Remarkable Response to Vismodegib in a Locally Advanced Basal Cell Carcinoma on the Nose

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PRACTICE **POINTS**

- Dermatologists should consider using vismodegib for treatment of unresectable basal cell carcinoma.
- Vismodegib dosing regimens can vary; drug holidays can be used to mitigate adverse effects while maintaining desirable treatment outcomes.

Basal cell carcinoma (BCC) is the most common cancer in the world, and its incidence continues to rise. Known risk factors for BCC include chronic UV exposure, advanced age, and genetic predisposition. A large majority of BCC cases have an altered Hedgehog (Hh) signaling pathway. When a large BCC develops on the face, it can pose unique treatment challenges due to functional and cosmetic considerations—even with Mohs micrographic surgery (MMS). Traditional treatment options may be limited, prompting the use of targeted therapies such as vismodegib for unresectable cases. Vismodegib, an Hh inhibitor, is approved by the US Food and Drug Administration for treatment of locally advanced or metastatic BCC. This case report details the successful management of a large BCC on the nose of an elderly patient using vismodegib.

A 90-year-old man presented for evaluation of a large basal cell carcinoma (BCC) involving the nasal region. The lesion was a 7×4-cm pink, crusted, verrucous plaque covering the majority of the nose and extending onto the malar cheeks that originally had been biopsied 26 years prior, and repeat biopsy was performed 3 years prior. Results from both biopsies were consistent with BCC. The patient had avoided treatment for many years due to fear of losing his nose.

Given the size and location of the tumor, surgical intervention posed major challenges for both functional and cosmetic outcomes. After careful consideration and discussion of treatment options, which included Mohs micrographic surgery (MMS), wide local excision, radiation therapy, and systemic therapy, the decision was made to start the patient on vismodegib 150 mg once daily as well as L-carnitine 330 mg twice daily to help with muscle cramps. A baseline complete metabolic panel with an estimated glomerular filtration rate was unremarkable.

By the patient's first follow-up visit after 2 months of therapy, he had experienced marked clinical improvement with notable regression of the tumor (Figure 1). He reported no adverse effects (eg, muscle cramps, dysgeusia, hair loss, nausea, vomiting, diarrhea). At subsequent follow-up visits, the patient continued to demonstrate clinical improvement. His only adverse effect was a 6-kg weight loss over the prior 6 months of initiating therapy despite no changes in taste or appetite. His dose of vismodegib was decreased to an alternative regimen of 150 mg daily for the first 2 weeks of each month with a drug holiday the rest of the month. Since that time, his weight has stabilized and he has continued with treatment.

Comment

Vismodegib was the first Hedgehog (Hh) inhibitor approved by the US Food and Drug Administration for management of selected locally advanced and metastatic BCC in adults.[1,2] Genetic alterations in the Hh signaling

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The authors have no relevant financial disclosures to report.

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Cutis. 2025 May;115(5):E9-E11. doi:10.12788/cutis.1228

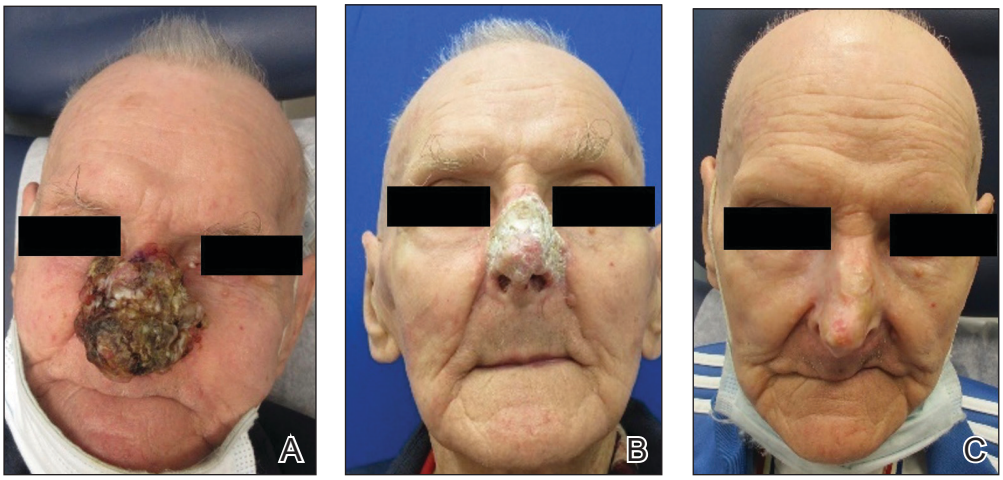

FIGURE 1. A-C, Improvment of a basal cell carcinoma on the nose of an elderly man from baseline to 2 and 6 months of treatment with vismodegib.

pathway resulting in proliferation of basal cells are present in nearly all BCCs.[2] In normal function, when the Hh ligand is absent at the patched (PTCH1) receptor, smoothened (SMO) is inhibited. When Hh ligand binds *PTCH1*, *SMO* is activated with downstream effects of triggering cell survival and proliferation in the nucleus via GLI. Loss of function mutations at the *PTCH1* receptor or *SMO*-activating mutations lead to the same downstream effects, even when Hh ligand is absent.[1] This allows for unregulated tumor growth.

Vismodegib is a small-molecule SMO inhibitor that blocks aberrant activation of the Hh signaling pathway, thereby slowing the growth of BCCs (Figure 2).[3,4] Vismodegib and sonidegib have been used to treat patients with basal cell nevus syndrome as well as metastatic or locally advanced BCCs. At least 50% of advanced BCCs develop resistance to vismodegib, commonly via acquiring mutations in *SMO*.[4]

Basal cell carcinoma can be classified as low or high risk based on risk for recurrence. First-line treatments for low-risk BCC are surgical excision, electrodessication and curettage, and MMS.[4] Second-line treatment includes radiation therapy. High-risk tumors include those involving anatomic locations of Area H near the eyelids, nose,

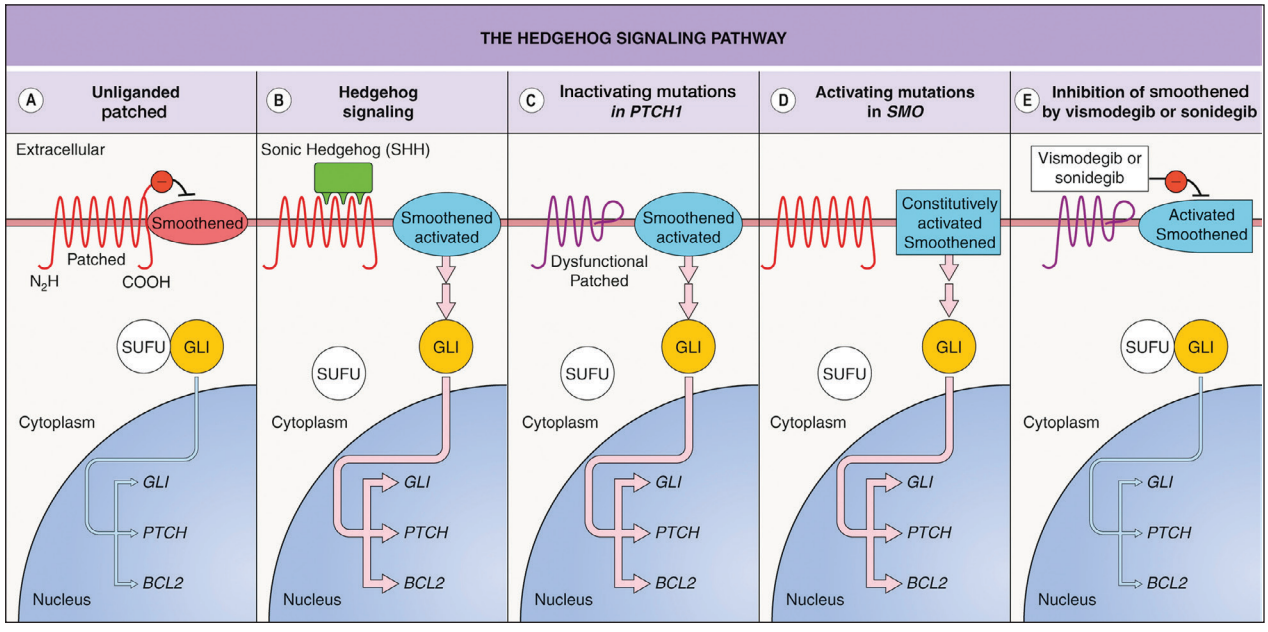

FIGURE 2. The Hedgehog signaling pathway. A, Unliganded PTCH1 silences SMO signaling. B, As Hedgehog binds to its receptor PTCH1, the repression of SMO is removed and signals are transduced via GLI to the nucleus. C, Inactivating mutations lead to PTCH1, and this simulates Hedgehog binding and results in constitutive activation of GLI and downstream target genes. D, An activating mutation in SMO results in constitutive signaling to GLI and downstream target genes. Such mutations are detected in sporadic BCCs in which PTCH1 is intact. E, Vismodegib and sonidegib are inhibitors of SMO that have been used to treat patients with basal cell nevus syndrome as well as metastatic or locally advanced BCCs. Abbreviations: PTCH1, patched; SMO, smoothened; BCCs, basal cell carcinomas.

ears, hands, feet, or genitals in addition to tumors with an aggressive histologic subtype.[4,5] First-line treatments for high-risk BCC are MMS or surgical excision. Second-line treatments are radiation therapy or systemic therapy, such as vismodegib.[4]

Although Hh inhibitors are not a first-line treatment, our case highlights vismodegib's effectiveness in the management of a large unresectable BCC on the nose of an elderly patient. Our patient opted out of surgical first-line options due to functional and cosmetic concerns.[4] He also declined radiation treatment due to financial cost and difficulty with transportation. The patient chose to pursue systemic vismodegib therapy through shared decision-making with dermatology. Vismodegib treatment alone granted our patient a highly remarkable result.

There are limited clinical data on the effectiveness and safety profile of vismodegib in elderly patients, even though this is a high-risk population for BCC.[6] In a study that categorized responses to vismodegib in 13 patients with canthal BCC, 5 experienced a complete clinical response (defined as complete regression of the tumor), and 8 achieved partial clinical response (defined as regression but not to the extent of a complete response).[7] Our patient's successful response is notable, as it reinforces vismodegib's effectiveness as a treatment option for BCC in a sensitive facial area. In addition, our patient's minimal adverse effect profile is evidence in support of establishing visogemib's role as a viable treatment option in advanced BCC in the elderly.

Alternative dosing regimens of vismodegib involve the use of drug holidays.[8] Utilizing a regimen of 1 week with and 3 weeks without vismodegib for 5 to 14 cycles has led to the resolution of BCC with decreased adverse effects.[8] Furthermore, the MIKIE study demonstrated the efficacy of 2 dosing regimens: 12 weeks of vismodegib 150 mg followed by 3 cycles of 8 placebo weeks and 12 weeks of vismodegib 150 mg and 24 weeks of vismodegib 150 mg followed by 3 cycles of 8 placebo weeks and 8 weeks of vismodegib 150 mg.[9] Both regimens appeared viable to treat BCC in patients who were at risk for treatment discontinuation due to adverse effects.[10]

One adverse effect associated with vismodegib is muscle cramps, which are a potential cause of treatment discontinuation. The mechanism by which vismodegib causes cramps is not fully understood but is attributed to contractions from Ca^{2+} influx into muscle cells and a lack of adenosine triphosphate to allow muscle relaxation.[11] This is due to vismodegib's inhibition of the SMO signaling pathway and activation of the SMO–$Ca2^{+}$/AMP-related kinase axis.[12] L-carnitine can be used as an adjuvant with vismodegib to address this adverse effect. L-carnitine is found in muscle cells, where its role is to produce energy by utilizing fatty acids.[13] It is hypothesized that L-carnitine helps prevent cramps through production of adenosine triphosphate via fatty acid β-oxidation that aids in stabilizing the sarcolemma and promoting muscle relaxation in skeletal muscle.[13,14] Evidence suggests that making L-carnitine a common adjuvant to vismodegib can aid in preventing this adverse effect.

Vismodegib can be an effective treatment option for large nasal BCCs that are difficult to resect. Our case demonstrates both clinical efficacy and a favorable safety profile in an elderly patient. Further studies and long-term follow-up are warranted to establish the role of vismodegib in the evolving landscape of BCC management.

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