Vismodegib for Basal Cell Carcinoma and Beyond: What Dermatologists Need to Know

Salim S. Alkeraye, MD; Ghadah A. Alhammad, MBBS; Faisal K. Binkhonain, MBBS

PRACTICE **POINTS**

- The recommended dosage of vismodegib is 150 mg/d until unendurable side effects develop or disease progression occurs.
- The efficacy of vismodegib in the management of locally advanced basal cell carcinoma (BCC) and metastatic BCC is promising. Thus, it is now considered an effective substitute to surgical therapy.
- Patients using vismodegib must be closely monitored, as it is commonly associated with adverse events.

Basal cell carcinoma (BCC) is the most common cutaneous malignancy. Although indolent, BCCs can be locally aggressive if untreated. Dysregulated hedgehog (Hh) signaling leads to uncontrolled proliferation in BCC. Vismodegib is a small-molecule antagonist of the Hh pathway that binds to smoothened (SMO), a transmembrane protein, and causes inhibition of an aberrant activation of the Hh pathway. Vismodegib is the first drug approved by the US Food and Drug Administration (FDA) for the management of locally advanced or metastatic BCC.

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Basal cell carcinomas (BCCs) are considered the most common cutaneous cancers. Approximately 80% of nonmelanoma skin cancers are BCCs.[1,2] Surgical management is the gold standard for early-stage and localized BCCs; it may include simple excision vs Mohs micrographic surgery.[3,4] However, if left untreated, these lesions can progress to an advanced stage (locally advanced BCC) or infrequently may spread to distant sites (metastatic BCC). In the advanced stage, the lesions are no longer manageable by surgery or radiation therapy.[5,6] Recently, inhibitors targeting the hedgehog (Hh) pathway have shown great promise for these patients. The first drug approved by the US Food and Drug Administration (FDA) for locally advanced and metastatic BCC is vismodegib.[7] In this article, we provide a clinical review of vismodegib for the management of BCC, including a discussion of the Hh pathway in BCC, adverse effects of vismodegib, use of vismodegib in adnexal skin tumors, recommended doses for vismodegib therapy in BCC, and management of the side effects of treatment.

Hh Pathway in BCC

In embryonic development, the Hh signaling pathway is crucial across a broad spectrum of species, including humans. Various members of the Hh family have been recognized, all working as secreted regulatory proteins.[8] The name of the Hh signaling pathway is derived from a polypeptide ligand called *hedgehog* found in some fruit flies. Mutations in the gene led to fruit fly larvae that had a spiky hairy pattern of denticles similar to hedgehogs, leading to the name of this molecule.[9] The transmembrane protein smoothened (SMO) is the main component of the Hh signaling pathway and initiates a signaling cascade that in turn leads to an increased expression of target genes, such as *GLI1*. Patched (PTCH), also a

From the Department of Dermatology, College of Medicine, King Saud University, Riyadh, Saudi Arabia.
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Correspondence: Salim S. Alkeraye, MD, King Khalid Rd, King Saud University, Riyadh, Saudi Arabia (drsaleem121@hotmail.com).
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transmembrane protein and a cell-surface receptor for the secreted Hh ligand, suppresses the signaling capacity of SMO. Upon binding of the Hh ligand to the PTCH receptor, the suppression of SMO is relieved and a signal is propagated, evoking a cellular response.[10] Molecular and genetic studies have reported that genetic alterations in the Hh signaling pathway are almost universally present in all BCCs, leading to an aberrant activation of the pathway and an uncontrolled proliferation of the basal cells. Frequently, these alterations have been shown to cause loss of function of PTCH homologue 1, which usually acts to inhibit the SMO homologue signaling activity.[11,12]

Because of the potential importance of Hh signaling in other solid malignancies and the failure of topical inhibition of SMO,[13] subsequent studies on the development of Hh pathway inhibitors have mostly focused on the systemic approach. A multitude of Hh pathway inhibitors have been developed thus far, such as SANT1-SANT4, GDC-0449, IPI-926, BMS-833923 (XL139), HhAntag-691, and MK-4101.[14] Many of these inhibitors have been clinically investigated.[13,15,16]

Systemic SMO Inhibitor: Vismodegib

Vismodegib was the earliest systemic SMO inhibitor to fulfill early clinical evaluation[15,16] and the first drug to receive FDA approval for the management of advanced or metastatic BCC. Vismodegib is a small-molecule SMO inhibitor used for the management of selected locally advanced BCC and metastatic BCC in adults.[3,17] Although there is a possibility of recurrence following drug withdrawal, vismodegib constitutes a new therapeutic strategy presenting positive benefits to patients. It may provide superior improvement over sunitinib, which has shown efficacy in a few patients; however, the efficacy and tolerance of sunitinib have been shown to be limited.[18,19]

Adverse Effects of Vismodegib Therapy

Adverse events with vismodegib use have been reported in 98% of patients (N=491); most of these were mild to moderate.[20] However, the frequency of adverse events could prove to be a therapeutic challenge for patients requiring extended treatment. The most frequently reported reversible side effects were muscle spasms (64%), alopecia (62%), weight loss (33%), fatigue (28%), decreased appetite (25%), diarrhea (17%), nausea (16%), dysgeusia (54%), and ageusia (22%).[20] In clinical trials, amenorrhea was noticed in 30% (3/10) of females with reproductive potential.[2] Apart from alopecia and possibly amenorrhea, these side effects are reversible.[17] Alkeraye et al[17] reported 3 clinical cases of persistent alopecia following the use of vismodegib. Amenorrhea is a possible side effect of unknown reversibility.[7]

Vismodegib is a pregnancy category D medication.[4] Severe birth defects, including craniofacial abnormalities, retardations in normal growth, open perineum, and absence of digital fusion at a corresponding 20% of the recommended daily dose, were found in rat studies. Embryo-fetal death was noted when rats were exposed to concentrations comparable to the recommended human dose.[4]

Hepatic events with the use of vismodegib have been reported. The use of vismodegib in randomized controlled trials resulted in elevation of both alanine aminotransferase and aspartate aminotransferase levels compared with placebo.[21] Moreover, severe hepatotoxicity with vismodegib has been reported.[22-24] A study conducted by Edwards et al[25] concluded that the use of vismodegib in patients with severe liver disease must include thorough risk-benefit assessment, with caution in using other concomitant hepatotoxic medications.

Rare adverse events also have been reported in the literature, including vismodegib-induced pancreatitis in a 79-year-old patient treated for locally advanced, recurrent BCC that was cleared following cessation of therapy.[26] Additionally, atypical fibroxanthoma was observed in an 83-year-old patient after 30 days of treatment with vismodegib for multiple BCCs.[27] The development of other secondary malignancies, such as squamous cell carcinoma, melanoma, keratoacanthomas, and pilomatricomas, during or after the long-term use of vismodegib also have been described.[28-35]

Use of Vismodegib for Adnexal Skin Tumors

The role of the sonic Hh–PTCH pathway in the pathogenesis of adnexal tumors varies in the literature. Some studies propose the involvement of this pathway in the formation of adnexal tumors such as trichoblastoma, trichoepithelioma, and cylindroma, as in BCC. Various lines of evidence support this involvement. Firstly, in mice, the spontaneous generation of numerous BCCs, trichoblastomas, trichoepitheliomas, and cylindromas has been observed following constitutive activation of the sonic Hh–PTCH pathway.[36] Secondly, in trichoepitheliomas, there have been positive results in molecular research into the tumor suppressor gene PTCH homologue 1, *PTCH1*, whose mutations cause constitutive activation of the sonic Hh–PTCH pathway.[37] Thirdly, GLI1[38] and SOX9[39] transcription factors associated with the signaling pathway of sonic Hh–PTCH appear to have increased levels in adnexal carcinomas.[19] Lepesant et al[19] reported a notable clinical response to vismodegib in trichoblastic carcinoma. Baur et al[40] reported successful treatment of multiple familial trichoepitheliomas with vismodegib. Nonetheless, more studies are required to assess the efficacy and reliability of vismodegib in the management of adnexal tumors.

Recommended Dose of Vismodegib Therapy

The vismodegib dosage that is approved by the FDA is 150 mg/d until disease progression or the development of intolerable side effects.[4] Higher dosing regimens were evaluated with 270 mg/d and 540 mg/d. No added

therapeutic benefit was noted with the increase in the dose, and no dose-limiting toxic effects were observed.[41]

Management of Vismodegib Side Effects

Managing patient expectations is a crucial step in improving dysgeusia. The experience of dysgeusia varies among patients; thus, patients should be instructed to adjust their diets according to their level of dysgeusia, which can be achieved by changing ingredients or dressings used with their diet. This step has been proven to be effective in overcoming vismodegib-related dysgeusia. Also, fluid taste distortion may lead to dehydration and an increase in creatine level. Thus, patients should be encouraged to monitor fluid intake. Moreover, a treatment hiatus of 2 to 8 months results in near-complete improvement of taste distortion.

For muscle spasms, quinine, treatment break for 1 month, gentle exercise of affected areas, or muscle relaxants such as baclofen and temazepam all are effective methods. For vismodegib-related alopecia, managing patient expectations is key; patients should be aware that hair may take 6 to 12 months or even longer to regrow. In addition, shaving less frequently helps improve alopecia.

For gastrointestinal disorders, loperamide with or without codeine phosphate is effective in resolving diarrhea, and metoclopramide is mostly adequate in treating nausea. Another adverse event is weight loss; weight loss of 5% or more of total body weight prompts dietetic referral. If weight loss persists, a treatment break might be needed to regain weight.

Overall, treatment breaks are sufficient to resolve adverse events caused by vismodegib and do not compromise efficacy of treatment. The duration of a treatment break should be considered before initiation. In one clinical trial, a longer treatment break was associated with fewer adverse effects without affecting the efficacy of treatment.[42]

Conclusion

Vismodegib provides an effective alternative to surgical intervention in the management of BCC. However, patients must be monitored vigilantly, as adverse events are common (>90%).

REFERENCES

1. Sekulic A, Migden MR, Oro AE, et al. Efficacy and safety of vismodegib in advanced basal-cell carcinoma. *N Engl J Med*. 2012;366:2171-2179.
2. Rogers HW, Weinstock MA, Harris AR, et al. Incidence estimate of nonmelanoma skin cancer in the United States, 2006. *Arch Dermatol*. 2010;146:283-287.
3. Von Hoff DD, LoRusso PM, Rudin CM, et al. Inhibition of the hedgehog pathway in advanced basal-cell carcinoma. *N Engl J Med*. 2009;361:1164-1172.
4. Cirrone F, Harris CS. Vismodegib and the hedgehog pathway: a new treatment for basal cell carcinoma. *Clin Ther*. 2012;34:2039-2050.
5. Ruiz-Salas V, Alegre M, López-Ferrer A, et al. Vismodegib: a review [article in English, Spanish]. *Actas Dermosifiliogr*. 2014;105:744-751.
6. Rubin AI, Chen EH, Ratner D. Basal-cell carcinoma. *N Engl J Med*. 2005;353:2262-2269.
7. Cusack CA, Nijhawan R, Miller B, et al. Vismodegib for locally advanced basal cell carcinoma in a heart transplant patient. *JAMA Dermatol*. 2015;151:70-72.
8. Aszterbaum M, Rothman A, Johnson RL, et al. Identification of mutations in the human PATCHED gene in sporadic basal cell carcinomas and in patients with the basal cell nevus syndrome. *J Invest Dermatol*. 1998;110:885-888.
9. Abidi A. Hedgehog signaling pathway: a novel target for cancer therapy: vismodegib, a promising therapeutic option in treatment of basal cell carcinomas. *Indian J Pharmacol*. 2014;46:3-12.
10. St-Jacques B, Dassule HR, Karavanova I, et al. Sonic hedgehog signaling is essential for hair development. *Curr Biol*. 1998;8:1058-1068.
11. Gailani MR, Ståhle-Bäckdahl M, Leffell DJ, et al. The role of the human homologue of Drosophila patched in sporadic basal cell carcinomas. *Nat Genet*. 1996;14:78-81.
12. Hall JM, Bell ML, Finger TE. Disruption of sonic hedgehog signaling alters growth and patterning of lingual taste papillae. *Dev Biol*. 2003;255:263-277.
13. Bai CB, Stephen D, Joyner AL. All mouse ventral spinal cord patterning by hedgehog is Gli dependent and involves an activator function of Gli3. *Dev Cell*. 2004;6:103-115.
14. Wang B, Fallon JF, Beachy PA. Hedgehog-regulated processing of Gli3 produces an anterior/posterior repressor gradient in the developing vertebrate limb. *Cell*. 2000;100:423-434.
15. Sekulic A, Mangold AR, Northfelt DW, et al. Advanced basal cell carcinoma of the skin: targeting the hedgehog pathway. *Curr Opin Oncol*. 2013;25:218-223.
16. Ingham PW, Placzek M. Orchestrating ontogenesis: variations on a theme by sonic hedgehog. *Nature Rev Genet*. 2006;7:841-850.
17. Alkeraye S, Maire C, Desmedt E, et al. Persistent alopecia induced by vismodegib. *Br J Dermatol*. 2015;172:1671-1672.
18. Battistella M, Mateus C, Lassau N, et al. Sunitinib efficacy in the treatment of metastatic skin adnexal carcinomas: report of two patients with hidradenocarcinoma and trichoblastic carcinoma. *J Eur Acad Dermatol Venereol*. 2010;24:199-203.
19. Lepesant P, Crinquette M, Alkeraye S, et al. Vismodegib induces significant clinical response in locally advanced trichoblastic carcinoma. *Br J Dermatol*. 2015;173:1059-1062.
20. Basset-Seguin N, Hauschild A, Grob JJ, et al. Vismodegib in patients with advanced basal cell carcinoma (STEVIE): a pre-planned interim analysis of an international, open-label trial. *Lancet Oncol*. 2015;16:729-736.
21. Catenacci DV, Junttila MR, Karrison T, et al. Randomized phase Ib/II study of gemcitabine plus placebo or vismodegib, a hedgehog pathway inhibitor, in patients with metastatic pancreatic cancer. *J Clin Oncol*. 2015;33:4284-4292.
22. Sanchez BE, Hajjafar L. Severe hepatotoxicity in a patient treated with hedgehog inhibitor: first case report. *Gastroenterology*. 2011;140:S974-S975.
23. Ly P, Wolf K, Wilson J. A case of hepatotoxicity associated with vismodegib. *JAAD Case Rep*. 2018;5:57-59.
24. Eiger-Moscovich M, Reich E, Tauber G, et al. Efficacy of vismodegib for the treatment of orbital and advanced periocular basal cell carcinoma. *Am J Ophthalmol*. 2019;207:62-70.
25. Edwards BJ, Raisch DW, Saraykar SS, et al. Hepatotoxicity with vismodegib: an MD Anderson Cancer Center and Research on Adverse Drug Events and Reports Project. *Drugs R D*. 2017;17:211-218.
26. Velter C, Blanc J, Robert C. Acute pancreatitis after vismodegib for basal cell carcinoma: a causal relation? *Eur J Cancer*. 2019;118:67-69.
27. Giorgini C, Barbaccia V, Croci GA, et al. Rapid development of atypical fibroxanthoma during vismodegib treatment. *Clin Exp Dermatol*. 2019;44:86-88.
28. Saintes C, Saint-Jean M, Brocard A, et al. Development of squamous cell carcinoma into basal cell carcinoma under treatment with vismodegib. *J Eur Acad Dermatol Venereol*. 2015;29:1006-1009.
29. Zhu GA, Sundram U, Chang ALS. Two different scenarios of squamous cell carcinoma within advanced basal cell carcinomas: cases illustrating the importance of serial biopsy during vismodegib usage. *JAMA Dermatol*. 2014;150:970-973.

30. Poulalhon N, Dalle S, Balme B, et al. Fast-growing cutaneous squamous cell carcinoma in a patient treated with vismodegib. *Dermatology*. 2015;230:101-104.
31. Orouji A, Goerdt S, Utikal J, et al. Multiple highly and moderately differentiated squamous cell carcinomas of the skin during vismodegib treatment of inoperable basal cell carcinoma. *Br J Dermatol*. 2014;171:431-433.
32. Iarrobino A, Messina JL, Kudchadkar R, et al. Emergence of a squamous cell carcinoma phenotype following treatment of metastatic basal cell carcinoma with vismodegib. *J Am Acad Dermatol*. 2013;69:E33-E34.
33. Giuffrida R, Kashofer K, Dika E, et al. Fast growing melanoma following treatment with vismodegib for locally advanced basal cell carcinomas: report of two cases. *Eur J Cancer*. 2018;91:177-179.
34. Aasi S, Silkiss R, Tang JY, et al. New onset of keratoacanthomas after vismodegib treatment for locally advanced basal cell carcinomas: a report of 2 cases. *JAMA Dermatol*. 2013;149:242-243.
35. Magdaleno-Tapial J, Valenzuela-Oñate C, Ortiz-Salvador JM, et al. Pilomatricomas secondary to treatment with vismodegib. *JAAD Case Rep*. 2018;5:12-14.
36. Nilsson M, Undèn AB, Krause D, et al. Induction of basal cell carcinomas and trichoepitheliomas in mice overexpressing GLI-1. *Proc Natl Acad Sci U S A*. 2000;97:3438-3443.
37. Vorechovský I, Undén AB, Sandstedt B, et al. Trichoepitheliomas contain somatic mutations in the overexpressed *PTCH* gene: support for a gatekeeper mechanism in skin tumorigenesis. *Cancer Res*. 1997;57:4677-4681.
38. Hatta N, Hirano T, Kimura T, et al. Molecular diagnosis of basal cell carcinoma and other basaloid cell neoplasms of the skin by the quantification of Gli1 transcript levels. *J Cutan Pathol*. 2005;32:131-136.
39. Vidal VP, Ortonne N, Schedl A. SOX9 expression is a general marker of basal cell carcinoma and adnexal-related neoplasms. *J Cutan Pathol*. 2008;35:373-379.
40. Baur V, Papadopoulos T, Kazakov DV, et al. A case of multiple familial trichoepitheliomas responding to treatment with the hedgehog signaling pathway inhibitor vismodegib. *Virchows Arch*. 2018;473:241-246.
41. LoRusso PM, Rudin CM, Reddy JC, et al. Phase I trial of hedgehog pathway inhibitor vismodegib (GDC-0449) in patients with refractory, locally advanced or metastatic solid tumors. *Clin Cancer Res*. 2011;17:2502-2511.
42. Fife K, Herd R, Lalondrelle S, et al. Managing adverse events associated with vismodegib in the treatment of basal cell carcinoma. *Future Oncol*. 2017;13:175-184.