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Profile of vismodegib and its potential in the treatment of advanced basal cell carcinoma

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Abstract: Basal cell carcinoma (BCC) is the most common human malignancy. Recent advances in our understanding of the critical biologic pathways implicated in the development and progression of BCC have led to the development of the first molecular targeted therapy for this disease. The hedgehog pathway is mutated in virtually all patients with BCC and recent trials with vismodegib, an inhibitor of this pathway, have shown significant responses. This review will discuss the importance of the hedgehog pathway in the pathogenesis of BCC and describe in detail the pharmacology of vismodegib in relation to its activity in advanced BCC.

Keywords: basal cell carcinoma, vismodegib, hedgehog pathway

Introduction
Basal cell carcinoma (BCC) is the most common human malignancy. Since it is not always included in cancer registries, the true incidence is unknown. It is estimated that approximately 3.5 million nonmelanoma skin cancers in 2.2 million patients are treated annually in the United States, the majority of which are BCC (American Cancer Society, Facts and Figures 2013). The American Academy of Dermatology estimates that approximately 2 million BCC are treated every year (http://www.aad.org/dermatology-a-to-z/diseases-and-treatments/a—a-d/basal-cell-carcinoma). Fortunately, these tumors are usually amenable to local therapy and only 1%–5.3% of lesions recur after initial resection.1

Interestingly, even locally aggressive tumors seldom metastasize and metastatic BCC is quite rare. Since accurate incidence records of this disease are not available, the burden of metastatic disease is difficult to ascertain. Rates ranging from 0.0028% to 0.55% of patients with BCC developing metastases have been reported,2–7 but even these have been questioned.8 The median age of patients with metastatic BCC at the time of diagnosis of the primary lesion is about 45–56 years, and metastases appear at a median of about 9 years later.9–11 Factors that may predispose to the development of metastatic BCC include male gender,9 primary lesion in the ear region9,11,12 and face,11 large11 and locally invasive13 primary tumors, recurrence following initial treatment,11 and impairment of cell mediated immunity (eg, acquired immunodeficiency syndrome, therapeutic immunosuppression).14,15

Recent advances in our understanding of the biologic pathways that appear to be important in the development and progression of BCC have led to the development of the first molecular targeted therapy for this disease, vismodegib. The hedgehog (Hh) pathway is mutated in virtually all patients with BCC and inhibition of this pathway with vismodegib appears to result in significant clinical responses. The following
sections will discuss the importance of the Hh pathway in the pathogenesis of BCC and describe in detail the pharmacology of vismodegib in relation to advanced BCC.

**Hh pathway and its role in BCC**

The Hh pathway is one of the most common signal transduction pathways used by mammalian cells for normal embryonic development of the neural tube, axial skeleton, skin, and hair, and for wound healing during postnatal life. While this pathway appears to be silenced in most adult tissues, it has been shown to promote the proliferation of stem cells from various tissues in the adult. These include hematopoietic cells, mammary, mesenchymal, and neural stem cells. This pathway also appears to play a role in the transition of hair follicles from the resting to the growth phase. This could explain the alopecia noted in patients treated with the Hh pathway inhibitor, vismodegib. In addition, this pathway seems to be involved in the repair of various organs in the adult following injury.

Recent studies have shown that aberrant Hh signaling pathway is involved in the pathogenesis, self-renewal of stem cells, and chemotherapeutic resistance of BCC. Besides BCC, Hh signaling is also activated in other malignancies such as medulloblastoma, colon, prostate, breast, lung, and various hematologic malignancies. The Hh pathway dependent gene upregulation leads to increased cell proliferation and cell survival, and promotes bone metastases. This pathway has been shown to regulate the epithelial–mesenchymal transition and dissemination of cancer stem cells in solid tumors, and enhance metastatic disease progression. These observations suggest that targeted inhibition of Hh signaling may be an effective treatment strategy for several human cancers.

The signaling cascade of the Hh pathway in mammalian cells is initiated by binding of one of three Hh ligands (sonic, Indian, or desert Hh) to the 12 pass transmembrane receptor patched 1 (Ptc1) (Figure 1). This causes internalization and degradation of Ptc1, thereby releasing smoothened (SMO),

![Figure 1](image-url) **Figure 1** A schematic diagram showing inhibition of Hedgehog (Hh) signaling by vismodegib.

**Notes:** The extracellular Hh ligands (Sonic, Indian, or Desert Hh) bind to Patched 1 (Ptc1), relieving the inhibition of Smoothened (SMO) by Ptc1. SMO disrupts the cytoplasmic complex containing the Suppressor of Fused (SUFU)-glioma-associated oncogene homologue (Gli) complex resulting in degradation of Gli3 and translocation of Gli1 and Gli2 to the nucleus to upregulate target genes like Ptc1, Gli1, c-Myc, Bcl2, vascular endothelial growth factor, and cyclin D1. Vismodegib binds to the extracellular domain of SMO, markedly inhibiting the release and translocation of Gli1 and Gli2 to the nucleus.

**Abbreviations:** Gli, glioma-associated oncogene homologue; Ptc1, patched 1; Shh, sonic hedgehog; SMO, smoothened; SUFU, Suppressor of Fused; VEGF, vascular endothelial growth factor.
a 7 pass transmembrane G protein coupled receptor like protein. This protein then enters the primary cilia and disrupts the cytoplasmic complex containing Suppressor of Fused (SUFU)-glioma-associated oncogene homologue (Gli). The SUFU regulates transcriptional factors (Glis) through posttranslational modifications like phosphorylation, sumoylation, and selective proteolysis. Release of Gli transcription factors (Gli 1–3) from SUFU inhibition results in nuclear translocation and upregulation of Gli1 associated target genes that include Gli1, Ptch1, cyclin D1, c-Myc, vascular endothelial growth factor, Bcl-2, and snail, depending upon cell type and degradation of the repressor transcription factor Gli3. Depending on the Gli2 posttranscriptional and posttranslational processing events, Gli2 has been shown to act as either a positive or negative regulator of Hh pathway signaling. Deregulated Hh signaling has been associated with either mutations in pathway genes or overexpression of signaling molecules in either tumor cells themselves or in cells within the supportive tumor microenvironment.

The first link between the Hh pathway and BCC came from the discovery of loss-of-function mutations of Ptch1 gene in Gorlin syndrome. Patients with Gorlin syndrome are strongly predisposed to the development of BCC at an early age. Recent molecular and genetic studies have shown that almost all BCC tumors contain genetic alterations in components of the Hh signaling pathway and these tumors have elevated Ptc and Gli1 messenger (m)RNA levels. This ligand-independent mechanism of Hh activation, driven by specific Hh gene mutations within the tumor cells, is termed Type I Hh signaling. It has been estimated that almost 90% of sporadic BCCs have loss-of-function mutation in at least one allele of Ptch1 and in addition, around 10% have activating mutations in the SMO, rendering it resistant to Ptch1 inhibition.

In contrast, mutations in other downstream molecules of the Hh pathway appear to be rare in BCC. In a study of 42 patients with sporadic BCC, only two patients had mutations in SUFU, one of which was a missense mutation and the other a silent mutation. No mutation was seen in Gli1.

**Pharmacology of vismodegib**

**Structure**

Vismodegib is an orally active SMO inhibitor (2-chloro-N-[4-chloro-3-pyridin-2-yl-phenyl]-4-methanesulfonyl benzamide) with a molecular weight 421.30 g/mol (Figure 2).
Although it has not been specifically studied, based on the pharmacokinetic profile, it is unlikely that renal dysfunction affects the safety profile of vismodegib significantly. Hence, patients with renal dysfunction are not likely to need a modification of their dose. The need for dose modification in patients with hepatic dysfunction is currently unknown.

**Pharmacodynamics**

Vismodegib binds to, and inactivates, SMO. This prevents its translocation when Ptch1 is stimulated by Hh ligands and leads to the inhibition of the downstream signaling pathways and a decrease in the production of downstream proliferation factors (Figure 1).

Exposure to vismodegib leads to the downregulation of Gli1. In a Phase I trial of vismodegib in patients with locally advanced or metastatic solid tumors there was 2-fold downmodulation of Gli1 expression in skin biopsies from almost 75% patients, compared with pretreatment specimens. In the same study, a similar proportion of patients with BCC showed 2-fold downmodulation of Gli1 expression. However, the downmodulation of Gli1 expression was not associated with plasma concentrations of the drug.

**Adverse effects**

Vismodegib is relatively well tolerated. The most common adverse reactions seen in clinical trials have been muscle spasms (70%), alopecia (60%), dysgeusia (55%), weight loss (45%), fatigue (40%), nausea (30%), diarrhea (30%), decreased appetite (25%), constipation (20%), arthralgias (15%), vomiting (12%), and ageusia (10%). Approximately 30% of premenopausal women developed amenorrhea while on vismodegib. Other laboratory abnormalities noted by patients on clinical trials included hyponatremia (4%), hypokalemia (1%), and azotemia (2%). A recent report described the development of keratoacanthomas in two patients, who did not have a history of previous squamous cell carcinomas, while being treated with vismodegib. The authors were not able to establish a causal relationship with vismodegib, clinicians need to be alert to these findings.

The vismodegib package insert contains a black box warning regarding the risk of severe birth defects and embryonic fetal death. This is based on rat studies, which demonstrated that vismodegib administered at a dose of 10 mg/kg/day showed teratogenic effects. This dose corresponds to an exposure of 20% of the human exposure at the recommended dose of 150 mg daily. Similarly, there is a potential risk of exposure to the drug through semen. Hence, sexually active individuals receiving vismodegib should be advised of the need for contraception (Source: Erivedge™ package insert. [http://www.gene.com/download/pdf/erivedge_prescribing.pdf](http://www.gene.com/download/pdf/erivedge_prescribing.pdf)).

**Drug resistance**

Resistance mechanisms to vismodegib have not been extensively studied, which is understandable given the relatively short clinical experience with this drug. However, anecdotal reports of acquired resistance to vismodegib are beginning to emerge. In the only case reported thus far, a 26 year old man with treatment refractory metastatic medulloblastoma who was treated with vismodegib responded initially, but developed progressive disease after 3 months, suggesting the development of resistance. A molecular analysis of the biopsy specimen obtained at disease progression showed a heterozygous G to C missense mutation at position 1697, which is responsible for a change in codon 473 from aspartic acid to histidine (D473H). This mutation prevents the binding of vismodegib to SMO, thereby leading to resistance.

This was further studied in vitro by Dijkgraaf et al who replaced the aspartic acid at position 473 of the SMO gene with every other amino acid and found that vismodegib did not bind to SMO in any of the mutant variations, thereby suggesting that D473 is critical for SMO binding. It is unclear, however, if D473 is directly involved in the binding of vismodegib or if its main role is to maintain the necessary SMO conformation for binding.

Other potential resistance mechanisms identified in vitro include mutations at E518. Substitution of glutamic acid at this site conferred complete resistance to vismodegib. Other possible mechanisms of resistance include focal amplifications of the transcription factor Gli2 and the target gene Cend1, which exert their actions downstream of SMO.

There are initial data on resistance to vismodegib in BCC, which are described below.

Mechanisms to overcome this resistance are currently being studied. Dijkgraaf et al screened multiple chemically diverse Hh pathway inhibitors and were able to identify several compounds that were active against the two known SMO resistance mutations, SMO-D473H and SMO-E518K. Available data also suggest that Hh pathway resistant medulloblastoma allografts may respond to inhibition of phosphoinositide-3-kinase.

**Clinical data on vismodegib**

The Phase I trial of vismodegib included 68 patients with different malignancies, of which 33 had advanced BCC.
Vismodegib was well tolerated with only six patients (8.8%) developing grade 4 adverse events (hyponatremia, fatigue, pyelonephritis, presyncope, resectable pancreatic adenocarcinoma, and paranoia with hyperglycemia). A maximum tolerated dose was not reached and based on achievement of maximal plasma concentration and response, the recommended Phase II dose was 150 mg daily. Interestingly, 20 patients (19 with BCC and one with medulloblastoma) had a response based on Response Evaluation Criteria in Solid Tumors (RECIST) criteria. At the time of publication, the median duration of response in patients with advanced BCC was 12.8 months (range 3.7–26.4 months). This led to further investigation of vismodegib in BCC.

A multicenter, international, two cohort, nonrandomized Phase II study, administered 150 mg of oral vismodegib daily to patients with either metastatic or locally advanced BCC (inoperable disease or for whom surgery was inappropriate, ie, multiple recurrences and a low likelihood of cure, or substantial anticipated disfigurement). The response rate was 30% for patients with metastatic BCC and 43% (21% complete response) in patients with locally advanced BCC. The median duration of response was 7.6 months in both cohorts. The most common adverse events were muscle spasms, alopecia, dysesthesia, weight loss, and fatigue. Serious adverse events were reported in 25% of patients. Seven deaths were reported, although their relationship to the study drug was unclear. The results of these studies led to the approval of vismodegib for the treatment of metastatic BCC and locally advanced BCC in patients who are not candidates for surgery or radiation based on the location or size of the lesion.

More recently, vismodegib has been studied for its potential to prevent the development of BCC in patients with basal cell nevus syndrome. In a randomized placebo controlled trial, 42 patients with the basal cell nevus syndrome were randomly assigned to either vismodegib (150 mg daily) or placebo for 18 months. The primary end point of this study was the rate of development of new BCC that were eligible for surgical resection. Vismodegib significantly reduced the rate of new surgically eligible basal cell carcinomas when compared to placebo (2 versus 29 new surgically eligible BCC per group annually; P < 0.001). Vismodegib also reduced the size of existing BCC (median decrease 71%) when compared to placebo (median decrease 21%; P = 0.003). Patients receiving vismodegib had fewer surgeries for BCC (mean of −0.31), compared with those receiving placebo (mean −4.4; P < 0.001). Palmar and plantar pits, pathognomonic signs of the basal cell nevus syndrome, also disappeared with vismodegib. However, almost half of the patients had to discontinue treatment due to drug related adverse events.

Recently, an interesting phenomenon of tumor regrowth was reported in patients treated with vismodegib. In a retrospective analysis of 28 patients on vismodegib, Chang et al noted tumor regrowth within or adjacent to (≤1 cm) the prior tumor bed in 6 (21%) patients. Surprisingly, none of the eight patients with metastatic BCC in their analysis demonstrated regrowth after initial shrinkage. Hence, close clinical examination of patients, even examination of those who have a response to therapy, is warranted to detect the development of secondary resistance to vismodegib. These findings would also suggest that vismodegib and other agents targeting the Hh pathway are unlikely to cure BCC, and surgery still would be considered the best curative option for patients who can undergo the procedure without major cosmetic deformity.

Conclusion
The Hh pathway is critical to the development of BCC. Mutations in this pathway are seen in virtually all patients with BCC. Inhibition of this pathway with the SMO inhibitor, vismodegib, leads to significant responses in patients with metastatic and locally advanced BCC. While vismodegib can delay the development of BCC in patients with the basal cell nevus syndrome, its adverse effect profile tempers its use in this setting. Finally, there are reports of resistance to vismodegib and those mechanisms are currently being studied.

Acknowledgments
The authors on this manuscript, in part, were supported by the VA Career Development Award (AKG) and NIH grants (U01 EDRN CA 111294, P50 SPORE CA127297, and U54 TMEN CA160163) (SKB).

Disclosure
The authors report no conflicts of interest in this work.

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