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Advanced Basal Cell Carcinoma: Therapeutic Options and Considerations for Patient Care

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EDITORIAL

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Statement of Need

The standard of care for non-melanoma skin cancers (NMSC), including the advanced stages of basal cell carcinoma (BCC), are currently surgery and radiation. However, if the tumor is located where such treatment may cause significant change in appearance or loss of function, or if it reoccurs after traditional therapy, these treatments prove ineffective or are not an option. This leaves the dermatologist with few viable options to manage the disease, and presents a challenge for improving patient quality of life and general health.

Recently there has been increased research into treatment options for NMSCs that reports on the advanced understanding of their genetics. This has led to increased interest in the role of the sonic hedgehog (Hh) pathway, its role in the pathogenesis of advanced BCC, and a new oral inhibitor of the Hh pathway as a systemic treatment for patients not amenable to surgery or radiation. This supplement will educate dermatologists about advanced BCC, including the signs, symptoms and early detection, patient classification, epidemiology, limitations of current treatment regimens, and emerging new treatments. By drawing on research from recently published literature, as well as clinical evidence and perspectives of leading experts from the discipline of dermatology and dermatologic surgery/oncology, it presents the most current information on new targeted treatment strategies, including inhibition of the Hh signaling pathway for the treatment of locally advanced BCC.

Educational Objectives

This activity is a multi-specialty, evidence-based initiative designed to increase the knowledge and competence of dermatological practitioners by providing them with the simultaneous integration of knowledge, skills, and judgment from thought-leader testimonials, science-based research, and evidence-based data to address the difference between present patient outcomes and those considered achievable in the field of dermatology.

Upon completion of this activity, participants should be able to:

1. Recognize the impact of inoperable advanced BCC, including the economic, physical, and psychological burden of the disease
2. Differentiate disease characteristics and diagnostic markers to better identify patients with advanced BCC
3. Discuss the mechanism of action of vismodegib and the role of Hh pathway inhibition in the management of advanced BCC
4. Evaluate data from recent clinical trials and published literature on the use of biologic response modifiers in the treatment of advanced BCC
5. Integrate innovative treatment plans for patients with positive margin BCC whenever appropriate

Target Audience

This activity is intended for dermatologists, residents in dermatology, and physician assistants who need continued education for understanding when vismodegib is applicable and when it is not, how the drug works, and which adverse events are associated with it.

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Introduction

Kenneth R. Beer MD FAAD

The treatment of basal cell carcinoma (BCC) has remained largely unchanged for the past 50 years. Recently, the use of immunomodulators such as imiquimod have been used to treat early lesions. However, the treatment of inoperable BCC did not evolve significantly until the advent of vismodegib. This drug inhibits the hedgehog pathway, which is often defective in BCC, and the United States Food and Drug Administration has approved vismodegib to treat BCC that is locally advanced or metastatic. The use of this drug requires physicians to have an understanding of where it is and where it is not applicable, how the drug works, and which adverse events are associated with it. This supplement details one case of locally advanced BCC and provides information on the therapeutic decisions made for the patient detailed. In addition, information about the mechanisms of action for vismodegib and the burden of disease imposed by advanced or metastatic BCC are provided to help clinicians gain an understanding of the true burden of this disease.

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Treatment of Margin Positive Basal Cell Carcinoma With Vismodegib: Case Report and Consideration of Treatment Options and Their Implications

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ABSTRACT

Historically, basal cell carcinomas (BCCs) that are neither surgically resectable nor candidates for radiation therapy have had few treatment options. The hedgehog pathway inhibitor, vismodegib, represents a new opportunity for the treatment of such patients. Vismodegib has approval from the United States Food and Drug Administration for treatment of metastatic BCC, locally advanced BCC recurring after surgery, and BCC that is not treatable via surgery or radiation. We present the case of a patient with a BCC infiltrating the spinal column that was neither possible to fully remove surgically nor a candidate for primary treatment with radiation. Treatment with vismodegib followed by adjuvant radiation therapy resulted in complete disease clearance. Vismodegib represents a promising treatment option for patients with surgically non-resectable BCCs that are not candidates for radiation therapy. Mechanism of action, benefits, and adverse events of vismodegib are reviewed, along with a brief discussion on newer options in the hedgehog inhibitor class.

J Drugs Dermatol. 2013;12(suppl 10):s147-s150.

INTRODUCTION

Basal cell carcinoma (BCC) is frequently associated with mutations in the s (PTCH) gene leading to dysregulation of the hedgehog (Hh) pathway.[1-3] This mutation is seen in more than 90% of BCCs and causes uninhibited tumor growth. Fortunately, the majority of BCCs are easily treated with a variety of modalities including surgery (electrodesiccation and curettage, Mohs), radiation, topical immunomodulation, and cryosurgery. However, for some patients, the removal of a BCC, either using Mohs micrographic surgery or intraoperative frozen sections, may not result in clear pathologic margins. For these patients, subsequent treatment is not standardized, but options usually include additional Mohs, radiation, or, for those unable to undergo further surgery or radiation, topical 5-fluorouracil, topical imiquimod, photodynamic therapy, or cryotherapy.[4-7] Lesions that are surgically non-resectable due to their proximity to vital structures or the risk of cosmetic deformation may also not be subject to radiation therapy. Moreover, when surgical extirpation of BCCs is aborted because of their proximity to adjacent sensitive structures, such as peripheral motor nerves or the central nervous system, the possibility of adjunctive radiation therapy is often ruled out too. Until recently, traditional chemotherapy has been ineffective for the treatment of BCCs, and patients with non-resectable BCC have had few treatment options. However, the advent of vismodegib (Erivedge®; Genentech) presents an opportunity to treat patients with partially resected disease.

This population of patients represents an unmet need with historically few treatment options. In this report, we discuss one patient treated with vismodegib following positive surgical margins. In addition to a discussion of vismodegib, therapeutic choices available to control BCC postoperatively when positive margins are obtained will also be discussed.

Case Report

A 69 year-old man presented to his primary care physician with a large lesion on his back (Figure 1). According to the patient, the lesion had been there for more than 10 years and was not causing him any discomfort. He had been caring for the lesion at home with simple dry dressing changes. However, when it began to bleed on a consistent basis, he sought care from his primary care physician. The patient was ultimately admitted to the hospital for evaluation and management of the lesion.

Examination at presentation revealed a 24 cm x 30 cm lesion on his middle back. There was adhesion to the underlying structures with a friable, hypergranulated surface. Computed tomography (CT) scans revealed a large lesion extending from T5 to T11 that measured approximately 17 cm (Figure 2). A surgical biopsy demonstrated an infiltrative BCC (Figure 3). Based on the physical examination, it was decided that resection of the lesion would be the optimal treatment approach.

FIGURE 1. Preoperative presentation of the basal cell, which spans the entire width of the patient's back. The surface is friable and bleeding.

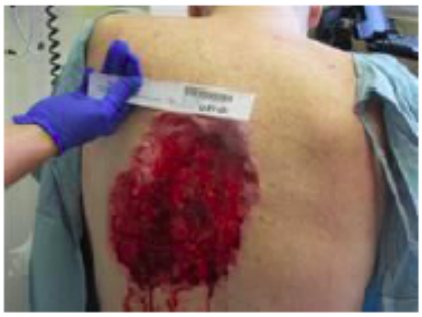


FIGURE 2. Computed tomography scan obtained prior to surgery demonstrates the depth and span of the lesion. The size of the lesion fulfills criteria for use of oral treatment with vismodegib.

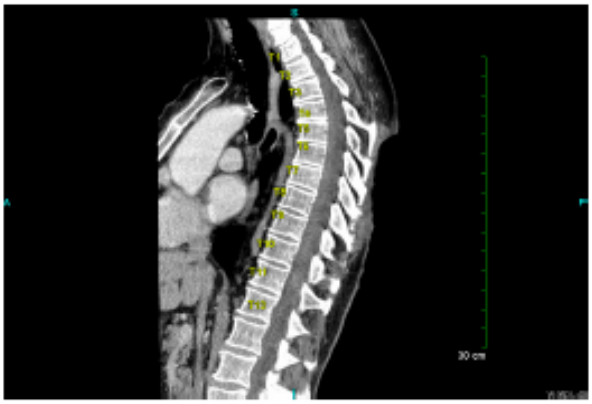


FIGURE 3. Pathologic evaluation of a biopsy revealed an infiltrative basal cell carcinoma.

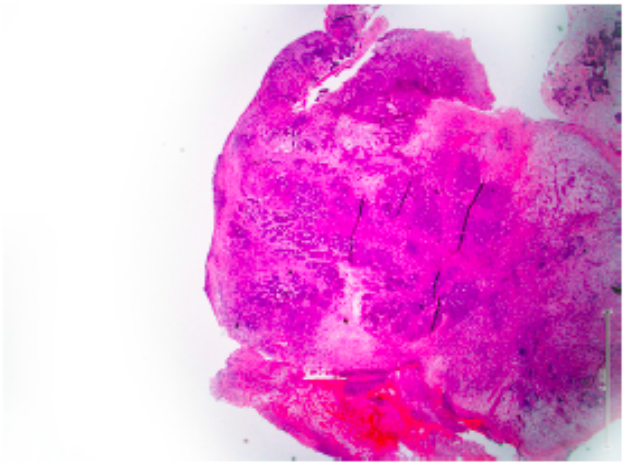
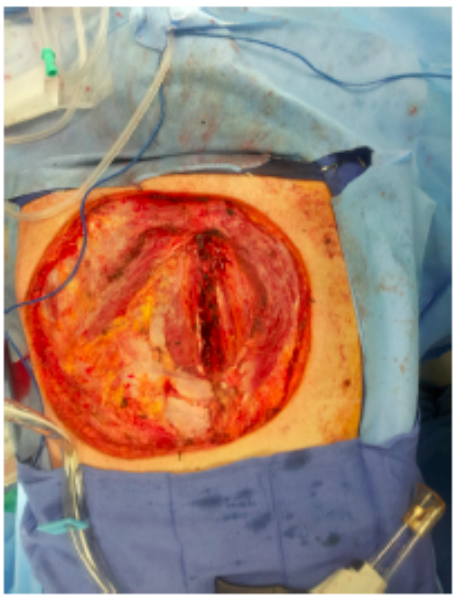


FIGURE 4. Intraoperative examination of the depth and breadth of the lesion. Clear surgical margins were not achievable.



Alternatives to surgery, including radiation and topical imiquimod, were considered. Given the extensive size of the tumor and the dose of radiation required with proximity to the spinal cord, radiation would pose significant risk to the central nervous system. Topical imiquimod was considered inappropriate because it would likely be ineffective for such a deep tumor.

During surgery, it became apparent that the size and depth of the tumor were substantially greater than initially appreciated via CT scan and that the tumor had infiltrated into the spinous processes of multiple vertebrae (Figure 4). Alternatives for treatment included complete resection of the affected spinous processes or termination of the surgical procedure. Because of the length of the procedure and the involvement of multiple vertebral levels, it was elected to terminate the resection and reconstruct the defect using left and right paraspinous muscle flaps as well as right and left latissimus dorsi flaps. A second stage operation was performed for skin graft closure over the muscles.

The patient had an uneventful recovery and his surgical site healed without any complications. Treatment options for the patient were discussed based on the depth and location of the tumor. These included radiation, observation, additional surgery with neurosurgical participation, or treatment with an oral Hh inhibitor, such as vismodegib.

After consultation with an oncologist and a dermatologic surgeon, it was decided to initiate treatment with vismodegib at 150 mg per day.

After using vismodegib for approximately 3 months, the patient elected to discontinue this treatment due to adverse events (AEs), primarily lethargy and dysgeusia. He was subsequently evaluated by radiation oncology and treated with radiation; the risk of radiation injury to the spinal column at this point was determined to be less than the risk of leaving the remaining

BCC untreated. At the time of publication, 6 months after this course of treatment, there is no evidence of disease. As with other high-risk patients, he will be monitored closely.

"Vismodegib represents a promising treatment option for patients with surgically non-resectable basal cell carcinomas that are not candidates for radiation therapy."

DISCUSSION

There are significant issues in the treatment of partially resected BCCs, the most salient of which has been the lack of treatment options for patients with BCCs located near vital structures. Patients with large BCCs are a second category of patient for whom treatment options have been suboptimal to date. One consideration when considering treatment options for patients with positive margins is the fact that approximately one-third of these patients are subsequently found to have no residual tumor when repeat surgery is performed.[8] Fortunately, other treatment options exist, such as topical 5-fluorouracil, topical imiquimod, photodynamic therapy, or cryotherapy.[4-7] However, these options are not sufficient for locally advanced or metastatic BCCs. In January 2012, the United States Food and Drug Administration (FDA) approved vismodegib for the treatment of metastatic BCC or locally advanced BCC that has recurred after surgery, as well as for patients who are not candidates for surgery or radiation.

Patched homologue 1 (PTCH1) normally functions to inhibit smoothened (SMO) signaling. Without this inhibition, SMO induces transcription factors in basal cells that promote cell proliferation and growth. Hedgehog is key in the development of BCC by inhibiting PTCH1, and thus eliminating the inhibition of SMO, ultimately resulting in cell proliferation.[9,10] Basal cell carcinomas most often result from loss of function mutations in PTCH1, but may also arise from activating mutations in SMO. The significance of vismodegib to BCC is in its ability to bind to and inhibit SMO, thereby bringing about crucial inhibition of basal cell proliferation regardless of whether the mutation is in PTCH1 or SMO.

In a phase 1 study to assess the safety and tolerability of vismodegib, 15 patients with locally advanced basal tumors, as with our patient, were enrolled. Two of these patients demonstrated complete clinical response, 7 showed partial response, 4 had stable disease, and 2 had progressive disease. In those who responded, median duration of response was 8.8 months.[9] A phase 2 study to further assess efficacy and safety showed complete response in 13 patients (21%) with locally advanced BCC with a median duration of response of 7.6 months and median progression-free survival of 9.5 to 1.3 months.[3]

Adverse events identified during these studies included fatigue, muscle spasms, alopecia, dysgeusia, weight loss, anorexia, dyspnea, nausea, diarrhea, arthralgias, vomiting, and constipation. Three of 10 premenopausal women developed amenorrhea. Hyponatremia, azotemia, and hypokalemia were the most serious laboratory anomalies that arose. Rare events included atrial fibrillation, dyspepsia, aspiration, back pain, corneal abrasion, dehydration, keratitis, lymphopenia, pneumonia, urinary tract infection, prolonged QT interval, cholestasis, pulmonary embolism, dehydration and/or syncope, hypocalcemia, elevated alkaline phosphatase, and hyperkalemia; most of these developed in no more than one patient.[3,9,11-13] All patients in the phase 2 trial experienced at least one AE.[3]

While the most common side effects are generally considered to be minor-to-moderate in severity, they can be unbearable for some patients. Their high frequency has resulted in many patients opting to discontinue the medication, a very unfortunate dilemma for patients in need of vismodegib as a therapeutic option. Another concern and potential limitation of vismodegib is the potential for resistance as well as a recurrence of BCC once the medication is discontinued. In one retrospective review, 21% of patients with advanced BCC experienced tumor regrowth while still on vismodegib treatment.[14]

Future options for these difficult to treat advanced BCCs are under study. Several inhibitors of GLI, a transcription factor downstream of SMO, have been identified.[10,15,16] The antifungal itraconazole is also a Hh inhibitor and is under investigation for its applicability to BCC treatment, potentially in combination with arsenic trioxide.[10] While the common AEs associated with vismodegib are thought to be a class effect of Hh inhibitors, it remains to be seen whether or not the side effects with these newer therapeutic options will be as significant or as unpleasant for patients, and how their efficacy compares to that of vismodegib.

CONCLUSION

The patient presented represents an unusual and instructive case because he presented with easily monitored disease, but no traditional treatment alternatives seemed to offer promise for disease control. The proximity of his tumor to his spinal cord mandated that some type of treatment be instituted to protect his central nervous system.

Patients with partially treated BCCs often present with similar circumstances to the patient presented in this report: they may have had Mohs surgery or other margin-controlled surgery that was not successful because of anatomic boundaries that could

not be breached. Metastatic BCC and BCCs that cannot be resected are rare. Whereas some of these non-resectable patients may be treated with radiation, many are not candidates for this modality due to proximity to vital structures. For these patients, vismodegib offers a valuable alternative for treatment.

DISCLOSURES

Kenneth Beer MD FAAD receives fees from Genentech for speaking and research. Stephanie Bayers BSBA, Daniel Kapp MD FACS, and Benjamin Slavin have no conflicts of interest to disclose.

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The Impact of Inoperable Advanced Basal Cell Carcinoma: the Economic, Physical, and Psychological Burden of the Disease

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ABSTRACT

The development of vismodegib and its recent approval by the United States Food and Drug Administration for use in patients with locally advanced or metastatic basal cell carcinoma (BCC) carries with it a renewed sense of optimism. Once BCC has progressed to an advanced, or so-called inoperable stage, there has been a paucity of effective therapies, making the new small molecule inhibitors targeting the hedgehog pathway particularly hopeful prospects. In order to better understand the utility of these new treatments, it is important to assess the existing economic, physical, and psychological burden of advanced BCC. This review aims to recognize the impact of inoperable and metastatic BCC, as well as to better characterize the various types of advanced BCC. The use of vismodegib as a prophylactic treatment in patients with basal cell nevus syndrome is also addressed, including possible adverse events, tumor resistance, and new onset malignancies.

J Drugs Dermatol. 2013;12(suppl 10):s151-s153.

INTRODUCTION

While the overwhelming majority of basal cell carcinoma (BCC) is effectively managed with surgery, causing minimal distress to the patient, individuals whose BCC has metastasized or progressed to an inoperable state are severely affected by their disease.[1] The physical disfigurement from advanced lesions as well as concern about life expectancy affect both quality of life (QOL) and the psychological state of the patient.[2] In interviews with clinicians, Shingler et al found that the most common symptom of patients with advanced BCC was embarrassment from either the dressings or the lesions themselves. Metastatic lesions may weep or bleed, have the potential to become infected, and consequently can become malodorous.[2] As a result, patients with advanced BCC may isolate themselves from family, friends, and the workplace, despite the fact that they may be physically able to carry on with the normal activities of daily life. Anxiety and depression can also often accompany this social isolation.[2]

Because BCC metastasis is extremely rare, with a reported incidence of 0.0028% to 0.5%, it is difficult to quantify the economic, physical, and psychological impact of the disease.[3,4] There has been very little in the medical literature that attempts to investigate how and to what extent the QOL is affected in patients with advanced BCC, as case reports only offer qualitative information regarding the burden of the disease. In an attempt to capture social utility values associated with different levels of advanced BCC, Shingler et al employed a newer methodology known as the time trade-off (TTO) measurement.[2] A representative sample of the general public in the United Kingdom was asked to choose between living in a particular health state with advanced BCC for 10 years vs living in a state of full health for 10-x years.[2] The TTO method was used to calculate utility values based upon the responses to these scenarios.[2] The health states of advanced BCC used in the valuation exercise included the following: complete response (CR), post-surgical state, partial response (PR) with small growth, PR with large growth, stable disease (SD) with small growth, SD with multiple growths (at 2 cm), SD with large growth, progressed disease (PD) with small growth, and PD with large growth.[2] Small growth was defined as 2 cm and large growth as 6 cm. While the study was limited in its ability to capture all possible presentations of advanced BCC, several important findings did emerge.

Not unexpectedly, the highest mean utility value, or amount of time participants were willing to trade for a full state of health, was for the complete response state (94%). The lowest utility value was progressed disease with large growth (67%).[2] The size and number of lesions was also found to be an important influence on QOL, and those states were accordingly valued. The most interesting finding of all was that the post-surgical state was valued second to last at 74%.[2] The post-surgical state was found to have even more impact on QOL than progressed disease with small growth, suggesting that the general public perceives the impact of disfigurement from extensive surgery for advanced BCC just as debilitating as the experience of progressed disease. From these data, Shingler et al concluded that patients with larger lesions as well as those with numerous lesions would benefit from non-surgical intervention.[2] Additionally, treatment efforts to reduce the size and number of lesions were also highly valued by patients.

In addition to the physical and psychological impact of advanced BCC, the financial burden of non-melanoma skin cancer

(NMSC) is also significant. As the prevalence of NMSC has globally increased over the past 3 decades, the costs involved in treatment and management have also risen.[5] Between 1992 and 2006, the number of procedures performed for NMSC in the United States rose by 76.9%.[6] Although treatment for an individual case of BCC is low compared with other malignancies (approximately $492 in a physician's office setting), NMSC ranks fifth for cancer cost in the Medicare population.[6,7] This equates to 4.5% of all Medicare cancer costs.[6,8]The cost of treatment for an episode of BCC is positively correlated with tumor size and anatomical site. Lesions on the head and neck or feet are associated with a higher cost.[6] In 2004, the total direct cost associated with treatment for NMSC was $1.5 billion.[9]

For patients with multiple BCCs requiring frequent and recurrent treatment, preventative management with a targeted molecular therapy offers promise. Genentech offers a one-month supply of once-daily capsules of vismodegib for $7,500, which comes out to $250 per capsule.[9] While the length of treatment may vary by patient, the expected length of therapy is 10 months. This is a conservative estimate since the endpoint for BCC treatment remains undefined. Thereby, the total average cost is $75,000.[9] This represents a cost increase of 150-fold over the current modalities. The sales projections in Europe are predicted to reach $401 million by 2015, and peak at $533 million in 2022.[9]

Differentiate Disease Characteristics and Diagnostic Markers to Better Identify Patients With Advanced Basal Cell Carcinoma With the Presence of Basal Nevus Syndrome

While the majority of BCC cases are found early and effectively cured by surgery and other treatment modalities, the minority that present late can progress to life-threatening, unresectable, advanced BCC, either in the form of locally advanced BCC or metastatic BCC tumors.[2,8] Late presentations and progression to advanced disease can occur due to a variety of factors. The patient may not have sought out timely treatment due to denial or neglect, or perhaps due to lack of finances or access to health care.[5] Psychiatric comorbidities can also play a role in the progression of BCC to advanced disease.[5] The point at which BCC becomes "advanced" or "inoperable" is somewhat subjective, as some physicians may be more willing than others to attempt surgical treatment, based on experience and expertise. Additionally, surgery may be precluded as a treatment modality secondary to patient age or comorbidities. In these situations, a multidisciplinary team comprised of experts in dermatologic surgery, surgical oncology, head and neck oncologic surgery, radiology, medical oncology, and radiation oncology should be considered.[10]

The instances when advanced BCC tumors develop despite aggressive treatment are known as "high risk BCC." These lesions are characterized by several markers hypothesized to be related to a more aggressive BCC tumor phenotype.[5] Characteristics include long duration, location on central face or ears, diameter greater than 2 cm in size, aggressive histologic subtype, perivascular or perineural spread, a history of radiation exposure, incomplete treatment, or previous treatment failure.[5,11,12] Other reasons, however, for this high risk phenotype are not fully understood at this time.[8]

> "Once basal cell carcinoma has progressed to an advanced, or so-called inoperable stage, there has been a paucity of effective therapies, making the new small molecule inhibitors targeting the hedgehog pathway particularly hopeful prospects."

While large BCCs are difficult to manage, the size itself does not necessarily deem a BCC "inoperable" or metastatic. In fact, certain BCCs that appear "typical" may very well be recurrences requiring multiple procedures, which, in turn, become inoperable or metastatic. In the past, radiation was the only alternative for these patients. However, there are certain skin conditions in which radiation is contraindicated, such as basal cell nevus syndrome (BCNS) or xeroderma pigmentosum.[8]

Basal cell nevus syndrome is an autosomal dominant disorder characterized by multiple basal cell carcinomas with onset occurring between puberty and 35 years of age.[13] The current prevalence is estimated to be 1/57,000 to 1/256,000.[13] Males and females are equally affected, and the syndrome has been found across multiple ethnicities and geographic locations.[13] The classical clinical triad of BCNS is multiple BCCs, jaw keratocysts, and bifid ribs. Additional clinical features may include craniofacial defects such as macrocephaly, frontal bossing, and coarse facial features, facial milia, downward sloping shoulders, palmar-planar pits, ectopic intracranial calcifications, and central nervous system defects.[12,13] As the syndrome may manifest in a variety of ways, the diagnosis of BCNS is fulfilled with 2 major criteria and 1 minor criterion, or 1 major criterion and 3 minor criteria.

Basal cell nevus syndrome is caused by mutations in the sonic hedgehog (SHh) pathway, with the most common mutation located in the patched homologue 1 (PTCH1) gene, a tumor suppressor gene mapped to chromosome 9q22.3.[13] The SHh pathway, while essential during embryogenesis for cell proliferation and growth, typically becomes inactive during adulthood.[10] Patched homologue 1 is a SHh receptor on the cell membrane that suppresses the activation of another transmembrane protein, smoothened (SMO), a SHh pathway activator.[13] When the

secreted SHh protein binds to its receptor, PTCH1, it activates SMO. Once activated, SMO promotes downstream transcription of target genes and activates other transcription factors in the glioma-associated oncogene (GLI) family, including GLI1 which is specifically involved in cellular proliferation and growth.[8,12] Glioma-associated oncogene 1 serves as a transcription factor for itself, as well as inducing PTCH1 transcription, creating a negative feedback loop.[13] In an individual with BCNS, however, PTCH1 genes are mutated and inappropriately inactivated, leading to unregulated simulation of the SHh pathway because the PTCH1 protein cannot effectively inhibit SMO. Constitutive activation of SHh causes abnormal cell growth and carcinogenesis, leading to multiple BCCs.[13] In cases of sporadic BCC, not only have loss-of-function mutations in PTCH1 been implicated in 30% to 40% of cases, but also gain-of-function mutations activating SMO are also a possible mechanism as SMO is mutated in about 10% of sporadic BCC cases.[5,11]

Because radiation is contraindicated in BCNS and other genetic syndromes that predispose one to skin cancer, few treatment options remain for these patients. Topical therapy, such as 5-floro-uracil and imiquimod, photodynamic therapy, and cryotherapy, may be used, but they are less effective than the conventional treatments of surgery and radiation.[9] Prior therapies have included chemotherapy (ie, cisplatin-based chemotherapy) as well as molecular targeted therapies (ie, cetuximab).

One of the most recent additions to the armamentarium of therapies for patients with BCNS has been vismodegib (Erivedge®; Genentech). Vismodegib was approved by the United States Food and Drug Administration in January 2012 as the first oral medication for adults with metastatic or locally advanced BCC that has recurred after surgery or for patients who are not candidates for surgery or radiation.[9] This medication is particularly promising as a prophylactic agent because the number of BCCs among patients with BCNS is high, ranging from hundreds to thousands in a single patient.[14] Tang et al studied the use of vismodegib in patients with BCNS and found that the drug significantly reduced existing BCC tumor burden as well as blocked the growth of new BCCs.[14] However, adverse events (AEs), such as dysgeusia, hair loss, muscle cramps, and weight loss, led to discontinuation of over half the patients enrolled in the study.[14] In addition to these AEs, there are recent reports in the literature of patients on vismodegib experiencing secondary (acquired) resistance to treatment, even in patients with BCNS.[15] Chang et al studied 28 patients with advanced BCC on continuous vismodegib therapy and found that 21% developed at least one tumor regrowth.[16] While the molecular mechanism for this acquired resistance is still unclear, it is important to closely monitor patients on vismodegib as this may be an increasing phenomenon that is only beginning to be described.[16] Additionally, there have been reports in the literature of the development of rapid new onset keratoacanthomas (KAs) and squamous cell carcinomas (SCCs) associated with vismodegib treatment.[17] While KAs and SCCs have previously not been associated with SMO inhibitors, such cases warrant further investigation, especially since hereditary disorders such as BCNS would require long-term therapy. As promising as vismodegib may be, systemic therapy for advanced BCC is not curative, requires long-term treatment, and should not take the place of curative procedures such as surgery.[10]

DISCLOSURES

John A. Carucci MD PhD has served as an advisory board participant and clinical investigator for Genentech, Novartis, and Pfizer. Arielle W. Haves BA and Panta Rouhani Schaffer MD PhD MPH have no conflicts of interest to disclose.

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

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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.

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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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1. Vismodegib is approved for the treatment of:
   a. Metastatic basal cell carcinoma
   b. Basal cell carcinoma that is greater than 10 mm in size
   c. Basal cell carcinoma that not operable because of anatomic or cosmetic structures in the area
   d. All of the above

2. Vismodegib works by:
   a. Inhibiting the hedgehog pathway.
   b. Inhibiting replication of basal cell carcinoma cells based on inhibition of DNA synthase
   c. Amplification of BRAF proteins
   d. Stimulation of toll-like receptors

3. Among the most common adverse events associated with the use of vismodegib are the following:
   a. Dysgeusia
   b. Loss of vision
   c. Fatigue
   d. a and c

4. Advanced basal cell carcinoma may be defined as all of the following EXCEPT:
   a. Inoperable basal cell carcinoma due to size or anatomic location of lesion
   b. Metastatic basal cell carcinoma
   c. Inoperable basal cell carcinoma due to patient's age, comorbidities, and/or overall health status
   d. Localized superficial basal cell carcinoma
   e. Locally advanced basal cell carcinoma

5. Characteristics of high risk basal cell carcinomas include:
   a. Location on central face or ears
   b. Diameter greater than 2 cm in size
   c. Perivascular or perineural spread
   d. A history of radiation exposure
   e. All of the above

6. The classical clinical triad of basal cell nevus syndrome includes:
   a. Palmoplantar pits, sternal clefting, and frontal bossing
   b. Multiple basal cell carcinomas, jaw keratocysts, and bifid rib
   c. Absence of patella, dermoids cysts, hirsutism
   d. Multiple basal cell carcinomas, palmoplantar pits, and frontal bossing
   e. Mutiples basal cell carcinomas, diabetes insipidus, and pilomatricomas

7. BCNS is due to a mutation of the _____ pathway:
   a. Ras-Raf
   b. Sonic hedgehog
   c. Wnt/*β-catenin*
   d. BRAF
   e. Mismatch repair

8. Vismodegib targets which of the following receptors:
   a. Nuclear membrane bound transcription receptor GLi1
   b. Tyrosine kinase transmembrane receptor
   c. PTCH1 transmembrane receptor
   d. Smoothened transmembrane receptor
   e. Cytoplasmic steroid receptor

9. During normal adult life, the hedgehog pathway is:
   a. Largely inactivated, except for times of cell proliferation
   b. Essential to normal epithelial differentiation
   c. Critical to maintain immune system tolerance
   d. Key to DNA repair activities

10. The most common hedgehog pathway mutation found in sporadic basal cell carcinomas leads directly to:
    a. Increased affinity for Hh ligand
    b. Inactivated PTCH1
    c. Decreased smoothened activity
    d. Increased tyrosine kinase phosphorylation
    e. Hyperactive JAK/STAT signaling

11. Phase 1 and 2 trials of vismodegib in advanced basal cell carcinoma demonstrated response rates of approximately:
    a. 10%-15%
    b. 25%
    c. 30%-60%
    d. 50%-80%

Evaluation Form

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