Systemic Targeted Treatments for Basal Cell Carcinoma

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PRACTICE **POINTS**

- The sonic hedgehog (SHH) inhibitors vismodegib and sonidegib currently are the only 2 oral medications approved by the US Food and Drug Administration for the first-line treatment of locally advanced basal cell carcinoma (BCC). Vismodegib also is approved for metastatic BCC.
- Cemiplimab, a programmed cell death protein 1 inhibitor, is now an approved treatment for patients with advanced BCC refractory or intolerant to SHH inhibitor therapy.
- Adverse effects of SHH inhibitors, most commonly muscle spasms, often lead to treatment discontinuation, but intermittent dosing regimens can be used to increase tolerability and adherence.
- Combining SHH inhibitors with radiotherapy or antifungal therapy as well as maintenance dosing strategies may help reduce the risk of recurrence.
- Neoadjuvant administration of a SHH inhibitor may enable surgical excision of previously inoperable cases through tumor shrinkage.

The sonic hedgehog (SHH) inhibitors vismodegib and sonidegib are the only 2 first-line systemic medications approved for the treatment of locally aggressive basal cell carcinoma (BCC). Vismodegib is the only SHH inhibitor approved for metastatic BCC. Cemiplimab, an immune checkpoint inhibitor (ICI), is now an approved second-line therapy for locally advanced or metastatic BCC. Efficacy and adverse effect profiles of vismodegib and sonidegib appear comparable, although head-to-head clinical trials have not been conducted. Despite the remarkable efficacy demonstrated by the 2 SHH inhibitors, adverse effects are common and often lead to treatment discontinuation. Alternative dosing schedules may help to manage these side effects, with recent approval of dose interruptions of up to 8 weeks. Given the high rate of recurrence and emerging concern regarding drug resistance, maintenance dosing regimens and potential synergism with other treatment modalities, such as radiotherapy or antifungal therapy, should be further explored. The use of SHH inhibitors in the neoadjuvant setting also is warranted, as it may allow for surgical management of previously inoperable cases of BCC.

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Basal cell carcinoma (BCC) is the most common keratinocyte carcinoma and affects more than 3 million individuals per year in the United States.[1] Approximately 40% of patients diagnosed with BCC will develop another BCC within 5 years of the initial diagnosis.[2] Most cases are successfully treated with surgical excision and occasionally topical therapy or radiotherapy. Despite the high cure rate with conventional treatments, BCC can recur and can cause substantial destruction of the surrounding tissue if left untreated.[3-5] In some instances, BCC can even metastasize and lead to death.[6] For patients who are poor candidates for surgical or topical treatment modalities because of locally advanced BCC (laBCC) or metastatic BCC (mBCC), systemic treatment may be indicated. Vismodegib, sonidegib, and cemiplimab are the only systemic medications approved by the US Food and Drug Administration (FDA) for the treatment of laBCC and/or mBCC. Vismodegib and sonidegib target the sonic hedgehog (SHH) signaling pathway that is abnormally activated in more than 90% of BCCs.[7] Cemiplimab is an immune checkpoint inhibitor (ICI) that targets the programmed cell death protein 1 (PD-1) receptor.[8] Herein, we review the clinical utility of these medications and their evolving roles in the treatment of BCC.

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SHH Pathway Inhibitors

The SHH pathway is a key regulator of cell proliferation and differentiation during embryogenesis.[7] During adulthood, SHH signaling decreases but still plays an important role in stem cell activation and in regulation of the hair follicle growth cycle.[9,10] However, de novo mutations in the genes that comprise the SHH pathway can result in aberrant constitutive activation, leading to unrestricted cell proliferation. Genetic mutations resulting in activation of Smoothened (SMO), a G-protein–coupled receptor involved in the signal transduction and propagation of the SHH pathway, have been implicated in the pathogenesis of BCC. Inactivating mutations also are commonly observed in patched homolog 1, an upstream cell-surface protein that inhibits SMO.[7] The mechanism by which vismodegib and sonidegib, 2 of the FDA-approved oral medications for the treatment of advanced BCC, block the SHH pathway is through the selective inhibition of SMO.[7,11]

Vismodegib first received FDA approval in 2012 for the treatment of laBCC and mBCC after initial results from the pivotal ERIVANCE phase 2 trial demonstrated an objective response rate (ORR) of 43% (27/63) and 30% (10/33) in patients with locally advanced and metastatic disease, respectively. In this single-arm study, all enrolled patients (63 with laBCC and 33 with mBCC) received 150 mg of oral vismodegib daily.[12] Updated results at 39 months demonstrated improved ORRs of 60% (38/63) and 48% (16/33) for the laBCC and mBCC groups, respectively. A complete response (CR) and partial response (PR) were observed in 32% (n=20) and 29% (n=18) of patients with laBCC, respectively.[13] These results have been confirmed in subsequent studies, including the large international open-label trial known as STEVIE, with ORRs of 68.5% for 1119 cases of laBCC and 37% for 96 cases of mBCC.[14-17] The CR and PR rates were 33% and 35%, respectively, for the laBCC group. The CR and PR rates for the mBCC group were 5% and 32%, respectively.[14]

The FDA approval of sonidegib for laBCC—but not mBCC—occurred in 2015 after the pivotal BOLT randomized phase 2 trial demonstrated an initial ORR of 43% (18/42) for laBCC and 15% (2/13) for mBCC after administration of 200 mg of sonidegib daily.[18] A final follow-up analysis at 42 months resulted in ORRs of 56% (37/66) and 8% (1/13) for the laBCC and mBCC groups, respectively.[19] Additionally, improved efficacy was not observed in the 151 patients who were randomized to receive treatment with the higher 800-mg dose; however, they did experience a higher incidence of adverse events.[18,19]

Currently, the true clinical differences between vismodegib and sonidegib remain uncertain, as no head-to-head trials have been conducted. Moreover, direct comparison of the data from the ERIVANCE and BOLT trials is challenging owing to fundamental differences in methodologic design, including the criteria used to assess BCC severity. The ERIVANCE trial utilized the conventional Response Evaluation Criteria in Solid Tumors (RECIST), while BOLT used the rigorous modified RECIST. However, an expert consensus study attempted to compare the 2 trials by modifying the outcomes from BOLT with the former RECIST criteria. The expert group found that the 2 SHH inhibitors had comparable efficacy and adverse event profiles.[20] Nevertheless, a recent meta-analysis found that although ORRs for laBCC were similar between the 2 drugs, the CR rate for vismodegib was 31% compared with 3% for sonidegib. Additionally, for mBCC, they reported the ORR of vismodegib to be 2.7 times higher than that of sonidegib (39% vs 15%).[21]

Immune Checkpoint Inhibitors

Immune checkpoint inhibitors have successfully been utilized in the treatment of cutaneous squamous cell carcinoma (cSCC); however, their use for treating BCC has been limited until recently.[22-25] In February 2021, cemiplimab became the first and only ICI approved for the treatment of laBCC and mBCC in patients who did not respond to or were intolerant to prior SHH inhibitor therapy.[26] Cemiplimab—a human monoclonal antibody against the PD-1 receptor expressed on T cells—blocks its interaction with programmed cell death ligand 1 and programmed cell death ligand 2 present on tumor cells. The blockade of the PD-1 pathway releases the inhibition of the antitumor immune response and enables appropriate cytotoxic T-cell activity to occur.[8]

The FDA approval of cemiplimab for the treatment of advanced BCC was based on an open-label, multicenter, single-arm phase 2 trial (NCT03132636) evaluating 84 patients with laBCC refractory or intolerant to SHH inhibitor therapy.[26] Patients received an intravenous infusion of cemiplimab 350 mg every 3 weeks for up to 93 weeks or until disease progression or unacceptable toxicity. An ORR of 31% (26/84) was observed with a CR and PR of 6% (5/84) and 25% (21/84), respectively. The median duration of follow-up was 15 months.[26] Given the clinically meaningful results of this trial, investigating the efficacy of other PD-1 inhibitors, such as pembrolizumab and nivolumab, for treatment of advanced BCC may prove worthwhile.

Adverse Effects of Systemic Treatments

The 2 approved SHH inhibitors—vismodegib and sonidegib—appear to have similar side-effect profiles, with the most common adverse effects being muscle spasms, dysgeusia, alopecia, nausea, vomiting, diarrhea, weight loss, and fatigue.[20,21,27] These side effects occur at high frequencies (>40%) for both SHH inhibitors and often lead to discontinuation of the medication.[21] Rates of treatment discontinuation range from 15% to 50% on average.[12-14,18] Fortunately, the majority of these adverse effects do not appear to increase in severity or frequency with prolonged use of these medications.[14,16,28]

Various conservative and pharmacologic measures can be implemented to help manage side effects. For muscle spasms, which are the most commonly reported adverse effect, supplementation with magnesium, transcutaneous

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electrical nerve stimulation, acupuncture, massages, stretching, and thermal compresses can potentially be beneficial.[29] Calcium channel blockers also may be effective, as one small prospective cohort study reported a reduction in the frequency of muscle cramps with amlodipine 10 mg daily.[30] For alopecia, which typically is reversible and caused by SHH inhibition of the normal hair cycle, minoxidil theoretically can help, as it reduces telogen arrest and extends the anagen growth phase.[31,32] Although usually mild and self-limiting, management of dysgeusia, weight loss, and gastrointestinal upset often can be managed with dietary changes, such as smaller, more frequent meals.[33,34] Finally, alternative dosing strategies and drug holidays have been employed to mitigate these side effects and increase drug tolerability.[35,36] These are discussed in the Alternative Dosing section.

Given the essential role of the SHH pathway in embryologic development, SHH inhibitors carry a black box warning of embryofetal teratogenicity and are contraindicated in females who are pregnant or breastfeeding. For females of reproductive potential, verification of pregnancy status should be performed prior to initiating treatment with an SHH inhibitor. These patients should be counseled on the use of contraception during treatment and for at least 24 months and 20 months after cessation of vismodegib and sonidegib, respectively.[27,37,38] Male patients, even after a vasectomy, should use barrier contraception during treatment and for at least 3 months and 8 months after the final dose of vismodegib and sonidegib, respectively.[37,38]

Laboratory abnormalities commonly associated with SHH inhibitors include elevated hepatic enzymes, particularly with vismodegib, and elevated creatine kinase levels, particularly with sonidegib.[28,39] Other laboratory abnormalities that can occur include hypercholesterolemia, hypercreatininemia, hyperglycemia, and increased serum lipase levels.[19,28] Although these laboratory abnormalities usually are asymptomatic and self-limiting, regular monitoring should be performed.

There also is concern that SHH inhibitors may induce the development of cSCC. A case-control study of 55 cases and 125 control patients found an increased risk for cSCC in those previously treated with vismodegib, with a hazard ratio of 8.12.[40] However, a subsequent retrospective cohort study of 1675 patients with BCC failed to find any association with cSCC among those treated with vismodegib compared to those who received standard surgical therapy.[41] Clinical data for sonidegib are lacking, but the BOLT trial found that cSCC occurred in 3 patients receiving treatment with the SHH inhibitor.[18] Thus, further studies are needed to more thoroughly assess this concern. Close monitoring for cSCC may be warranted in patients prescribed SHH inhibitors at this time.

Cemiplimab has demonstrated an acceptable safety profile and is generally well tolerated. In the phase 2 trial of cemiplimab for cSCC, approximately 5% of patients discontinued treatment because of adverse effects. The most commonly reported side effects of cemiplimab were diarrhea (27%), fatigue (24%), nausea (17%), constipation (15%), and rash (15%).[23] In the phase 2 trial for laBCC, grade 3 or 4 adverse events occurred in 48% of patients, with hypertension (5%) being the most common.[26] Although rare, immune-mediated adverse reactions also can occur, given the mechanism of action of ICIs. These side effects, ranging in severity from mild to fatal, include pneumonitis, colitis, hepatitis, nephritis, myocarditis, and hypophysitis. Therefore, close monitoring for these immune-mediated reactions is critical, but most can be managed with corticosteroids or treatment interruption if they occur.[42,43]

No absolute contraindications exist for cemiplimab; however, extreme caution should be taken in immunosuppressed individuals, such as solid organ transplant recipients and those with chronic lymphocytic leukemia (CLL), as safety data are limited in these patients.[44,45] Although small retrospective studies have reported reasonable tolerability in solid organ transplant recipients treated with ICIs, an allograft rejection rate of 41% was found in a meta-analysis of 64 patients.[46-48] In CLL patients with keratinocyte carcinomas, ICIs have been safely used and have even demonstrated efficacy for CLL in some cases.[49-52]

Alternative Dosing

The side effects of SHH inhibitors have led to alternative dosing strategies to prevent medication discontinuation and improve adherence. In patients with basal cell nevus syndrome, multimonth drug holidays have been shown to increase drug tolerability without compromising efficacy.[35,36] Weekly intermittent dosing regimens of vismodegib ranging from 1 week on followed by 1 to 3 weeks off demonstrated efficacy in a retrospective study of 7 patients with advanced BCC.[53] All 7 patients experienced improvement in their BCCs, with 3 patients experiencing CR. Importantly, treatment-related adverse effects were mild and well tolerated, with no patients terminating the medication.[53] Two other retrospective case series of patients with advanced BCC treated with vismodegib reported similar findings for those placed on an intermittent dosing schedule ranging from once every other day to once per week.[54,55]

In the large phase 2 randomized trial known as MIKIE, 2 different intermittent dosing regimens of 150 mg vismodegib daily for patients with multiple BCCs were found to have good activity and tolerability.[56] The first group (n=116) received vismodegib for 12 weeks, then 3 rounds of 8 weeks of placebo, followed by 12 weeks of vismodegib; there was a 63% reduction in clinically evident BCCs after 73 weeks. The second group (n=113) received the medication for 24 weeks, then 3 rounds of 8 weeks of placebo, followed by 8 weeks of vismodegib; there was a 54% reduction at the end of 73 weeks.[56] Subsequent analyses found improvements in health-related quality-of-life outcomes that were similar for both groups.[57]

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Consequently, alternative dosing schedules appear to be a viable option for patients at risk of discontinuing treatment because of adverse effects, and current data support the recently approved recommendations of dose interruptions of up to 8 weeks to manage adverse effects in patients with laBCC or mBCC.[58] Nevertheless, further clinical studies are required to determine the optimal intermittent dosing regimen for patients treated with SHH inhibitors.

Neoadjuvant Administration

Recently, vismodegib has been studied as a neoadjuvant therapy for BCC with promising results. Several small retrospective studies and case reports have documented successful treatment of both operable and inoperable periocular laBCC, with preservation of the eye in all patients.[59-61] An open-label trial of 15 patients with advanced BCC who received neoadjuvant vismodegib for 3 to 6 months prior to surgical excision reported a mean reduction of 35% in the final surgical defect size, with no recurrence at 22 months.[62,63] The latest and largest study performed was a phase 2 open-label trial known as VISMONEO, where 44 of 55 laBCC patients (80%) receiving neoadjuvant vismodegib for a mean duration of 6 months (range, 4–10 months) achieved the primary end point of tumor surgical downstaging.[64] Of the 44 patients who had tumor downstaging, 27 (61%) experienced histologically proven CRs. Additionally, a 66% reduction in the average target lesion size was reported in this group compared to 29% in the 11 patients who did not have tumor downstaging (P=.0002).[64] Thus, SHH inhibitors may hold an important neoadjuvant role in the treatment of BCC by decreasing surgical defect size and allowing for surgical management of previously inoperable cases.

Synergism With Radiation

Preliminary data suggest SHH inhibitors may help potentiate the effects of radiation therapy for the treatment of BCC. Currently, the evidence primarily is limited to case studies, with several reports describing complete remission in patients with advanced BCCs who were considered unsuitable candidates for surgery. In these cases, vismodegib was administered either prior to or concurrently with radiation treatment.[65-69] An in vitro study also documented the radiation-sensitizing effects of vismodegib in a BCC cell line.[70] Recently, a phase 2 trial (ClinicalTrials.gov identifier NCT01835626) evaluating the concurrent use of vismodegib and radiotherapy for patients with advanced BCC was completed, but data has yet to be published.

Synergism With and Benefit of Antifungal Therapy

The antifungal drug itraconazole is a potent inhibitor of the SHH pathway and may have an adjunctive role in the treatment of BCC. Similar to vismodegib and sonidegib, itraconazole acts as a direct antagonist of SMO. However, it is thought to bind to a distinct site on SMO.[71,72] An open-label, exploratory phase 2 trial of 19 patients with BCC found that oral itraconazole 200 to 400 mg daily decreased tumor proliferative index by 45% (P=.04), as measured by Ki-67; SHH activity by 65% (P=.03), as measured by *GLI1* messenger RNA; and mean tumor area by 24%.[73] In a case series of 5 patients with mBCC refractory to conventional SHH inhibitor therapy, combined treatment with itraconazole and arsenic trioxide resulted in stable disease and a 75% reduction in SHH activity (P<.001).[74] One case report documented tumor regression leading to stable disease for 15 months in a patient with laBCC treated with itraconazole monotherapy due to being unable to afford vismodegib or sonidegib. However, within 2 months of treatment discontinuation, the lesion progressed considerably.[75] The efficacy of a topical formulation of itraconazole also has been tested in an open-label, placebo-controlled phase 2 trial, but no benefit was observed.[76]

Posaconazole is a second-generation antifungal agent that may serve as a potential alternative to itraconazole.[77] Although clinical data are lacking, a basic science study found that posaconazole could inhibit the growth of SHH-dependent BCC in vivo (in mice).[78] Furthermore, posaconazole has demonstrated a better safety profile with fewer and more mild side effects than itraconazole and does not require dose adjustment for those with hepatic or renal failure.[79,80] Thus, posaconazole may be a safer alternative to itraconazole for the treatment of BCC. Further clinical studies are needed to elucidate the potential synergistic effects of these antifungal agents with the 2 currently approved SHH inhibitors for the treatment of advanced BCC.

Drug Resistance

Treatment resistance to SHH inhibitors, though uncommon, is a growing concern. Acquired mutations in the SMO binding site or downstream mediators of the SHH pathway have been shown to confer resistance to vismodegib and sonidegib.[72,81-83] In addition, it appears that there may be shared resistance among the drugs in this class. One study assessing the efficacy of sonidegib in 9 patients with laBCC resistant to vismodegib found that these patients also did not respond to sonidegib.[84] Interestingly, 1 case report documented tumor regression of an intracranial BCC in a patient treated with sonidegib and itraconazole after failure with vismodegib.[85] An in vitro study also found that itraconazole maintained SHH inhibitory activity for all drug-resistant SMO mutations that have been reported.[72] Therefore, itraconazole monotherapy or combination therapy with a canonical SHH inhibitor may be considered for patients with recalcitrant BCC and warrants further investigation.

Taladegib is a newly developed SMO inhibitor that may serve as another promising alternative for patients who develop resistance to vismodegib or sonidegib. A phase 1 trial of taladegib for advanced BCC found an

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ORR of 69% (11/16) in the SHH inhibitor–naïve group and an ORR of 36% (11/32) in the group previously treated with a SHH inhibitor.[86] Additionally, the safety profile and frequency of adverse effects appear to be similar to those associated with vismodegib and sonidegib.[86,87] Unfortunately, no clinical trials evaluating taladegib for BCC are ongoing or in development at this time.

Recurrence

There appears to be a relatively high rate of recurrence for BCC patients who achieve a CR to SHH inhibitors. In a retrospective study of 116 laBCC patients who experienced a CR after vismodegib therapy, 54 patients (47%) relapsed at 36 months. Among the 54 patients that relapsed, 27 were re-treated with vismodegib, which resulted in an ORR of 85% (23/27), a CR rate of 37% (10/27), and a PR rate of 48% (13/27).[88] Another retrospective study of 35 laBCC patients who relapsed after vismodegib treatment reported a 31% (11/35) clinical recurrence rate at 6-month follow-up.[89] An observational retrospective study also assessed the efficacy of SHH inhibitor maintenance therapy for advanced BCC patients who achieved a CR.[90] In the study, 27 (64%) patients received a maintenance dose of 150 mg vismodegib once per week for 1 year, while 15 (36%) patients decided not to take a maintenance dose following CR of their BCC. All patients who took the maintenance therapy did not experience clinical recurrence at 1-year follow-up, whereas 26% of patients not on the maintenance dose relapsed.[90] Consequently, these results indicate that BCC recurrence is frequent after SHH inhibitor therapy and highlights the importance of close surveillance after CR is attained. Nevertheless, most patients still respond to treatment with SHH inhibitors after relapsing, and intermittent maintenance doses may be an effective means to reduce risk of recurrence.

Conclusion

Vismodegib and sonidegib are SHH inhibitors approved for the treatment of laBCC and mBCC. Cemiplimab is now also approved for patients who do not respond to SHH inhibitors or for whom SHH inhibitors are not tolerable. Although these systemic targeted therapies can lead to notable tumor shrinkage and even complete regression in some patients, recurrence is common, and adverse effects may limit their use. Drug resistance is an emerging issue that requires additional examination. Further clinical studies are needed to determine which patients are likely to respond to these targeted treatments.

Various intermittent and maintenance drug regimens should be evaluated for their potential to mitigate adverse effects and reduce risk of recurrence, respectively. The synergistic effects of these medications with other therapies as well as their neoadjuvant and adjuvant roles should be further investigated. For example, administration of an SHH inhibitor prior to surgical excision of a BCC may allow for a smaller surgical defect size, thereby improving cosmetic and functional outcomes. Moreover, these systemic targeted medications may allow for previously inoperable tumors to become amenable to surgical treatment.

Although SHH inhibitors and PD-1 inhibitors represent a major advancement in the field of oncodermatology, real-world efficacy and safety data in the upcoming years will be important for elucidating their true benefit for patients with BCC.

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