Abstract

The most common cancer in both men and women is basal cell carcinoma (BCC). Although most primary and recurrent BCCs have high cure rates with standard therapies, advanced BCCs present a greater treatment challenge, especially in cosmetically and functionally sensitive areas. In patients unable to undergo surgery or radiation therapy, hedgehog inhibitors can be used neoadjuvantly to reduce tumor size, decreasing the extent and complexity of any subsequent surgery and providing either a cure or palliation. The goal of this review is to summarize the pharmacology, efficacy, and safety of systemic hedgehog inhibitors, as well as their role in daily practice as neoadjuvant therapy. Relevant English-language literature was identified and evaluated based on results from database searches of PubMed. Terms searched included, but were not limited to, “vismodegib,” “Erivedge,” “sonidegib,” “DE225,” “BCC,” and “neoadjuvant treatment.” Additional literature was identified from the reference lists of previously identified articles. The authors’ personal experience in treating advanced BCC using hedgehog inhibitors has been incorporated into the recommendations made herein.

The most common cancer in both men and women is basal cell carcinoma (BCC). Ultraviolet exposure is the major risk factor, although other factors, such as fair skin, immunosuppression, and light-colored hair, can also contribute. Although it can occur anywhere on the body, BCC is most likely to arise on the head and neck, which has the greatest ultraviolet exposure. Treatment of appropriately selected BCCs with standard excision or Mohs surgery results in high cure rates. Non-surgical treatments include topical 5-fluorouracil and imiquimod, photodynamic therapy, cryotherapy, and electrodesiccation and curettage of properly selected low-risk tumors, and radiation therapy (RT) treatment for other selected lesions.

This article discusses the implementation of Hedgehog (Hh) pathway inhibitors in daily practice as neoadjuvant therapy of locally advanced BCCs with aggressive, recurrent, or metastatic features, and presents a case illustrating the authors’ experience. Although results from clinical trials have been promising, currently Hh inhibitors should not replace surgical treatment for most BCCs, and no other pharmacologic therapies exist that are consistently effective. In select cases, Hh inhibitors may be used either alone to treat inoperable tumors or neoadjuvantly as part of a multimodality treatment plan, with the goal of decreasing primary tumor size before excision to ensure tumor clearance and improve functional outcome and cosmesis.

Mechanism of Action of Systemic Hh Inhibitors

The Hh signaling pathway plays a key role in vertebrate embryonic development, including cell differentiation, migration, proliferation, and stem cell maintenance. One member of this pathway, the PTCH1 gene, encodes a transmembrane protein that inhibits the activity of another transmembrane protein, smoothened (SMO), thus inactivating sonic hedgehog (Shh) pathway signaling of GLI transcription factors and induction of target

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genes. In adults, dysregulation of this pathway leads to abnormal proliferation, differentiation, and subsequent tumorigenesis. Approximately 90% of patients with BCC have a mutation in the Hh signaling pathway, with loss of function of PTCH1 and inappropriate activation of the Hh signaling pathway; the remaining 10% demonstrate activating mutations in SMO.5,6

**Vismodegib**

Vismodegib, the first-in-class small molecule Hh/SMO inhibitor, was approved by the FDA in 2012 to treat metastatic or recurrent locally advanced BCC in adults who cannot be treated with surgery or RT. FDA approval was based on the meaningful and durable responses to vismodegib demonstrated in the ERIVANCE trial, a phase II study in which vismodegib at 150 mg/d was administered to patients with locally advanced BCC (n=63) until an objective response rate (>30% reduction in size) was met.7 A total of 43% of patients had a significant response and 21% had a complete response; 30% of patients with metastatic BCC in this trial also responded. Both cohorts had a median response duration of 7.6 months and the median progression-free survival was 9.5 months. The median study drug exposure was 10 months and adverse events (AEs) caused discontinuation in 51% of patients. AE rates are fairly consistent across studies of vismodegib for locally advanced or metastatic BCC. For example, in the STEVIE study (n=499 patients in an interim analysis), which had a 36.4-month median duration of treatment, AEs were commonly grade 1 or 2 and occurred in 98% of patients. The most common AEs were muscle spasms (64%), alopecia (62%), dysgeusia (54%), weight loss (33%), asthenia (28%), decreased appetite (25%), ageusia (22%), and diarrhea (17%). Of note, treatment was discontinued in 80% of patients because of AEs (36%), progressive disease (14%), or request to stop treatment (10%).8

Hh inhibitors have considerable side effects that affect a large majority of patients, and often result in treatment discontinuation. Nutritional screening should be performed given the high rate of taste disturbance, loss of appetite, and weight loss. Interval dosing may be one strategy to maintain efficacy while diminishing the side effects of these agents and making them more tolerable; however, tumor resistance and regrowth during such alternate dosing regimens is possible and warrants further investigation (ClinicalTrials.gov identifier: NCT01556009).

**Sonidegib**

Sonidegib is an additional SMO antagonist approved in 2015 for patients with locally advanced BCC that recurs after surgery or RT, or in those who are not candidates for these therapies. The phase II BOLT trial was pivotal in forming the basis of FDA approval at the approved dosage of 200 mg/d. In 230 patients with a median follow-up of 13.9 months, 36% achieved an objective response. Side effects were comparable to those reported with vismodegib, including muscle spasms, alopecia, and taste disturbances, which are class effects associated with on-target inhibition of the Hh signaling pathway.9 The most common grade 3/4 AEs associated with sonidegib were elevated creatine kinase (CK; 6%) and lipase (5%) levels.10–12 It may be judicious to monitor CK in patients who are at risk for elevated creatine phosphokinase, including those with hypothyroidism or who are taking statins.

**Unique Considerations in the Treatment of Advanced or Metastatic BCC**

Although BCC is typically slow growing, it can progress over time into advanced cases, which can be debilitating and cause extensive local destruction of muscle, cartilage, or even bone. These tumors often require imaging for complete evaluation, as well as referral to specialists in oculoplastic surgery, radiation oncology, otolaryngology, or surgical oncology. It should be noted that the determination of whether a tumor is surgically resectable is variable and may be surgeon-dependent. Thus, interdisciplinary care is helpful in determining the appropriate treatment algorithm for each individual patient.

With the aging population and its increasing prevalence and incidence of BCC, there are now even greater numbers of tumors that, on first presentation, are advanced, carrying a higher risk of developing metastases. The incidence of metastatic BCC is poorly characterized because it is so uncommon, but it has been estimated to constitute between 0.0028% and 0.55% of all BCCs.13,14 BCC metastases
most often affect the regional lymph nodes (60%), lung (40%), bone (20%), and skin (10%), and there are no commonly accepted chemotherapeutic regimens for them. Cisplatin and doxorubicin may be used, but are not well tolerated in an older population. Thus, Hh inhibitors offer another option for palliation of advanced disease.

Another challenging population includes those with a genetic predisposition to multiple or advanced BCCs, as seen in Rombo syndrome, xeroderma pigmentosum, and Bazex-Dupré-Christol syndrome. Gorlin syndrome, also known as nevoid BCC syndrome, is a hereditary condition due to a PTCH1 gene mutation that causes affected individuals to have anywhere from a few to thousands of BCCs over a lifetime, as well as meningiomas, medulloblastomas, jaw keratocysts, and a variety of other benign and malignant growths. The challenge in these patients is managing their multiple oncologic surgical and medical procedures while minimizing the impact on their quality of life. RT is contraindicated as neoadjuvant therapy in patients with a hereditary predisposition to skin cancer, making Hh inhibitors a reasonable alternative. Patients who are immunosuppressed (those with chronic lymphocytic leukemia, lymphoma, or organ transplants) can also present with multiple or advanced BCCs and may need to undergo repeated procedures. The development of Hh inhibitors is an opportunity to provide neoadjuvant treatment in any of these populations in an effort to reduce tumor size, thereby decreasing the extent and complexity of subsequent surgery.

**Neoadjuvant Use of Hh Pathway Inhibitors**

Although there is certainly a role for Hh inhibitors in patients with unresectable tumors or who are not candidates for surgery, neoadjuvant treatment with Hh pathway inhibitors can make some previously inoperable tumors operable.

One example of the authors’ experience in using a Hh inhibitor as neoadjuvant therapy in a patient with large, aggressive, facial BCCs is described herein. The patient was a 95-year-old woman referred for previously untreated lesions present for many years over her chin, right forehead, left temple, and right temple. Biopsies revealed BCC. Given the significant extent of surgery needed to treat these multiple lesions, as well as the fact that the patient would have had difficulty attending numerous sessions of RT, vismodegib at 150 mg/d was initiated. Two of the largest lesions, on the chin and right forehead, showed significant tumor shrinkage on clinical observation after vismodegib treatment. After 5 months, the chin lesion decreased in size from 2.0 x 2.0 to 1.0 x 1.0 cm, at which time Mohs micrographic surgery was performed. One stage was required for clearance and reconstruction was performed using a linear closure.

After 6 months, the right forehead lesion had decreased in size from 5.0 x 3.5 to 3.1 x 3.5 cm, at which time Mohs micrographic surgery was performed. One stage was also required for clearance, and reconstruction was performed with a pursestring closure and full-thickness skin graft. Both sites had residual tumor clinically and histologically; there were residual islands of tumor in the debulking layer. Vismodegib was discontinued immediately after Mohs micrographic surgery and the patient had no evidence of recurrence at 7 months’ follow-up.

In this patient with multiple large tumors, we found that the combination of vismodegib before Mohs micrographic surgery was safe and well-tolerated, and allowed for less extensive surgery with excellent oncologic control.

**Degree of Histologic Clearance in Hh Inhibitors**

It is important to note that a histologic cure is not guaranteed with Hh inhibitor therapy alone and that tumors generally regrow when therapy is stopped, supporting the use of Hh inhibitors with other modalities of treatment. Most previous studies measured response based on clinical observation and not true histologic margin control. Alcalay et al, however, reported on 2 patients with 3 aggressive BCCs in which vismodegib was successfully used as neoadjuvant treatment before Mohs surgery. Both patients completed 6 months of vismodegib at the FDA-approved dosage of 150 mg/d and had either a 60% or complete clinical disappearance of their tumors. Even so, remnants of tumor nests were found on histology despite obtaining clear margins at the end of surgery. There was an overall benefit to the use of vismodegib in terms of reduced tumor area and surgical defect size, but these results suggest that discontinuation of Hh inhibitor therapy without additional treatment could result in a residual or noncontiguous
tumor, eventually leading to a recurrent tumor that may be more aggressive or difficult to treat.

Superfluous Role of Hh Inhibitors in the Treatment of Operable Tumors
Although vismodegib has only been approved for cases of advanced BCCs, the question has been raised whether it would be useful for the greater majority of BCCs that present in the typical office setting (ie, nonadvanced). One phase II study evaluating patients with biopsy-confirmed, nodular, operable BCCs receiving vismodegib followed by Mohs micrographic surgery found that complete histologic clearance (CHC) was seen in only 42% of patients receiving the drug for 12 weeks (cohort 1), 16% in patients receiving it for 12 weeks followed by 24 weeks of observation before excision (cohort 2), and 44% of patients receiving it for 8 weeks on/4 weeks off/8 weeks on (cohort 3). The study had predefined primary efficacy end points of CHC >50% for cohorts 1 and 3 and >30% in cohort 2, which were not achieved in any cohort. There was a similar safety profile whether vismodegib was dosed continuously or intermittently. In addition, vismodegib-related AEs were reversible on treatment discontinuation, generally within 6 to 12 weeks for muscle spasms, dysgeusia, and ageusia and within 24 weeks for delayed-onset alopecia. These findings are generally consistent with other studies. Studies such as those by Sofen et al do not support the use of vismodegib as a surrogate treatment for the vast majority of operable BCCs, because more conventional treatment modalities have higher cure rates.

Effects of Hh Inhibitors on Surgical Defect Size
Although Hh inhibitors cannot reliably achieve complete histologic cure, its use as neoadjuvant therapy may have a role in decreasing surgical defect size. In a small study of only 11 patients, Ally et al observed a 27% decrease from baseline in the surgical defect area in patients treated with vismodegib after a mean of 4 ±2 months. The study patients had BCCs that were twice as large as most BCCs on average, and 50% were cleared after 1 Mohs stage. They found that longer treatment generally resulted in smaller surgical defects, and that vismodegib was not effective in patients receiving therapy for <3 months. Of note, the observed clinical appearance of tumors after vismodegib varied and did not necessarily predict histologic cure. A reduction in surgical defect area by 31% if vismodegib is used for at least 3 months supports its potential short-term use as neoadjuvant treatment before surgery. Further studies are needed to assess how a decrease in surgical defect size may affect complexity and extent of closure.

RT in Combination With Hh Inhibitors
Although RT may be used as neoadjuvant treatment before surgery in advanced BCC, it may be feasible to perform concurrent vismodegib and RT. Pollom et al reported a man with a left nasal tip BCC recurrent after Mohs surgery who had facial nerve palsies, pain, and perineural invasion. His left infraorbital nerve; left cranial nerves V2, V3, and VII; left Meckel’s cave; and cavernous sinus were treated with 66 Gy in 33 fractions, and the left infratemporal fossa and parotid were treated with 50 Gy in 33 fractions with concomitant vismodegib. After 9 months, he had stable disease on imaging and improvement in facial weakness and pain. Other cases of vismodegib combined with RT for successful BCC palliation have also been published. One study successfully used trimodality therapy with vismodegib, RT, and local excision for a locally aggressive BCC of the cheek. Currently, there is a phase II study of RT and vismodegib for advanced head and neck BCCs, the results of which are still pending (ClinicalTrials.gov identifier: NCT01835626). This combined approach may be useful for patients with inoperable tumors who have demonstrated disease relapse after Hh inhibitors have been withdrawn, at which time referral to radiation oncology can be considered.

Use in Gorlin Syndrome
Another potential use for neoadjuvant Hh inhibitors exists in the treatment of patients affected by hereditary syndromes. A study by Tang et al of patients with Gorlin syndrome yielded a significantly lower rate of new BCCs and reduction in the burden of preexisting BCCs in patients treated with vismodegib. More than half of patients discontinued vismodegib due to AEs. Notably, when vismodegib was discontinued, dysgeusia and muscle cramps resolved within 1 month, and hair growth returned within 3 months. Similarly, Ojevwe et al reported successful treatment using vismodegib in a 31-year-old man with Gorlin syndrome who had multiple unresectable facial BCCs. The patient tolerated treatment...
well and visible change was evident within 1 month. Follow-up studies are needed to further assess Hh inhibitors as neoadjuvant therapy in the management of syndromic BCCs before surgery. Use of vismodegib in syndromic patients may be limited by medication side effects.

**Treatment of BCCs in High-Risk Locations and the Increased Risk of Squamous Cell Carcinoma**

Advanced BCCs represent a challenge for management because conventional treatments may cause functional impairment or significant disfigurement, especially around the ears, eyes, nose, and lips, leading to significant morbidity. Multiple studies have shown the benefit of Hh inhibitors for patients with tumors in these high-risk areas. A prospective case series by Gill et al.\(^\text{31}\) examined 7 patients with locally advanced, infiltrative, inoperable, and recurrent periocular and/or orbital BCC treated with vismodegib for a mean duration of 11 weeks. Greater than 80% tumor shrinkage was seen in 5 patients (71%) and was maintained during a mean follow-up duration of 7.3 months.\(^\text{31}\) Loss of function after surgical treatment in high-risk areas could potentially be minimized by reducing tumor size with neoadjuvant Hh inhibitor therapy before excision.

An interesting AE occurring in this series, and reported in the literature elsewhere, was the development of new squamous cell carcinomas (SCCs) at uninvolved sites in 2 patients, suggesting the need for close monitoring and prompt biopsy of suspicious lesions in patients receiving Hh inhibitors.\(^\text{32,33}\) Cases of SCC developing within advanced BCCs while on vismodegib therapy have also been reported, possibly supporting rebiopsy or serial biopsy if a significant change in gross tumor appearance occurs.\(^\text{34,35}\)

**Resistance to Hh Pathway Inhibitors**

Although side effects often limit the length of treatment, it is not yet clear whether long-term monotherapy and management using Hh inhibitors will be feasible given the question of both primary and secondary resistance. Primary resistance is seen in up to 50% of patients for whom initial treatment fails, and >20% of tumors exhibit acquired resistance despite initial tumor regression.\(^\text{36–38}\)

A recent pooled analysis of patients treated with vismodegib showed lower resistance rates and higher response rates than previous studies.\(^\text{39}\) The study included a total of 705 clinically evaluable patients showing an average complete response of 28% and average partial response of 34.1%. The median duration of drug exposure ranged from 11.0 to 51.6 weeks, with a weighted duration of 35.8 weeks. The objective response for locally advanced BCC was almost twice as high as for metastatic BCC. There were too few sonidegib publications for inclusion in the analysis of the study. Follow-up times were relatively short and ranged from 7.3 to 22.4 months, and therefore long-term responses and AEs are not known.

Elucidation of resistance mechanisms will play important roles in achieving durable responses in the treatment of patients with advanced BCC. In a study analyzing tumor biopsies from patients with BCC that initially responded to vismodegib but then subsequently did not, resistance was linked to Hh pathway reactivation via drug-binding pocket and activating mutations of SMO and through copy number changes in SUFU and GLI2.\(^\text{40}\) The investigators found significant intratumor heterogeneity of resistance mechanisms, with even a single relapsed tumor having clones with numerous resistance mechanisms.

Just as combination treatment for melanoma with BRAF and MEK inhibitors has been successfully, and now more frequently, used, a similar approach may be needed to prevent SMO inhibitor resistance by combining treatments that act downstream in the Hh pathway. There is therefore a need for the development of new inhibitors targeting molecules downstream from SMO, such as GLI. Although currently there are no effective GLI inhibitors, Long et al.\(^\text{41}\) examined the epigenetic enzymes and modulators involved in the transcription of Gli proteins and found that the bromodomain-containing protein inhibitor I-BET151 was able to reduce the expression of several components of the Hh pathway, including Gli. Furthermore, although there was hope that patients would not develop resistance to sonidegib as they had with vismodegib, that hope has been diminished. Patients previously resistant to treatment with vismodegib were similarly refractory to treatment with sonidegib.\(^\text{42}\)
Conclusions

Most BCCs will not require neoadjuvant vismodegib. However, in addition to their FDA-approved use for locally advanced or metastatic tumors not amenable to surgery or RT, Hh inhibitors may provide a bridge to curative therapy or at least palliation in patients with tumors in functionally sensitive areas, such as the periorbital region or the exit point of the facial nerve at the stylomastoid foramen. For some patients, treatment with an Hh inhibitor may reduce tumor size sufficiently that defect size after surgery is significantly decreased, thereby lessening the need for a more complicated reconstructive procedure. Hh inhibitors therefore represent a valuable tool in advanced BCC management, especially when combined with conventional treatments, such as surgical excision or RT, and may provide cure in some instances and effective palliation in others. This multimodality approach is of particular importance, because CHC is not guaranteed with Hh inhibitors alone. Most studies involving SMO inhibitors thus far have measured clinical tumor shrinkage but not true histologic margin control. Undetected positive margins in patients whose disease appears to have resolved clinically could potentially develop delayed tumor recurrence, and subsequent difficulties in treatment, by creating skip areas of tumor-free tissue alternating with the presence of tumor. This would be a problem particularly relevant to tumors treated with Mohs surgery, which is best for contiguous tumors. Such tumors would require wide-margin Mohs surgery, as opposed to narrow-margin Mohs surgery, to optimize local control and minimize the risk of recurrence.

The specific indications beyond those already approved for Hh inhibitors will need to be further delineated after more studies are completed. Appropriate patient selection, close monitoring, and multidisciplinary care are essential for optimal care of patients with advanced BCC treated with Hh inhibitors. It is our opinion that patients with inoperable tumors, or tumors in cosmetically sensitive areas that will have significant surgical and/or functional compromise, and who have been well counseled on the common side effects, are the most appropriate patients for neoadjuvant vismodegib therapy. Although the side-effect profile of these drugs may limit treatment duration and decrease compliance, leading to concerns regarding their cost-effectiveness, dose interruptions of up to 4 weeks, or a prespecified 3- to 4-month minimum treatment duration, can be considered to make these agents more tolerable. Patients in our practice are followed monthly while on vismodegib and are referred to specialists, such as oculoplastic surgery, otolaryngology, surgical oncology, or radiation oncology if required.

Follow-up studies to further assess Hh inhibitors as neoadjuvant therapy in the management of syndromic and nonsyndromic BCCs before surgery with long-term follow-up are needed, as are studies examining the cost-efficacy of neoadjuvant vismodegib before excision. However, it currently seems that patients with advanced BCC can benefit considerably from these agents, despite their known limitations.

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