January 2017

Treatment of Basal Cell Carcinoma with Vismodegib

Sunitha Johns  
*Ohio Northern University*

Katlyn Brown  
*Ohio Northern University*

Emily Loudermilk  
*Ohio Northern University*

Crystal Zheng  
*Ohio Northern University*

Anh Dao Le  
*Ohio Northern University*

*See next page for additional authors*

Follow this and additional works at: [https://digitalcommons.onu.edu/paw_review](https://digitalcommons.onu.edu/paw_review)

Part of the *Dermatology Commons*, *Medical Pharmacology Commons*, *Oncology Commons*, *Pharmaceutics and Drug Design Commons*, and the *Skin and Connective Tissue Diseases Commons*

**Recommended Citation**

Treatment of Basal Cell Carcinoma with Vismodegib

Authors
Sunitha Johns, Katlyn Brown, Emily Loudermilk, Crystal Zheng, Anh Dao Le, and Sophocles Chrissobolis

This article is available in Pharmacy and Wellness Review: https://digitalcommons.onu.edu/paw_review/vol8/iss1/4
Treatment of Basal Cell Carcinoma with Vismodegib

Sunitha Johns, Katlyn Brown, Emily Loudermilk, Crystal Zheng, Anh Dao Le, Sophocles Chrissobolis, Ph.D., assistant professor of pharmacology

Abstract

The most prevalent nonmelanoma skin cancers are basal cell carcinoma (BCC) and locally advanced basal cell carcinoma (aBCC). Current, effective first-line treatments for BCC aim to remove and destroy cancerous skin cells through excision surgery, Mohs surgery, radiation therapy and cryotherapy, while treatment of aBCC remains limited. An emerging treatment option for aBCC that promotes tumor size reduction is vismodegib, a pharmaceutical product approved in 2012 by the U.S. Food and Drug Administration (FDA). Vismodegib was approved for the treatment of aBCC, metastasized BCC (mBCC) or recurrent BCC after surgery as well as for use in adults who are not candidates for surgery or radiation. Vismodegib is an inhibitor of the hedgehog (Hh) pathway which is essential for cell differentiation and organ formation in embryonic development. When the Hh pathway is inappropriately activated in tissues, Hh pathway cellular growth mechanisms promote the formation of several carcinomas. Two studies reported similar responses of tumor reduction to vismodegib in patients with aBCC and mBCC. One reported the assessed response rate of 30 percent tumor shrinkage in patients with mBCC and a response rate of 43 percent tumor shrinkage in patients with aBCC. Another reported objective responses in 46.4 percent of aBCC and 30.8 percent in mBCC. While vismodegib is an option for treatment, caution should be used. Pharmacists play a critical role by counseling on proper skin care, potential drug interactions and the different side effects of treatment. Vismodegib should be continuously studied as there is currently not enough information on long-term treatment options for patients.

Key Terms

Carcinoma; Basal Cell; Hedgehog Proteins; Melanoma; Pharmacists; Skin Neoplasms; Vismodegib

Introduction

In the United States, about 3.3 million people are diagnosed with nonmelanoma skin cancers each year, causing skin cancer to be the most prevalent cancer.1 Over the past two decades, the rate of diagnosis and treatment for nonmelanoma skin cancers has increased 77 percent, with women under the age of 40 years being a fast growing, at-risk population.2 Basal cell carcinoma (BCC) is characterized by the growth of cancerous cells located in the lower epidermis. Although BCC has a lower mortality rate in comparison to its counterpart, melanoma, BCC is the most prevalent nonmelanoma skin cancer and comprises 80 percent of all skin cancers.3 About 2,000 people die from BCC and squamous cell carcinoma each year; in comparison, an estimated 10,130 people will die from melanoma in 2016.13 However, BCC deaths rates are best depicted as estimates since it is not required to report BCC or squamous cell carcinoma to cancer registries. When BCC is not treated effectively or in a timely manner, progression of the disease can result in local tissue invasion and significant morbidity and mortality.4

Basal cell carcinoma presents as nonpainful red patches or shiny bumps on the skin of the head and neck. Risk factors for BCC include sun and radiation exposure, elderly age, light-colored skin and extended exposure to certain chemicals such as coal and tar as well as arsenic found in well waters and pesticides.1-3 Current, effective first-line treatments aim to eradicate and destroy cancerous skin cells through excision surgery, Mohs surgery, radiation therapy and cryotherapy.4 Treatment options depend on tumor size and location as well as disease progression. Large tumors located on the face, fingers and genital areas have a better cure rate when treated with Mohs surgery, a complex but effective surgical option. When BCC progresses to invade significant local tissue, health care costs increase because treatment requires specialized surgical teams, postoperative hospital stays and expensive pharmacologic options.2 From 2005 to 2008, nonmelanoma skin cancer accounted for 4.5 percent of Medicare expenses making it the fifth most costly cancer to treat. Although the incidence rate of locally advanced BCC (aBCC) is hard to determine due to lack of standardized staging systems and lack of uniform reporting requirements, it has been speculated that aBCC comprises roughly 1 to 10 percent of BCC. In rare cases where the cancer advances beyond its initial site, surgery is not recommended due to potential risks for surgical disfigurement and tissue damage, depending on the extent of tissue invasion. An emerging treatment option for aBCC is vismodegib, a pharmaceutical product approved in 2012 by the FDA which promotes tumor size reduction through its inhibitory action on the hedgehog (Hh) pathway.4 This article will discuss the Hh pathway, the pharmacology of vismodegib, research studies supporting its clinical use and the role of the pharmacist in monitoring vismodegib therapy.

The Hedgehog Pathway

The Hh pathway is essential for cell differentiation and organ formation in embryonic development.5 The Hh pathway is normally suppressed in adult tissues; however, when it is inappropriately activated, Hh pathway cellular growth mechanisms promote the formation of several carcinomas. The Hh pathway was first discovered in 1980 when researchers learned of gene mutations that caused deformed bodies in fruit flies. Mutation to the Drosophila hedgehog gene resulted in the formation of the mutated polypeptide ligand (Hh ligand) which activated the abnormal Hedgehog pathway. It was subsequently reported that the gene muta-
tions were involved in early embryonic development which linked the pathway to several cancers.5,6

The first molecule developed to inhibit the Hh pathway was cyclopamine, a teratogen isolated from corn lilies.5 This naturally derived product was found to bind and inhibit Smoothened (SMO), a seven-member transmembrane protein resembling a G-protein coupled receptor. By inhibiting SMO signal transduction, cyclopamine inhibits the activation of GLI, a protein first isolated in human glioblastoma which is also an oncogene transcriptional activator. GLI has multiple actions: it mediates cell proliferation, causes upregulation of antiapoptotic proteins, causes down-regulation of apoptotic proteins, increases production of vascular endothelial growth factor (VEGF) and angiogenesis factors and decreases E-cadherin and tight junctions holding the epithelial cells together.5,7 Thus, inhibition of SMO by cyclopamine inhibits transcriptional responses of GLI, ultimately inhibiting tumor formation. As an endogenous natural defense against tumor formation, patched-1 (PTCH-1), a 12-member transmembrane protein receptor, suppresses SMO and prevents downstream activation of the Hh pathway. Abnormal reactivation of the Hh pathway occurs when a mutated PTCH-1 is unable to suppress SMO, or when the Hh ligand binds to and inactivates PTCH-1, allowing for SMO to activate tumorigenesis.5 Vismodegib was developed as a cyclopamine analog to inhibit SMO signal transduction, and thus inhibit GLI oncogene transcription (Figure 1a).8

**Vismodegib Pharmacology**

**Mechanisms of Action, Uses, Pharmacokinetics and Cost**

Vismodegib (Erivedge® Capsule, Figure 1b) was developed by Genentech, Inc. as the first selective Hh pathway inhibitor which had a higher affinity for SMO and improved pharmacokinetic properties compared to cyclopamine.5 The FDA approved vismodegib in January 2012 in adults for the treatment of the following: local aBCC, metastasized BCC (mBCC), recurrent BCC and recurrent aBCC following surgery. Vismodegib is also indicated to treat BCC patients who are not candidates for surgery or radiation.7 The National Comprehensive Cancer Network guidelines for basal cell skin cancer list vismodegib as an option for high-risk patients.9 Patients may be classified as "high-risk" if they are immunosuppressed. Basal cell carcinoma may also be deemed high-risk if the skin lesions are recurrent, have badly defined borders or have an aggressive growth pattern. Vismodegib and other Hh pathway inhibitors are limited to use in high-risk cases most likely due to the resistance potential and the known fertility issues.

---

**Figure 1. The Hedgehog (Hh) Pathway.**

The Hedgehog (Hh) pathway, which is normally suppressed in adults, is reactivated in BCC to promote tumorigenesis. In healthy individuals, patched-1 (PTCH1) inhibits signal transduction of Smoothened (SMO). In cancer patients, PTCH1 is mutated or is suppressed by the Hedgehog ligand (represented as a red hexagon in Figure 1a), and SMO is fully functional to cause the activation of oncogene transcription activator, GLI. Vismodegib inhibits SMO to prevent GLI activation. As a result, vismodegib inhibits cell proliferation, apoptosis and angiogenesis mediated by GLI.
Vismodegib is available as 150 mg capsules taken orally daily for 28 days or until remission. Vismodegib can be taken with or without food. Additional pharmacokinetic properties of vismodegib are presented in Table 1. The cost for a 28-day supply of vismodegib is $12,305.52. Vismodegib is available in the United States at specialty pharmacies through the Evredge Access Solution program.

### Adverse Effects, Warnings and Drug Interactions
Side effects (with incidence rate in parentheses) of vismodegib include: nausea (30 percent), fatigue (40 percent), weight loss (45 percent), dysgeusia (55 percent), muscle spasms (72 percent), amenorrhea (30 percent) and alopecia (64 percent). Vismodegib should be avoided in patients who have concerns about hair loss, who operate machinery and require full muscle functionality and in women who have irregular menstrual cycles. Cyclobenzaprine administration is recommended when patients experience drug-related muscle spasms. To relieve nausea and poor oral intake, dronabinol and megestrol acetate have been used, respectively.

There are no contraindications on the manufacturer’s labeling, but use in pregnant women (Pregnancy Category D) or women who are breastfeeding is strongly discouraged. Vismodegib can cause severe birth defects and embryo-fetal death, so pregnancy status needs to be verified prior to starting vismodegib therapy. During an in vivo study in pregnant rats, vismodegib caused craniofacial abnormalities, anorectal defects and absent or fused digits in hindlimbs. Therefore, it is recommended that patients and their partners use two forms of medically reliable birth control to avoid pregnancy during vismodegib therapy. Vismodegib is also present in the semen, so it is important to advise male patients to avoid donating semen during therapy and for three months after the final dose of vismodegib. Men should also be counseled to use condoms while he or his male or female partner is on treatment. In addition, since women have a risk of developing amenorrhea while on vismodegib (33 percent of patients), it is important to counsel on potential infertility. Patients should also be advised not to donate blood or blood products during therapy and within seven months after the end of treatment. Since vismodegib is a substrate for p-glycoproteins, co-administration with p-glycoprotein inhibitors such as azithromycin, clarithromycin and erythromycin may increase blood concentrations of vismodegib and thus increase risk of side effects. Drugs that alter the pH of the upper gastrointestinal tract such as proton pump inhibitors, histamine 2-receptor antagonists and antacids may affect the solubility of vismodegib and reduce its bioavailability. In addition, patients taking vismodegib concurrently with warfarin should be monitored for elevation in international normalized ratio (INR) and signs of bleeding as the high protein binding ability of vismodegib can displace warfarin from plasma proteins. A specific example of the interaction of vismodegib with warfarin was detailed in a case study published in the American Journal of Health-System Pharmacists. One patient who had been well controlled on warfarin for nine months prior to vismodegib therapy had supratherapeutic INR levels of 4.6, 9.5 and 9.3 after starting vismodegib. Other causes of the INR increase such as change in diet, alcohol or cigarette use, medications and acute illness were ruled out, so the vismodegib-warfarin drug interaction was deemed to be the probable cause of the increase in INR. Anticoagulation therapy may be necessary in vismodegib patients due to the increased risk of venous thromboembolism that occurs in malignancy. However, an alternative prophylaxis medication may be required in place of warfarin if adequate INR control cannot be maintained in patients taking concurrent warfarin and vismodegib.

### Efficacy and Safety
Two important studies evaluated the efficacy and safety of vismodegib. In the first study, Sekulic et al. conducted an experiment which involved two cohorts with the goal of measuring the efficacy and safety of vismodegib. There were 104 participants enrolled in the study over 13 months at 31 sites in the United States, Europe and Australia. The study began on Feb. 10, 2009, and was concluded nine months after the

### Table 1. Pharmacokinetics of Vismodegib

| Absorption | Highly permeable with low aqueous solubility (Biopharmaceutical Classification System Class II) Bioavailability 32% |
| Distribution | Vd = 16.4-26.6 L Plasma protein binding > 99%, primarily to albumin and alpha1 acid glycoprotein (AAG) |
| Metabolism | Oxidation, glucuronidation, pyrimidine ring cleavage carried out by CYP2C9, CYP3A4, CYP3A5 enzymes; P-glycoproteins promote efflux of drug |
| Excretion | Hepatic (82% of administered dose found in feces) Renal (4.4% of administered dose found in urine) Elimination t1/2: 4 days (for continuous once daily dosing) and 12 days (after single dose) No hepatic or renal dosing adjustments |
first treatment of the last enrolled patient on Nov. 26, 2010. Vismodegib was given until there was disease progression, unacceptable toxic effects or the discontinuation of the study. The primary endpoint was the objective response rate, and the primary hypotheses were that the response rate would be greater than 20 percent for patients with locally aBCC and greater than 10 percent for those with mBCC. For the primary endpoint, response evaluation criteria in solid tumors (RECIST) guidelines were used. This set of guidelines measures tumor shrinkage along with the development of disease progression (defined as an increase in tumor size of 20 percent or more) or regression (defined as a decrease in tumor size of 30 percent or more).

Due to the small patient population and lack of effective therapeutic options, there was no control group in the study. Patients were divided into two cohorts: 33 patients had mBCC and 71 had local aBCC. Each patient was given 150 mg vismodegib once daily. Patients received physical examination and lab testing every four weeks (including pregnancy testing for women of childbearing potential). All patients with radiographically measurable disease received a radiographic assessment of tumors, performed at baseline and every eight weeks thereafter. Both cohorts experienced a significant reduction in tumor size: 30 percent reduction in patients with mBCC ($p < 0.001$) and 43 percent reduction in patients with aBCC ($p < 0.001$). Furthermore, 64 percent of mBCC patients and 36 percent of aBCC patients were considered to have stable disease after treatment with vismodegib. Of the 63 patients included in the trial, 21 percent had a complete response (defined as the absence of residual metastatic growth of BCC on assessment of a biopsy specimen). At the end of data collection, 77 percent of patients who had a complete response had not experienced disease progression. Overall results showed that the majority of patients within the study experienced tumor shrinkage. Adverse events were reported by all patients during the study, but more than half of the patients (57 percent) experienced only mild or moderate effects. Common adverse effects included muscle spasms, alopecia, dysgeusia, diarrhea, nausea, fatigue and weight loss, were mild to moderate and occurred showing moderate symptoms requiring minimal, local, non-invasive intervention. The majority of adverse events, including muscle spasms, dysgeusia, alopecia, diarrhea, nausea, fatigue and weight loss, were mild to moderate and occurred within the first seven treatment cycles. Grade 3 adverse events were seen in 24 patients, meaning that the patients experienced severe or medically significant but not immediately life-threatening effects. The only vismodegib-related serious adverse event reported was muscle spasm, seen in 1 percent of the population. Grade 4 responses, defined as life-threatening events requiring immediate care, were seen in nine patients. These included diarrhea and muscle spasms. Only two patients experienced a grade 5 adverse event, which resulted in death. All deaths were considered due to disease progression and not treatment related.

A study by Chang et al. assessed efficacy and safety of vismodegib in patients in an open-label multicenter study with two cohorts: local aBCC and mBCC. The study population consisted of 120 patients; 62 in the aBCC cohort and 58 in the mBCC cohort. However, only 119 patients were considered safety-evaluable, of which 95 were considered efficacy-evaluable. Patients included in the study had to be at least 18 years of age with good organ function and having measurable disease state based on RECIST version 1.0 guidelines. Exclusion criteria included major organ dysfunction, pregnant or lactating mothers, women unwilling to practice birth control, completion of anti-tumor therapy less than 21 days before treatment initiation, a history of other diseases or uncontrolled medical conditions, or those who had less than 12 weeks of life expectancy. Patients received 150 mg of vismodegib daily until either the disease progressed or there was intolerable toxicity. Tumors were assessed with the RECIST guidelines. One treatment cycle was defined as 28 days, and patients were physically assessed every one to two treatment cycles. Patient assessment parameters included complete blood cell count, metabolic panel and adverse event recordings.

Within the patient population, 56 patients with local aBCC and 39 patients with mBCC were evaluated for efficacy. Objective tumor responses of 46.4 percent and 30.8 percent were met by local aBCC and mBCC patients, respectively. Objective tumor responses, defined as the best overall complete response or partial response, were confirmed by investigators using two consecutive tumor assessments performed at least four weeks apart according to RECIST version 1.0. Complete response was achieved in 8.4 percent of total patients, partial response was seen in 31.6 percent of total patients and 49.5 percent of all study patients experienced stable disease. Overall, 94.6 percent patients in the local aBCC cohort and 82.1 percent patients in the mBCC cohort had complete response, partial response or stable disease. Only three patients with mBCC exhibited progressive disease, whereas no patient within the local aBCC cohort experienced progressive disease.

Almost all safety-evaluable patients experienced a treatment emergent adverse event, typically within grades 1 and 2. A grade 1 adverse event is characterized by mild symptoms or no symptoms, while a grade 2 adverse event is defined as showing moderate symptoms requiring minimal, local, non-invasive intervention. The majority of adverse events, including muscle spasms, dysgeusia, alopecia, diarrhea, nausea, fatigue and weight loss, were mild to moderate and occurred within the first seven treatment cycles. Grade 3 adverse events were seen in 24 patients, meaning that the patients experienced severe or medically significant but not immediately life-threatening effects. The only vismodegib-related serious adverse event reported was muscle spasm, seen in 1 percent of the population. Grade 4 responses, defined as life-threatening events requiring immediate care, were seen in nine patients. These included diarrhea and muscle spasms. Only two patients experienced a grade 5 adverse event, which resulted in death. All deaths were considered due to disease progression and not treatment related.

Overall, both studies showed similar responses to vismodegib in patients with local aBCC and mBCC. This medication should be continuously studied, as there is not extensive information available regarding long-term vismodegib treatment. Vismodegib is FDA-approved for use in adults but has yet to be examined in children. Clinical trials examining the efficacy and safety of vismodegib in larger patient populations are currently underway.

Clinical Relevance and the Pharmacist’s Role
As one of the most accessible health care providers, pharmacists can play an important role in vismodegib therapy. In addition to answering questions patients may have about the drug or drug therapy, pharmacists can also counsel on the importance of proper skin care. Simple steps such as wearing a hat, wearing sunscreen with both ultraviolet A and ul-
travvet B protection and limiting exposure during midday when the sun is at its strongest can help to prevent new or worsening skin cancer. Pharmacists can also assist with monitoring the color, size, border and symmetry of moles.

As previously mentioned, it is critical that patients use proper pregnancy prevention while taking vismodegib and for a period after vismodegib is discontinued (seven months for women and three months for men). Pharmacists should remind both male and female patients of the teratogenicity risks associated with vismodegib and aid in selection of birth control methods. Vismodegib has been shown in animal models to have a potential for irreversible infertility which may be problematic for patients of childbearing age. It may be necessary to explore other drug options if a patient desires to expand his or her family. Pharmacists are well-positioned and qualified to aid patients in creating reproductive life plans and selecting the best birth control methods to fit the patient's lifestyle. Furthermore, pharmacists can make referrals for counseling or other services that would benefit patients. Importantly, pharmacists can also play a part in helping minimize drug interactions. This is particularly true for the interaction between vismodegib and warfarin, especially as pharmacist-run anticoagulation clinics become more prominent.

Since vismodegib is a specialty drug (a drug that is unable to be dispensed at a community pharmacy due to side effects or increased complexity of administration, handling or billing), pharmacists may not be included in every step of the billing process. Billing may be conducted by a specialty pharmacy division which handles prior authorizations and other steps necessary to get the medication covered by insurance. If a patient needs further financial assistance, he or she can be directed to the manufacturer's website, www.erivedge.com. In the website's financial support section, there are four simple questions to determine if the patient is eligible for a co-pay card from Genentech. The site also contains valuable information including tips for managing side effects, frequently asked questions and support for patients and health care professionals.

Conclusion

Overall, vismodegib therapy should be considered as an option for high-risk aBCC and mBCC patients who can be monitored monthly. Most patients have experienced stabilization or resolution of disease with this drug while experiencing only mild or moderate side effects. Still, monitoring of tumor size is important since there is resistance potential, which could lead to treatment failure. While vismodegib has shown benefits in patients being treated for local aBCC and mBCC, use of this drug in patients with a desire to start or expand a family should be done with extreme caution due to the importance of the Hh pathway in fetal development.

References