

## BRIEF ARTICLE

## Pulse Dosing Vismodegib Therapy as an Effective Treatment of Basal Cell Carcinoma: A Case Report

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### ABSTRACT

Basal cell carcinoma (BCC) is a common nonmelanoma skin cancer, frequently present on the face and head. BCC is linked to the Sonic Hedgehog (Shh) signaling pathway. Mutations within the Shh signaling pathway, involving the activation of the ligand-independent pathway by the Smoothed (Smo) protein, can lead to unregulated proliferation of basal cells, resulting in BCC. Vismodegib, a hedgehog pathway inhibitor, is a chemotherapy drug approved for targeting the Shh signaling pathway. We herein report a presentation of nodular BCC in a Caucasian female who was treated with Vismodegib. This case highlights the effectiveness of pulse dosing treatment to minimize side effects.

### INTRODUCTION

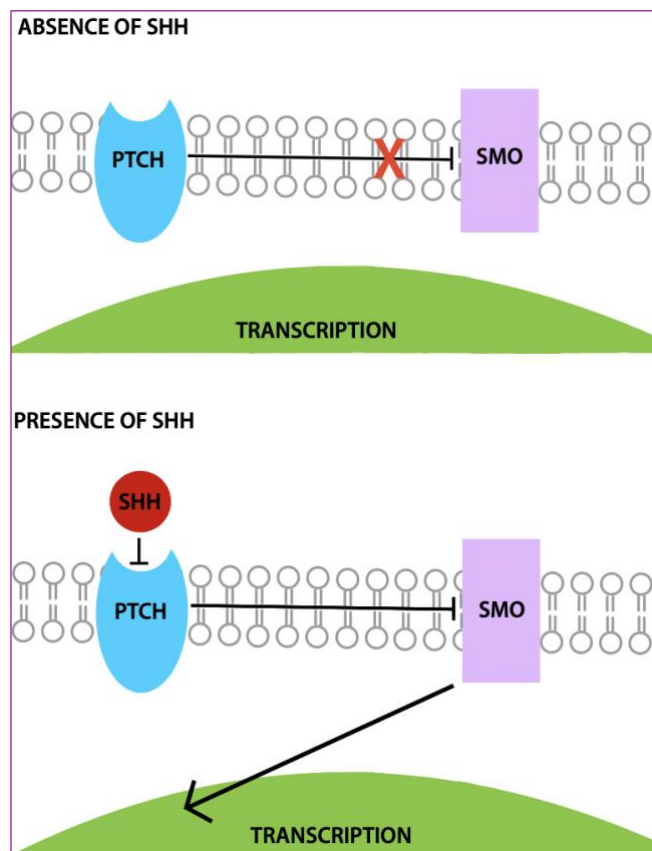
Basal cell carcinoma (BCC) is the most common type of nonmelanoma skin cancer. While it rarely metastasizes, BCC can spread to surrounding areas and cause local tissue destruction.<sup>1</sup> If metastasis of BCC does occur, the prognosis is poor.<sup>2</sup> Standard treatment of BCC is through curettage and electrodesiccation, surgical excision, or Mohs micrographic surgery.<sup>1</sup> Though surgical intervention is typical for BCC management, topical medications can be used in some low risk cases.<sup>1-3</sup> In locally advanced or metastatic BCC, radiation therapy may be used as an alternative to surgical treatment.<sup>1</sup>

The development of BCC is linked to abnormal regulation of the Sonic hedgehog (Shh) signaling pathway. The Shh signaling pathway is an essential regulatory pathway in embryologic development that is involved in

tissue homeostasis and regeneration.<sup>1,4</sup> Various malignancies have been linked to abnormal regulation of this pathway, including BCC.<sup>4</sup>

*PTCH1* is a tumor suppressor gene that encodes the Patched receptor and inhibits the Smoothed (Smo) protein, responsible for gene transcription, in the Shh pathway. In the presence of the Shh protein ligand, Patched activates the Smo protein, which then promotes downstream signaling<sup>3</sup> (**Figure 1**). *PTCH1* mutations that result in the uninterrupted activation of Smo are commonly found in BCC. Through animal model studies, overactivation of the Shh pathway has been linked to the development of BCC.<sup>1,3</sup>

Vismodegib is an FDA-approved Shh pathway inhibitor that is taken as an oral 150 mg capsule once daily.<sup>2</sup> Use of Vismodegib is indicated for locally advanced or metastatic



**Figure 1.** The Sonic Hedgehog (Shh) signaling pathway in the absence of presence of the Shh ligand (SHH).



**Figure 2.** Translucent papules with arborizing telangiectasia on the lateral left scalp measuring 10.8 cm x 9.0 cm.



**Figure 3.** Tumor at 9 months since starting Vismodegib therapy, compared to Figure 2.

BCC and for patients who are not candidates for surgery or radiation therapy. Adverse effects are common and include muscle spasms, fatigue, alopecia, dysgeusia, weight loss, GI upset, diminished appetite, ageusia, arthralgias, and electrolyte disturbances.<sup>3,5</sup> Vismodegib is contraindicated in pregnancy due to its embryotoxic effects.<sup>3</sup> Pulse dosing, a method of drug dosing that provides dose-free periods, can be used to mitigate possible side effects.<sup>6,7</sup>

### CASE REPORT

A 62-year-old Caucasian female with a past medical history of hypertension and anemia presented with a 10.8 cm x 9.0 cm ulcerated tumor on her scalp (**Figure 2**). A biopsy obtained from the lesion exhibited nodular BCC on histopathology. Due to the size and clinical appearance, the lesion was suspected to possibly have more aggressive features. The patient was not amenable to

surgical treatment and thus was started on Vismodegib 150 mg pulse dosing once daily for the first two weeks of each month.

It was recommended that the patient take the medication with L-carnitine 1500 mg daily to reduce muscle spasms. Prior to initiation of Vismodegib treatment, baseline labs were obtained and were unremarkable. A CT scan of the head and neck with contrast was performed and showed no evidence of bony invasion or metastases.

The patient was seen for a follow-up after 5 months of treatment and 9 months of treatment (**Figure 3**), both times at which showed a marked improvement in the width and thickness of the tumor. The patient did not exhibit any adverse effects aside from muscle cramps twice monthly lasting approximately five minutes at a time.

### DISCUSSION

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The Shh pathway is an essential regulatory pathway that is involved in the pathogenesis of BCC. Mutations in either the Smo or *PTCH1* genes result in overactivation of the Shh pathway. In the case of BCC, mutations in the Shh pathway result in an unregulated proliferation of transcription factors leading to tumorigenesis.<sup>3</sup>

In 2012, Vismodegib became the first FDA-approved agent to target the Shh signaling pathway.<sup>3</sup> As a selective inhibitor for the Shh pathway that competitively inhibits Smo, Vismodegib inhibits the transcription factors GLI1 and GLI2 and prevents the downstream expression of tumor-mediating genes.<sup>8</sup> Vismodegib is currently approved for the treatment of locally advanced or metastatic BCC.<sup>4</sup> Previous studies have demonstrated the use of pulse-dosing with Shh inhibitors to treat BCC while reducing adverse side effects.<sup>7,9,10</sup> Our case further supports this favorable safety profile of pulse-dosing while maintaining effective treatment.

The patient in this case has shown significant improvement with Vismodegib therapy and will continue pulse dosing, 150 mg PO daily, for the first two weeks of each month. As a result of pulse dosing, the patient has tolerated treatment with minimal side effects. Due to the size and features of the tumor, we felt it was in the best interest of the patient to try to initially shrink the tumor via a hedgehog inhibitor. The patient was not an ideal candidate for other treatment options including Mohs surgery, excision, electrodesiccation and curettage, radiation, or topical chemotherapy. The plan is to continue with Vismodegib, with the goal of treating any remaining cancer in the future with cryotherapy, surgery, and/or electrodesiccation and curettage. Due to the significant improvement of this tumor with Vismodegib therapy, the patient is now a

candidate for adjunctive treatment modalities.

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