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Ophthalmic Technology Assessment

Oral Hedgehog Inhibitor, Vismodegib, for Locally Advanced Periorbital and Orbital Basal Cell Carcinoma

A Report by the American Academy of Ophthalmology

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Purpose: To review the efficacy and safety of oral vismodegib (Erivedge; Genentech) in the management of locally advanced orbital and periorbital basal cell carcinoma (BCC).

Methods: A literature search was conducted last in September 2023 in the PubMed database for English language original research that evaluated the effect of oral vismodegib on orbital and periorbital BCC. Sixty articles were identified and 16 met the inclusion criteria.

Results: Most studies demonstrated high response rates, with up to 100% of patients responding to the medication in individual studies and initial complete regression occurring in up to 88% of patients. Vismodegib treatment resulted in significant reductions in tumor volume, resulting in globe preservation for most patients. However, in 12% of patients, the response was partial. Recurrences also occurred with substantial frequency, even after an initial complete response. As such, up to 79.4% of patients required surgical intervention, and up to 23% of patients still required exenteration. Use of these agents resulted in reductions in tumor volume that may delay or prevent the need for exenteration in some, but not all, patients. Importantly, molecular analysis of tissue excised after vismodegib therapy revealed persistent tumor in all patients, with frequent accumulation of mutations that may confer resistance to further hedgehog inhibitor therapy. Although most adverse events were rated as level I or II, side effects were common, with up to 100% of patients in studies experiencing at least 1 event. Muscle cramps, alopecia, weight loss, fatigue, and dysgeusia were the most common adverse events, and several patients discontinued therapy because of them. Furthermore, 1 patient died of sepsis that may have resulted from the therapy.

Conclusions: Although level I and II evidence are lacking, most studies indicate a benefit from the use of oral vismodegib to treat orbital and periorbital BCC tumor volume. However, patients should be cautioned about the adverse side effects of treatment and the persistence of tumor cells with mutations that may cause long-term resistance. Use of vismodegib as short-term neoadjuvant therapy may be effective in shrinking tumor volume to reduce surgical morbidity while reducing the frequency and severity of side effects.

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The American Academy of Ophthalmology prepares Ophthalmic Technology Assessments to evaluate new and existing procedures, drugs, and diagnostic and screening tests. The goal of an Ophthalmic Technology Assessment is to review the available research for clinical efficacy, effectiveness, and safety. After review by members of the Ophthalmic Technology Assessment Committee, other Academy committees, relevant subspecialty societies, and legal counsel, assessments are submitted to the Academy's Board of Trustees for consideration as official Academy statements. The purpose of this assessment by the Ophthalmic Technology Assessment Committee Oculoplastics and Orbit Panel is to review the efficacy and safety regarding the use of oral vismodegib (Erivedge; Genentech) in the management of locally advanced orbital and periorbital basal cell carcinoma (BCC).

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Background

Basal cell carcinoma is the most common cutaneous malignancy,[1] and the presence of significant eyelid or orbital tumor burden is termed *locally advanced disease*. Surgical resection with histopathologic evidence of clear margins remains the standard of care in the management of this neoplasm, although the sensitive nature of the ocular adnexa and the complex anatomic features of the orbit underscore the perilous nature of aggressive surgical intervention in this location. Specifically, extensive resection may result in loss of vision, loss of the eye itself, or both; diplopia; tearing; exposure keratopathy; dry eyes; eyelid malposition; significant orbitofacial deformity resulting from exenteration; necrosis of the surgical site; infection; and the development of a fistula.[2–4] Additionally, medical comorbidities may render patients poor candidates for surgical intervention, anesthesia, and recovery.

In light of these concerns, nonsurgical therapeutic alternatives have been developed to address advanced BCC based on refinements in our understanding of the cellular biological features of this disease. Under ordinary circumstances, the patched-1 cell surface receptor suppresses the activity of smoothened protein. However, when this receptor binds the hedgehog protein, smoothened protein enters an active state, thereby yielding cell proliferation and angiogenesis.[5] Mutations in this receptor are the hallmark of basal cell nevus syndrome (Gorlin syndrome, or Gorlin-Goltz syndrome), and these changes culminate in persistent disinhibition of smoothened protein and the development of BCC.[6] Loss of function of the patched gene occurs in 90% of sporadic BCCs, suggesting that therapeutic manipulation of this pathway represents a logical approach for nonsurgical management of BCCs.

Vismodegib and sonidegib are hedgehog inhibitors that were approved by the United States Food and Drug Administration in 2012 and 2015, respectively, to address locally advanced and metastatic BCC.[7,8] Several trials previously demonstrated the efficacy of these agents, with favorable response rates.[8–10] However, these investigations did not specifically explore the role of vismodegib in BCCs of the orbit and ocular adnexa or combined use of itraconazole with vismodegib, and only a single study, with 16 subjects, investigated sonidegib. As such, this assessment was undertaken to analyze the efficacy and safety of vismodegib alone in locally advanced periocular disease.

Question for Assessment

The focus of this assessment is to address the following question: What are the safety and efficacy of vismodegib in the management of orbital and ocular adnexal locally advanced basal cell carcinoma?

Description of Evidence

A literature search limited to English language studies was last performed in September 2023 in the PubMed database. Search terms for this review included the following: *Hedgehog inhibitor*[tiab], *vismodegib*[tiab], *sonidegib*[tiab], *glasdegib*[tiab], *ocular adnexal*[tiab], *periocular*[tiab], *periorbital*[tiab], *orbital*[tiab], and *eyelid*[tiab]. Sixty articles were identified, and 20 were selected for full-text review and data abstraction by the panel members. Sixteen studies met the criteria for inclusion. Articles were eligible for inclusion if they consisted of original research in which an English language abstract was available and those in which participants comprised at least 5 patients who received a hedgehog inhibitor for the management of ocular adnexal or orbital BCC and were followed up clinically with objective measurement of response for at least 3 months. Four studies were rejected because they did not use a standardized approach to measuring the response, did not include an adequate number of patients, or did not specify the duration of follow-up care.

The panel methodologist (V.K.A.) assessed the quality of the 16 studies and assigned a level of evidence rating using the guidelines of the American Academy of Ophthalmology adapted from the 2011 Oxford Centre for Evidence-Based Medicine rating scale.[11] A level I rating was assigned to well-designed and well-conducted randomized clinical trials. A level II rating was assigned to well-designed case-controlled and cohort studies and lower-quality randomized studies. A level III rating was assigned to case series, case reports, and lower-quality cohort and case-controlled studies. All 16 studies were rated level III.

Published Results

Sixteen articles were rated level III. Please see Table 1 for a summary of the published results. Several of the studies reported the results in a qualitative fashion, and the clinical response generally was determined by a change in the longest diameter of the tumor or a decrease in overall size.

In a post hoc subgroup analysis from the single-arm, multicenter, open-label Safety Events in Vismodegib study, Ben Ishai et al[12] reported the use of vismodegib in 244 patients with locally advanced or metastatic periorbital BCC. Although the dosing pattern was not specified by the authors, these patients received a median of 40 weeks of medication, and the change in tumor size was identified through measurement in millimeters. The overall response rate was 67% (29% complete response, 39% partial response), and the response to treatment was statistically significant ($P < 0.0001$). Of these patients, 95.1% experienced more than 1 adverse event, and 23.8% discontinued therapy because of these side effects. Alopecia (68%), muscle spasms (68%), dysgeusia (55%), and weight loss (49%) were the most common adverse events. One author served as an investigator in a trial of vismodegib.

Similarly, through a post hoc subgroup analysis from a single-arm, multicenter, open-label study, Tiosano et al[13] pooled data on 244 patients with locally advanced periocular BCC who were treated with at least 1 dose of vismodegib at multiple centers. Ninety-two percent of the patients responded to the medication. Complete responses were identified in 23% of tumors that measured at least 3 cm and in 55% of those that were smaller than 1 cm. The

Table 1. Summary of the Abstracted Studies Regarding the Role of Hedgehog Inhibitors in Ocular and Periorbital Basal Cell Carcinoma

Authors (Year)	No. of Patients	Agent	Study Design	Outcomes	Most Common or Serious Adverse Effects
Gill et al (2013)[18]	7	Vismodegib	Observational case series	Complete regression in 29%, at least 80% regression in 29%, < 35% regression in 29%	Alopecia, muscle cramps, dysgeusia, anorexia
Demirci et al (2015)[20]	6	Vismodegib	Retrospective chart review	Complete regression in 50%, at least 40% reduction in tumor in 50%	Muscle spasms, alopecia, dysgeusia, dysnomia
Ozgur et al (2015)[23]	12	Vismodegib	Retrospective case series	Complete response in 25%, partial response in 50%, progressive disease in 17%	Muscle spasms, weight loss, dysgeusia, alopecia
Sagiv et al (2019)[24]	42	Vismodegib	Retrospective chart review	Orbital exenteration decreased from 46% to 10% after approval of medication	Not recorded
Wong et al (2017)[14]	15	Vismodegib	Prospective single-arm trial	Complete response in 67%, partial response in 20%, recurrence in 6.7%	Dysgeusia, muscle spasms, alopecia, asthenia
Xavier et al (2021)[27]	13	Vismodegib	Retrospective longitudinal study	Complete response in 30.8%, partial response in 46.2%, progressive disease in 38.5%	Muscle spasms, fatigue, alopecia, dysgeusia
Eiger-Moscovich et al (2019)[21]	21	Vismodegib	Retrospective case series	Complete response in 47.6%, partial response in 47.6%	Hepatotoxicity, sepsis, muscle spasms, alopecia, dysgeusia, weight loss
Gonzalez et al (2019)[15]	8	Vismodegib	Prospective single-arm trial	87.5% were free of tumor after surgical resection, tumor progression in 12.5%	Dysgeusia, muscle spasms, weight loss, alopecia
Sagiv et al (2019)[25]	8	Vismodegib	Retrospective interventional study	Complete response in 62.5%, partial response in 37.5%	Fatigue, alopecia, dysgeusia, appetite loss, weight loss, muscle cramps
Ben Ishai et al (2020)[12]	244	Vismodegib	Post hoc subgroup analysis from single-arm, multicenter, open-label study	Complete response in 28.7%, partial response in 38.5%	Alopecia, muscle spasms, dysgeusia, weight loss
Oliphant et al (2020)[22]	13	Vismodegib	Retrospective chart review	Complete regression in 38%, partial regression in 62%, recurrence in 23%	Fatigue
Curragh et al (2021)[19]	8	Vismodegib	Retrospective case series	Decrease in tumor size from mean of 27.3 mm to 19.1 mm	Alopecia, muscle cramps, dysgeusia, diarrhea, fatigue
Kahana et al (2021)[16]	34	Vismodegib	Open-label nonrandomized trial	All patients maintained a successful visual assessment weighted score, 79.4% improved or stable	Dysgeusia, myalgia, alopecia
Tiosano et al (2022)[13]	244	Vismodegib	Post hoc subgroup analysis from single-arm, multicenter, open-label study	92.4% response rate	Not recorded
Villani et al (2022)[26]	13	Vismodegib	Retrospective case series	Complete response in 53.8%, partial response in 30.8%, recurrence in 7.7%	Muscle pain, dysgeusia, alopecia
Villani et al (2023)[28]	16	Sonidegib	Retrospective case series	Complete response in 56%, partial response in 25%	Muscle pain, dysgeusia, alopecia

authors developed a model that indicated that a 68% reduction in tumor size after 6 months of therapy suggested a 95% chance of a complete response. Adverse events were not recorded. One author served as an investigator for a trial of vismodegib.

In a prospective single-arm trial, Wong et al[14] characterized the use of vismodegib (150 mg daily) in 15 patients; 10 had orbital BCC and 5 demonstrated locally advanced adnexal disease. At a mean of 36 months of follow-up, 10 patients achieved a complete response, 3 achieved a partial response, and 2 did not respond. In 1 patient, the partial response facilitated surgical resection. However, 1 patient experienced a recurrence after 21 months and required orbital exenteration. Notably, 5 patients discontinued therapy because of side effects. Adverse events were documented in 93% of patients, including dysgeusia (87%), spasms (53%), alopecia (53%), and asthenia (40%). Three authors received honoraria from Roche.

In a prospective single-arm trial, Gonzalez et al[15] used vismodegib (150 mg daily) in 8 patients as neoadjuvant therapy before surgical resection of the tumor. The maximum clinical response was achieved at a mean of 4.8 months of treatment. At a mean follow-up of 14.4 months, 1 patient demonstrated tumor progression and required orbital exenteration. The remaining 7 patients (88%) were free of disease after surgical resection, although histopathologic analysis revealed that 1 patient still showed residual tumor in the excised specimen. In this series, all patients experienced adverse events, including dysgeusia (100%), muscle spasms (100%), weight loss (75%; mean of 12.6 pounds), and alopecia (50%). One patient withdrew from treatment because of side effects. Two of the study's authors received honoraria from Roche.

In the Vismodegib for Orbital and Periocular Basal Cell Carcinoma (VISORB) open-label nonrandomized trial, Kahana et al[16] identified 34 patients who were treated with vismodegib (150 mg daily) for a median of 261 days. Notably, 79.4% of these patients opted to undergo tumor resection before completing a full year of therapy because of side effects. The authors used the visual assessment weighted score to explore the efficacy of vismodegib. This scale compiles multiple metrics, including globe preservation, visual acuity, lacrimal drainage, and extraocular motility. All patients maintained a successful

visual assessment weighted score (defined as globe preservation plus at least 1 point for visual function), and 79.4% showed a stable or improved score after treatment. Fifty-six percent of the patients demonstrated complete tumor regression on clinical examination and 47% did so by radiographic assessment. Among the patients who underwent surgery, 67% did not show residual disease on standard histopathologic examination, and 22% demonstrated remaining tumor with clear surgical margins. However, 97% of patients experienced at least 1 adverse event, and 6% of patients discontinued therapy because of adverse events. Dysgeusia (74%), myalgia (67%), and alopecia (47%) were the most common side effects. One author served as a consultant to Genentech.

In a follow-up molecular analysis of tissue excised from patients in the Vismodegib for Orbital and Periocular Basal Cell Carcinoma trial, all patients were noted to have residual disease using an RNA-based technology. Genome sequencing revealed an accumulation of mutations in the hedgehog pathway, several of which are known to impart resistance to clinically available hedgehog pathway inhibitors that target Smoothened (SMO).[17]

In an observational case series, Gill et al[18] administered vismodegib (150 mg daily) to 7 patients with periocular and orbital BCC for a mean of 11 weeks. At a median of 8 months of follow-up, 2 patients (29%) achieved complete tumor regression, whereas 2 patients (29%) achieved at least 80% regression, 2 patients (29%) showed less than 35% regression, and 1 patient (14%) was noted to have tumor progression. Side effects included alopecia (2 patients), muscle cramps (2 patients), dysgeusia (2 patients), and anorexia (1 patient). One author served on the speakers' bureau for Genentech.

Retrospective case series were used by several authors. These studies evaluated between 8 and 42 patients who were followed for up to 53 months. Most patients were treated with vismodegib 150 mg daily. Complete response rates varied between 25% and 63%, and partial responses occurred in between 38% and 50%.[19–26] Vismodegib achieved disease stability in 5% to 25% of patients.[21,23] Despite initial complete responses, recurrences occurred as late as 38 months after therapy.[23,26] In fact, up to 39% of patients experienced recurrent disease and up to 23% required exenteration for tumor control.[22,27]

Sagiv et al[24] retrospectively reviewed the impact of vismodegib in 42 patients with orbital BCC; 13 patients were cared for before the approval of the medication and 29 received treatment after its approval. Orbital exenteration was required for tumor control in 46% of those who received care before the approval of vismodegib and in 10% of those who received care after the approval. This difference was statistically significant ($P = 0.016$). Nonetheless, the likelihoods of globe retention and the use of radiation therapy were not statistically significantly different between the two groups. Adverse events were not recorded in this study. No author had a financial conflict of interest.

In these retrospective studies, adverse events were common, with up to 100% of patients experiencing at least 1 side effect. These events resulted in discontinuation of therapy in up to 62% of patients.[27] Up to 10% of patients demonstrated hepatotoxicity, and 1 patient died of treatment-related sepsis.[21] Otherwise, most side effects were grade 1 or 2 and included muscle spasms (75%–100%), alopecia (47%–75%), weight loss (47%–83%), dysgeusia (25%–85%), fatigue (46%–62%), and dysnosmia in 2 patients (25%).

In addition to these studies of vismodegib, Villani et al[28] performed a 3-year retrospective analysis of 16 patients who received sonidegib for locally advanced periorbital BCC for at least 6 months (median, 9 months). No patient experienced progression of disease. Complete responses occurred in 9 patients (56.2%) and partial responses occurred in 4 patients (25%), whereas 3 patients (18.8%) showed stable disease. Fourteen patients (88%) demonstrated adverse events, including muscle spasms (81%), dysgeusia (75%), and alopecia (44%). The authors did not have any financial conflicts of interest.

Conclusions

The current literature, with only level III evidence available, demonstrates that vismodegib facilitated globe preservation and tumor clearance in some cases, making it possible for patients to avoid disfiguring, vision-threatening surgical interventions. The benefits demonstrated for a vision-threatening, disfiguring, and potentially fatal illness make the ethical design of a placebo-controlled prospective trial challenging. As a result, level I studies may not be forthcoming.

However, caution is warranted for the use of the vismodegib as a single therapy for this problem because this medication is not a panacea for ocular adnexal locally advanced BCC. Notably, tumor progression and recurrences, occurring in up to 39% of patients, and the need for orbit exenteration, occurring in up to 23% of patients, are important risks to consider before contemplating treatment.[15,19,21,23,24,26] Furthermore, molecular analysis of tissue excised after vismodegib therapy revealed the presence of residual tumor in 100% of patients, as detected through extremely sensitive RNA-based technology. These residual tumor cells frequently contained new mutations that could be associated with resistance to hedgehog pathway inhibitors. Clinical evidence of resistance to the vismodegib also has been noted.[29] The totality of evidence reveals that patients either should undergo excision of the tumor site (i.e., neoadjuvant approach) or careful monitoring for tumor recurrence and progression to ensure continued clinical benefit.

Despite the benefit in reduction of tumor burden, vismodegib is not a benign intervention. Most patients involved in each study experienced at least 1 adverse event. Although most of these complications were graded as mild or moderate in severity, hepatotoxicity was reported as a grade 3 event, and 1 patient died of sepsis that was likely related to the intervention.[18] The fact that several patients in these highly motivated cohorts discontinued therapy speaks to the severity of these side effects and the difficulty of prolonged therapy. Patients should be counseled specifically about the potential for adverse events and should be monitored for their development.

The cost of vismodegib is an important limitation. Vismodegib costs roughly $7500 per month,[30] and patients may require prolonged therapy. Future research may focus on cost efficacy or the dosing duration. However, these expenses must be juxtaposed against the risk of vision

loss, cosmetic deformity, loss of function, costs of surgery, loss of productivity, and globe loss likely resulting from surgical interventions that would become necessary to achieve tumor control without these agents.

Future Research

Several future investigations may be helpful in optimizing care for patients with locally advanced ocular adnexal and orbital BCC. First, given that adverse events are common with the use of vismodegib and may result in the discontinuation of treatment, additional research may uncover dosing regimens and treatment strategies to lessen the burden of these side effects. Additionally, the management of resistance remains unclear, although previous studies have hypothesized that the use of other inhibitors, the combination of these agents with radiation therapy, and the development of new medications that selectively target other proteins in this pathway (i.e., immunotherapeutic agents) ultimately may provide benefit.[30] Finally, several studies have indicated a beneficial role for immunotherapy in the setting of locally advanced BCC in other cutaneous distributions after disease progression during the use of vismodegib.[31,32] Additional research would clarify the role of this class of medication in ocular and periorbital disease.

The use of vismodegib as an adjuvant to surgery is a particularly promising addition to our armamentarium for locally advanced disease; ideally, by contracting the tumor, patients may benefit from less aggressive surgery with subsequent globe preservation. The optimal duration of therapy to shrink these tumors and the ideal timing of surgery are important factors that require additional investigation. Similarly, given the presence of tumor mutations, the optimal histologic approach to tracking tumor progression and the presence of clear postoperative tissue margins must be determined. Finally, the duration of therapy varied somewhat between investigations. In light of emerging information regarding tumor mutations, future studies may wish to explore the benefits of prolonged therapy.

Footnotes and Disclosures

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No animal subjects were included in this study.

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BCC = basal cell carcinoma.

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