Neoadjuvant Targeted Therapy for Locally Advanced Orbital Basal Cell Carcinoma: A Case Presentation and Discussion

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INTRODUCTION
Vismodegib was FDA-approved in January 2012 for metastatic basal cell carcinoma and locally advanced basal cell carcinoma.1 The latter is characterized by large tumor size, multiple lesions, or locally recurrent disease not appropriate for surgical treatment.2 Vismodegib is an antagonist of the hedgehog pathway, which has been found to be activated in basal cell carcinoma leading to cellular proliferation.3 Vismodegib may serve an important role in the future treatment of metastatic and locally advanced basal cell carcinoma. We present a case of locally advanced orbital basal cell carcinoma where Vismodegib was used as neoadjuvant therapy to assist in shrinking the tumor prior to surgery in the efforts of sparing the eye.

CASE PRESENTATION
The patient is a 56-year-old man, who presented with a 23 x 34 cm ulcerated plaque with a pink raised border involving the left medial canthus, and upper and lower eyelids (Figure 1). A biopsy of the left lower eyelid demonstrated a nodular proliferation of atypical basaloid cells within the dermis with peripheral nuclear palisading, stromal mucin, tumor-stromal clefting, and focal ulceration consistent with nodular basal cell carcinoma (Figure 2). As MRI of the brain, sinuses and orbits with and without contrast revealed abnormal soft tissue along the anterior aspect of the left orbit, extending over the proximal left nasofrontal region with no evidence of paranasal sinus involvement or intracranial metastatic disease.

The patient was referred for Mohs micrographic surgery consultation. Treatment options were discussed, including Mohs micrographic surgery at that point, which would likely sacrifice the eye, targeted therapy alone with Vismodegib, and neoadjuvant therapy with Vismodegib followed by Mohs micrographic surgery.

We initiated Vismodegib 150 mg/day with the plan that the patient would remain on Vismodegib until the tumor stopped responding or the patient could no longer tolerate the side effects of the medication. At that point, surgery could potentially reduce the surgical defect and hopefully preserve the eye.

The patient completed 11 months of Vismodegib with decrease in tumor size and improvement of ulceration (Figure 3). Throughout the treatment period, the patient experienced dysgeusia (disturbance of taste), alopecia, fatigue, nausea, decreased appetite, and diarrhea. While these adverse effects were generally regarded as minor, the necessary chronic use of Vismodegib and, therefore, the persistent side effects commonly led patients to discontinue therapy.5 These chronic adverse effects potentially limit the long term use of Vismodegib.

Other limitations hindering the chronic use of Vismodegib include the possibility of tumor skip areas (persistent tumor in clinically “cured” skin), acquired resistance, increase risk of squamous cell carcinomas, and cost-effectiveness due to the average monthly cost of $7500 per month.4 With the development of Vismodegib, there have been a few case reports and a small clinical trial evaluating neoadjuvant targeted therapy followed by surgery. This small clinical trial found that Vismodegib needed to be used for at least 3 months to elicit a response. It was found that Vismodegib use reduced the surgical defect area by 27% for the 11 patients that underwent surgery following Vismodegib. Finally, it showed that clinically resolved lesions do not necessarily correlate with histologic cure.

Another study was performed in seven patients with periocular and orbital basal cell carcinoma where the mean treatment duration was 11 weeks, and two patients demonstrated complete clinical regression, two patients demonstrated greater than 80% partial clinical regression, two patients demonstrated less than 35% partial clinical regression, and one patient progressed.6 However, two patients developed new squamous cell carcinomas at uninvolved sites.7 There are currently multiple treatment options for locally advanced basal cell carcinoma, including surgery, targeted therapy, and neoadjuvant therapy followed by surgery.8 Surgery remains the mainstay of treatment for locally advanced basal cell carcinomas with a much higher cure rate compared to the response rates of Vismodegib.1 However, there are limitations to surgery. For example, cases could potentially be inappropriate for surgery due to compromise of function or cosmesis, multiple recurrences or low likelihood of surgical cure. In our case, surgery at the initial presentation would have sacrificed the patient’s eye; therefore, neoadjuvant therapy was attempted to ideally shrink the tumor and spare the eye.

DISCUSSION
Most basal cell carcinomas contain alterations in the hedgehog signaling pathway resulting in its activation and uncontrolled proliferation of cells. Most commonly, 90% of basal cell carcinomas are due to loss of function of the tumor suppressor gene PATCHED (PTCH1), which inhibits the signaling activity of smoothened (SMO). There also can be an activating mutation in smoothened in 10% of basal cell carcinomas.8 Smoothered activates the Hedgehog pathway through downstream activation of GLI1. Vismodegib is the first, FDA approved, small-molecule, Hedgehog pathway inhibitor. It inhibits smoothened (SMO), thereby preventing downstream signaling of the pathway.9

Vismodegib is FDA-approved for the treatment of adults with metastatic or locally advanced basal cell carcinoma, when it is inoperable or when surgery is inappropriate. In a phase II trial of Vismodegib, patients with metastatic and locally advanced BCC showed response rates of 30% and 43% respectively. Response was defined as a decrease of 30% or more in the externally visible or radiographic dimension or complete resolution of ulceration if present at baseline.1

In several studies of Vismodegib use, multiple side effects were commonly experienced, including muscle spams or cramps, alopecia, dysgeusia (alteration of taste), weight loss, fatigue, nausea, decreased appetite, and diarrhea. While these adverse effects were generally regarded as minor, the necessary chronic use of Vismodegib and, therefore, the persistent side effects commonly led patients to discontinue therapy.5 These chronic adverse effects potentially limit the long term use of Vismodegib.

CONCLUSION
Vismodegib may serve an important role in the future treatment of metastatic and locally advanced basal cell carcinoma. However, due to Vismodegib’s new and exciting development, there potentially may be cases of Vismodegib use where surgery may have been indicated. Inappropriate use of Vismodegib could potentially place the patient at increased risk without an increased benefit compared to surgical treatment.

Vismodegib’s ideal treatment duration, long-term side effects, and cost effectiveness, as well as potential for causing resistance, residual skin lesions and squamous cell carcinoma remain unknown and warrant further investigation. These current limitations of Vismodegib may discourage its future use.

REFERENCES

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