oral vismodegib therapy was used in 2 cases with extensive periocular basal cell carcinoma and in 6 cases with orbital involvement. One of two cases with extensive periocular basal cell carcinoma had basal cell nevus syndrome. The clinical details of eight cases are presented in table 1. The mean age of our cases was 71 years (median 69 years, range 60 – 86 years). Six cases were men and two were women. All 8 cases had previous history of multiple, extensive surgeries for recurrent basal cell carcinoma. The median of treatment duration was 8 months (mean 9 months, range 5 to 18 months). Two cases received vismodegib medical therapy for 5 months: One case passed away at the fifth month of medical treatment due to an unrelated cardiac condition, and the other case could not tolerate the medication side effects and elected to undergo excision of the regressed tumor (Case 5). The case with basal cell nevus syndrome continued her systemic treatment for 18 months without any significant systemic side effects and complete response (Case 8). Of 8 cases, 4 (50%) showed a partial response and 4 (50%) showed a complete response after a median follow-up 13 months (mean 13 months, range 5 – 21 months). Two cases with extensive periocular basal cell carcinoma showed complete clinical response and were without evidence of recurrence 12 months after completing vismodegib medical therapy (Case 7) or without evidence of disease after 18 months of therapy in the case of basal cell nevus syndrome (Case 8). In the 6 orbital cases, the best response was obtained in 2 patients in whom vismodegib was used as an off-label neoadjuvant therapy before surgery (Case 5) or an off-label adjuvant therapy for residual microscopic disease after surgery (Case 6), with no evidence of tumor recurrence at 21 and 19 month follow-up, respectively. The other 4 orbital cases for whom medical treatment with vismodegib was used as sole therapy only achieved partial response ranging from 80% to 95% tumor mass reduction. The most common side effect were muscle spasms (6 cases), alopecia (4 cases), dysgeusia (2 cases) and dysosmia (2 cases). A 1 – 2 week “drug holiday” was given because of muscle spasms in 2 cases and diarrhea/constipation in 1 case.

DISCUSSION

In this study, we report on 8 consecutive patients with advanced periocular or basal cell carcinoma who were treated with the anti-hedgehog drug vismodegib. All patients with orbital extension of advanced basal cell carcinoma showed response to vismodegib therapy. None of these patients showed progression during follow-up, which ranged from 5 to 21 months. However, complete responses occurred only in two patients, both of whom had surgical excision either before or after vismodegib treatment. In one case, globe-sparing surgical excision was performed after severe muscle spasms complicated an otherwise an excellent tumor response, which served as a de facto neo-adjuvant treatment.⁸ In another

case, a complete response was obtained after vismodegib was used following an incomplete excision. In both cases, there was no tumor recurrences after 21 and 19 months of follow-up, respectively. Our experience with neo-adjuvant use of vismodegib was further supported by another report in which basal cell carcinoma infiltrating spinal column was reduced by the drug and eliminated with radiation therapy.¹⁸

The Hedgehog signal transduction pathway plays an important role in cell proliferation and survival, through regulation of gene expression.^{9–13} Following the initial discovery of loss-of-function mutations in the *PTCH1* gene in basal cell nevus syndrome, all basal cell carcinomas have been found to have gene mutations in the Hedgehog signaling pathway and to have elevated *PTCH1* and *GLI1* mRNA levels.^{14–16} Vismodegib suppresses the Hedgehog pathway by directly inhibiting SMO, bypassing the need for normal-functioning *PTCH1*. In 2 multicentered, phase II studies, tumor responded vismodegib therapy in 43% and 46% of patients with locally advanced basal cell carcinoma, and in 31% of patients with metastatic disease, with complete response rate in 21% of patients.^{4,17} Moreover, vismodegib therapy blocked tumor growth in half of the patients who did not show tumor shrinkage.¹⁷ Vismodegib was also reported as effective in managing periocular advanced basal cell carcinoma in a case report⁶ and small series of patients.⁷ Yin et al.⁶ reported a 30-year-old man with basal cell nevus syndrome who was treated for extensive medial canthal basal cell carcinoma which resolved after 12 weeks of therapy and did not recur for additional 80 weeks. After a mean follow-up of 7 months, Gill et al.⁷ found 2 complete response (29%), 4 partial responses (57%) and 1 progression (14%) in a group of 7 periocular, locally advanced basal cell carcinomas.

There is limited published information about re-growth of basal cell carcinoma after discontinuation of vismodegib therapy. In an animal study, Hutchin et al.¹⁹ demonstrated that vismodegib treatment left a small subset of non-proliferative tumor cells that could proliferate after the drug was discontinued. This contrasts with other animal models in which oncogene silencing rather than pathway inhibition leads to complete regression.^{20,21} In a clinical study, Chang and Oro²² reported tumor regrowth in 5% of all basal cell carcinomas following discontinuation of vismodegib therapy for a mean of 56 weeks. Tumor regrowth in a subset of patients following discontinuation of vismodegib suggests that subsets of tumor cells that regrow might have reduced sensitivity to the drug, enhanced anti-apoptotic pathways, or subject to reduced host immune response.

Sekulick et al.⁴ reported that 16% of patients with locally advanced basal cell carcinoma discontinue vismodegib due to unbearable side effects. These include muscle spasms, alopecia, dysgeusia, dysosmia, weight loss, fatigue/malaise, nausea, decreased appetite, and diarrhea.⁴ Some of these side effects are related to the role of Hedgehog signaling pathway in hair renewal and taste bud maintenance.²³ However, the underlying mechanisms of muscle spasm or diarrhea are unknown. Recent reports describe keratoacanthoma and squamous cell carcinoma following vismodegib therapy for basal cell carcinoma.^{24, 25}

In summary, vismodegib, an oral Hedgehog pathway inhibitor, appears to be effective for the treatment of orbital and periocular basal cell carcinoma. The optimal treatment protocol and duration, and long term follow-up results following cessation of therapy, are still

unknown. Additional studies, including prospective trials, will be necessary to fully evaluate the utility of this novel treatment approach.

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Table 1

Case	Age/Sex/ Race	Duration of basal cell carcinoma history (years)	Involved Side	Location of basal cell carcinoma	Orbit involvement	TNM classification	Systemic disease	Type of therapy	Duration of therapy (months)	Follow- up * (months)	Response	Complications
1	60/M/W	20	Left	Orbit, zygomatic, frontal and sphenoid bones	Yes (diffuse)	T4N0M0	None	Medical	5	5	Partial	Mild alopecia
2	79/M/W	7	Left	Nasal upper and lower eyelids, medial canthal area and orbit	Yes (medial)	T3bN0M0	None	Medical	13	13	Partial	None
3	63/F/W	7	Left	Nasal left lower and upper eyelid, medial canthus, and orbit	Yes (antero-medial)	T3bN0M0	None	Medical	7	7	Partial	Mild dysgeusia, muscle spasms
4	86/M/W	7	Right	Medial canthus, and orbit	Yes (medial)	T3bN0M0	None	Medical	7	7	Partial	Mild muscle spasms
5	79/M/W	10	Left	Lower eyelid, cheek, medial canthus, and orbit	Yes (medial)	T3bN0M0	None	Neo-adjuvant to decrease the tumor size before surgery	5	21	Complete	Severe muscle spasms, episodes of diarrhea and constipation
6	60/M/W	11	Right	Nasal upper eyelid, medial canthal area, and orbit	Yes (supero-nasal)	T3bN0M0	None	Adjuvant for post-surgical positive margins	8	19	Complete	Severe muscle spasms, alopecia, dysosmia
7	73/M/W	30	Left	Lower lid, cheek, and upper lip	No	T3aN0M0	None	Medical	9	12	Complete	Mild dysgeusia and dysosmia. muscle spasms and alopecia
8	65/F/W	50	Bilateral	Forehead, eyebrows and bilateral lower eyelids	No	T3aN0M0	Basal cell nevus syndrome	Medical	18	18	Complete	Mild muscle spasms, alopecia, tinnitus, rhinorrhea

* Since the beginning of treatment