

Vismodegib: A Hedgehog Pathway Inhibitor for Locally Advanced and Metastatic Basal Cell Carcinomas

Joesph F. Sobanko MD,[a] Jonathan Okman BA MBA,[b] and Christopher Miller MD[a]

[a]Division of Dermatologic Surgery and Cutaneous Oncology, University of Pennsylvania, Philadelphia, PA
[b]Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

ABSTRACT

Basal cell carcinomas (BCCs) are the most common cancer in the United States, and the overwhelming majority of BCCs are the result of hedgehog pathway activation. While locally advanced and metastatic BCC are rare, currently available treatments remain limited and are often unsuccessful. Vismodegib inhibits a key regulatory protein in the hedgehog pathway and was approved by the United States Food and Drug Administration in 2012. This orally-administered medication offers a novel approach for treating locally advanced and metastatic BCC. The following review will address vismodegib's mechanism of action, published clinical trial data, and the questions that still remain unanswered about this new medication.

J Drugs Dermatol. 2013;12(suppl 10):s154-s155.

INTRODUCTION

Approximately 2.8 million basal cell carcinomas (BCCs) occur in the United States each year, accounting for 80% of all non-melanoma skin cancers (NMSC); but fewer than 1,000 patients will die every year from BCC.[1,2] Effective surgical and destructive modalities allow for successful removal of the overwhelming majority of BCCs.[3] However, 0.5% of BCCs evade surgical control because of either advanced local growth or metastasis.[4] Systemic treatment with traditional chemotherapy offers mild improvement in progression-free survival and cure rates, with median survival times from diagnosis ranging from 6 months to 3.6 years.[5,6] A novel class of systemic medicines targeting the hedgehog (Hh) pathway may improve outcomes for patients with inoperable locally advanced or metastatic BCC.

The Hh pathway consists of a series of membrane and intracellular proteins that regulate cell proliferation and is of particular importance in BCC pathogenesis. During embryogenesis, Hh gene activation directs the orientation of body segments and initiates development of the limb buds and neural tube.[7,8] In adults, this pathway is typically inactive. An encoded transmembrane receptor (patched homologue [PTCH] 1) binds and inhibits smoothened (SMO), another transmembrane protein, preventing it from initiating a downstream intracellular pathway that eventually leads to transcription of the glioma-associated oncogene (GLI)1 and GLI2. Transcription of GLI1 and GLI2, zinc finger domain transcription factors, leads to increased expression of proteins essential for cell proliferation. When the Hh ligand binds to PTCH, PTCH releases its inhibition on SMO, leading to activation of the signaling cascade.

The Hh pathway is mutated and constitutively active in 90% of sporadic BCCs.[9,10,11] Patients with nevoid basal cell carcinoma syndrome (NBCCS) possess an inherited, inactivating mutation and loss of heterozygosity in PTCH1.[12,13] Patched homologue 1 mutations may lead to BCC formation by preventing the protein's normal inhibition of the SMO receptor. Without inhibition, the SMO receptor initiates the Hh pathway signaling cascade, GLI1 gene transcription and, ultimately, cell proliferation. Less frequently, a mutated smoothened receptor may act as an oncogene, constitutively activating the Hh pathway.[11,14]

Hedgehog Pathway Inhibition With Vismodegib

Vismodegib, a small-molecule inhibitor of the Hh pathway, was first approved by the United States Food and Drug Administration in January 2012 for locally-advanced and metastatic BCCs. This orally-administered medication inhibits SMO signal transduction and prevents nuclear localization of GLI1 transcription factors. Clinical trials of this medication reveal response rates between 30% and 60% for locally advanced and metastatic BCCs.[15,16] In patients with NBCCS, vismodegib also reduces the number of new and already-present surgically-eligible BCCs.[17]

In 2 of the largest published clinical trials, enrolled patients were categorized as metastatic BCC or locally-advanced BCC. This latter category included patients who had inoperable disease or were not appropriate surgical candidates, because of multiple recurrences and a low likelihood of surgical cure or the anticipation of substantial disfigurement. In the phase 2 study, patients received 150 mg of vismodegib daily until disease progression, unacceptable toxic effects, or discontinuation of the study.[16] The median duration of therapy for these trials was 9.8 months and 7.6 months, respectively. In neither study did a patient with metastatic BCC have a complete response to vismodegib; however, 50% and 30% of metastatic BCC patients did experience a partial response. An objective response was defined with the Response Evaluation Criteria in Solid Tumors (RECIST) in patients with metastatic BCC. In locally advanced BCCs, an objective response was defined as a decrease of 30% or more in the externally visible or radiologic dimension or complete resolution of ulceration (if present at baseline). In patients with locally-advanced BCC, 13% and 21% of patients experienced a complete response (absence of residual

BCC in a biopsy specimen), while 47% and 22% experienced a partial response with vismodegib.[15,16]

Questions That Still Remain

While early data appear promising, there is still much to be determined regarding vismodegib's role in BCC treatment. First, the category of "inoperable" BCC is rather subjective and must be better developed. Many recurrent BCCs that are considered inoperable by one surgeon may be deemed surgically appropriate by another surgeon. This decision has significant financial implications too, because the cost of 10 months of vismodegib is $75,000 compared with less than $2,000 for the surgical treatment of most BCCs.[18,19]

Second, vismodegib may not offer better results than chemotherapeutic agents currently used for metastatic BCCs. Cisplatin-containing regimens have been associated with overall response rates of up to 77%, including complete response rates of up to 45%.[20-23] Neutropenia and renal toxicity are feared adverse events (AEs) of cytotoxic cisplatin-based regimens; however, the side effects from vismodegib frequently result in medication termination.[24] Twenty-seven percent of NBCCS patients at 8 months and 54% of patients at 18 months discontinued their medication because of side-effect intolerability.[17] The most frequently reported AEs are muscle spasms, dysgeusia, weight loss, fatigue, nausea, diarrhea, and alopecia.[15,16,24]

Finally, the proper duration of vismodegib therapy must be determined. It appears that BCCs and other tumors that involve the Hh pathway develop resistance to vismodegib with subsequent disease progression.[25,26,27] This may be the result of a missense mutation in the SMO receptor that decreases vismodegib's affinity for the receptor. Additionally, the rebound of BCCs after vismodegib cessation have been reported in one patient.[28] Future avenues of research that warrant further investigation include the use of vismodegib as a neoadjuvant medication prior to surgical resection.[29] Other medications such as such as itraconazole and arsenic trioxide may also offer promising results for vismodegib-resistant BCCs that acquire SMO mutations.[30]

DISCLOSURES

The authors have no relevant conflicts of interest to disclose.

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AUTHOR CORRESPONDENCE

Joesph F. Sobanko MD

E-mail:.....joseph.sobanko@uphs.upenn.edu