

# Non-surgical Drug Therapy for Locally Advanced Periocular Cancer

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**T**argeted treatment with sonic hedgehog inhibitors for locally advanced basal cell carcinoma (BCC) has significantly improved our ability to preserve ocular function and avoid orbital exenteration in patients with locally advanced BCC of orbital and periorbital area. Epidermal growth factor receptor inhibitors can be considered as non-surgical treatment in elderly patients with locally advanced or metastatic squamous carcinoma of the orbit who are not good candidates for surgery. Topical application of imiquimod in the periocular region can be considered for cases of recurrent *in situ* lentigo maligna; however, an intense soft tissue reaction and conjunctival and eyelid injection and irritation are expected side effects.

## Keywords

Basal cell carcinoma, squamous cell carcinoma, targeted therapy, vismodegib, erlotinib

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Medical therapies for periocular tumors are emerging as alternatives to traditional surgical excision and radiation. These relatively new drugs are good options in patients who are unable or unwilling to undergo surgery, with locally advanced lesions, or, as in the case of basal cell nevus syndrome, with multitudes of large symptomatic tumor burden. Targeted drugs that are currently approved by the US Food and Drug Administration (FDA) include hedgehog pathway inhibitors for basal cell carcinoma (BCC), epidermal growth factor receptor (EGFR) inhibitors for squamous cell carcinoma (SCC), and topical agents such as imiquimod and 5-fluorouracil for BCC, SCC, and lentigo maligna melanoma. Here we discuss the current evidence for the use of these drugs in the periocular region.

## Hedgehog pathway inhibitors for basal cell carcinoma

The hedgehog pathway is involved in fetal development and postnatal tissue regulation and has been identified as pathogenic in BCC. Mutations in the Patched-1 transmembrane receptor and a downstream receptor, smoothened, have been implicated in sporadic BCC and in basal cell nevus syndrome and lead to cellular proliferation, tumorigenesis, and angiogenesis.<sup>1</sup> Two targeted hedgehog pathway inhibitors are approved by the FDA for treatment of locally advanced or metastatic BCC: vismodegib and sonidegib. Although no reports exist about the use of sonidegib in periocular BCC, vismodegib has been successfully used and reported in several series of patients with locally advanced or metastatic periocular BCC or with basal cell nevus syndrome with symptomatic periocular lesions.

These studies used the approved oral dose of 150 mg daily. In the three largest series, a majority of patients had some response to treatment.<sup>2–4</sup> Taken in aggregate, these studies reported results in 27 patients. Twenty-four had locally advanced periocular BCC, and three had basal cell nevus syndrome with symptomatic periocular lesions. Of these patients, 13 (48%) had a complete response, 14 (52%) had a partial response, three (11%) had stabilization of disease, and one progressed. Two patients with initial responses—one complete, one stable—later developed progressive disease at 38 and 16 months after starting treatment, respectively. The definitions of partial response differed in each paper: in one, response was quantified by percentage change lesion size (reported at 15–90%),<sup>2</sup> in the second, defined as at least a 30% decrease in the sum of diameters of target lesions, taking as a reference the baseline sum of diameters;<sup>3</sup> and, in the third, ‘at least 40% decrease in tumor size on clinical and/or radiologic evaluation.’<sup>4</sup> A complete response had disappearance of all target lesions.<sup>2–4</sup> Follow-up ranged in these studies from a mean of 7.3 to 12.5 months.<sup>2–3</sup>

Adverse events are commonly reported with vismodegib use. In the pivotal study that led to FDA approval of vismodegib for BCC, all 104 patients experienced adverse events. These were categorized as mild to moderate in half of the patients and included muscle spasms (71.2%), alopecia (65.4%), dysgeusia (53.8%), anorexia (50.0%), fatigue (40.4%), and nausea (32.7%).<sup>5,6</sup> The common adverse

events mostly occurred within the first 6 months of treatment. Eighteen patients (17%) discontinued treatment due to adverse events, and the most frequently reported adverse events that led to treatment discontinuation were muscle spasms, weight loss, and dysgeusia. Serious adverse events occurred in 31.7% of patients after a median duration of exposure to therapy of 12.9 months, including seven deaths during the treatment period. A detailed review of these deaths found no relationship to vismodegib treatment, and they were considered to be unrelated by the study site investigator.<sup>6</sup> In the three smaller studies specifically on periocular BCC, two patients discontinued treatment prematurely: one patient with locally advanced BCC who stopped treatment for economic reasons and was lost to follow-up;<sup>3</sup> and one patient with locally advanced BCC who discontinued treatment due to dysgeusia, weight loss, and a broken hip due to a fall with subsequent disease recurrence 3 months after discontinuing vismodegib.<sup>3</sup> The other 16 patients completed therapy.

### Epidermal growth factor receptor inhibitors for squamous cell carcinoma

Targets of the EGFR are used to treat advanced non-small cell lung cancer,<sup>7</sup> pancreatic cancer, and head and neck SCC.<sup>8</sup> The EGFR is a transmembrane receptor tyrosine kinase that is structurally and functionally similar to human EGFR 2 (HER2), HER3, and HER4. EGFR has been shown to be overexpressed in approximately 60–80% of head and neck cutaneous SCCs and plays a part in cellular proliferation, differentiation, and survival of epithelial tumors.<sup>9–10</sup> Chemotherapeutic agents that target EGFR include monoclonal antibodies against the extracellular domain of EGFR (cetuximab, panitumumab, matuzumab, nimotuzumab, and zalutumumab)<sup>8</sup> and tyrosine kinase inhibitors that interfere with intracellular signaling (erlotinib, gefitinib, and lapatinib).<sup>11</sup>

Targets of EGFR have been studied for locally advanced, non-metastatic head and neck SCC as a less toxic, better-tolerated alternative to traditional radiotherapy combined with cisplatin. In the first phase III study, radiation with concurrent cetuximab was found to improve loco-regional progression-free and overall survival compared to radiation alone.<sup>12</sup> Subsequent trials on combination therapy of an EGFR inhibitor—cetuximab and erlotinib, for example—in combination therapy with radiation and cisplatin have shown equivocal results without definitive survival benefit.<sup>13–15</sup>

Published reports on the use of EGFR targets in treating periocular cancer are limited to one small case series report published by our group.<sup>16</sup> We reported good clinical and radiographic tumor response to EGFR inhibitors in three patients who presented with locally advanced cutaneous SCC of the periocular skin with orbital extension.<sup>16</sup> One patient was treated with 150 mg of oral erlotinib, which led to marked treatment response at 12 weeks; follow-up that was sustained at 11 months without significant adverse events. Two patients were treated with intravenous cetuximab; a 400 mg/m<sup>2</sup> loading dose followed by 250 mg/m<sup>2</sup> weekly dose, which led to similarly impressive, sustained responses in tumor size and symptoms.<sup>16,17</sup> In the periocular region, the most well-known side effect of EGFR inhibitors is trichomegaly and trichiasis, which is reported in over 30% of patients.<sup>18,19</sup>

### Topical agents for basal cell carcinoma and squamous cell carcinoma

The topical agents imiquimod and fluorouracil have shown promise in treating both BCC and SCC. Both agents are approved by the FDA to treat

superficial BCC.<sup>20</sup> Imiquimod acts as an agonist at toll-like receptor 7 and 8, which induces cytokines that activate cytotoxic T cells against cancer cells. 5-Fluorouracil is an antimetabolite that interferes with DNA synthesis.

In a systematic review regarding the efficacy of topical imiquimod and fluorouracil, the authors reported the following local control rates for BCC: 43–100% for superficial BCC, 42–100% for nodular BCC, and 56–63% for infiltrative BCC.<sup>20</sup> The largest class A studies from which these data were derived specifically note that tumors within 1 cm of the eyes were excluded. Fluorouracil yielded a 90% clearance rate for superficial BCC. For SCC, imiquimod produced local control rates ranging from 73–88% for SCC *in situ* and 71% for invasive SCC, whereas fluorouracil resulted in clearance rates of 27–85% for SCC *in situ*. The authors recommend the use of imiquimod and fluorouracil for superficial BCC less than 2 cm in diameter and in low-risk locations in patients who are either unable or unwilling to undergo standard treatment. Tumors within 1 cm of the eye are considered ‘high-risk’ and specifically excluded from this recommendation, but it stands to reason that imiquimod could show similar control rates in the periocular region as well. However, the local tissue reaction to imiquimod may be an issue in the periocular region.

Several studies have evaluated the use of imiquimod for periocular tumors specifically. The majority are for BCC, and we are unable to find reports on the use of imiquimod for periocular SCC. In 19 patients with periocular nodular BCC treated with imiquimod 5% cream daily for a range of 8–16 weeks, the histological clearance rate was 81.8% (9/11) for lesions greater than 10 mm and 100% (8/8) for lesions smaller than 10 mm in greatest diameter at 3 years follow-up.<sup>21</sup> In the two patients with larger tumors in which only partial tumor regression was observed, the patients went on to have surgical excision of their BCC, which points to the potential for neoadjuvant use of imiquimod. Other authors have used imiquimod in the neoadjuvant setting as well.<sup>22</sup> One patient in this series had recurrence of tumor at 2 years after treatment, but this patient also had a 2-week interruption in treatment because of periocular inflammation. In a similar study of 15 patients with eyelid nodular BCC with mean tumor diameter of 7.6 mm (range 2–12 mm) treated with daily topical imiquimod, all patients experienced histopathologic tumor remission within 3 months and a sustained clinical remission at 24 months follow-up.<sup>23</sup> Treatment-related adverse events were typically self-limited and isolated to the ocular surface, including conjunctivitis, keratitis, and foreign body sensation.<sup>21,24</sup>

Imiquimod has also been successfully used for periocular lentigo maligna melanoma, or melanoma *in situ*. In a series of 11 patients with periocular lentigo maligna melanoma involving eyelid skin treated with topical imiquimod for a mean of 3 months, all patients achieved a complete histologic response with no atypical melanocytes on follow up biopsy.<sup>25</sup> One patient in this series discontinued treatment after 1 month due to irritation and, as a result, did not have resolution of disease.

### Conclusion

In conclusion, there is reasonable evidence to recommend the use of several non-surgical therapies for periocular tumors, although there are no large-scale randomized trials specific to periocular use. Vismodegib may be useful in locally advanced or metastatic BCC; erlotinib for SCC; and, imiquimod for BCC and lentigo maligna melanoma. There are few or no reports regarding imiquimod for periocular SCC and fluorouracil for SCC and BCC, and further study is necessary for these agents with these tumors. □

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