

Sonidegib: mechanism of action, pharmacology, and clinical utility for advanced basal cell carcinomas

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Abstract: The Hedgehog (Hh) pathway is critical for cell differentiation, tissue polarity, and stem cell maintenance during embryonic development, but is silent in adult tissues under normal conditions. However, aberrant Hh signaling activation has been implicated in the development and promotion of certain types of cancer, including basal cell carcinoma (BCC), medulloblastoma, and gastrointestinal cancers. In 2015, the US Food and Drug Administration (FDA) approved sonidegib, a smoothened (SMO) antagonist, for treatment of advanced BCC (aBCC) after a successful Phase II clinical trial. Sonidegib, also named Odomzo, is the second Hh signaling inhibitor approved by the FDA to treat BCCs following approval of the first SMO antagonist vismodegib in 2012. What are the major features of sonidegib (mechanism of action; metabolic profiles, clinical efficacy, safety, and tolerability profiles)? Will the sonidegib experience help other clinical trials using Hh signaling inhibitors in the future? In this review, we will summarize current understanding of BCCs and Hh signaling. We will focus on sonidegib and its use in the clinic, and we will discuss ways to improve its clinical application in cancer therapeutics.

Keywords: Hedgehog, smoothened, inhibitor, cancer, basal cell carcinoma, sonidegib

Introduction

Since the discovery of the Hedgehog (Hh) gene in the fruit fly in 1980, significant progress has been made in our understanding of the role of its signaling pathway, not only in the regulation of cell differentiation during development, but also in the development of cancer.¹ Three homologues of the Hh gene have been identified: Sonic hedgehog (Shh), Desert hedgehog (Dhh), and Indian hedgehog (Ihh).²⁻⁶ The Hh signaling pathway is highly conserved, including the ligands (Shh, Dhh, Ihh), patched receptors (PTCH1, PTCH2), signal transducer smoothened (SMO), and Gli transcription factors (Gli1, Gli2, Gli3). Without binding of Hh ligand to the transmembrane patched receptor, patched will inhibit the function of SMO. Binding of Hh ligand releases this inhibition, allowing SMO to signal downstream and activate the Gli transcription factors. Gli can bind to the promoter regions of their target genes, regulating their expression.⁷⁻⁹ Studies have revealed additional mechanisms controlling signaling of this pathway, such as the role of cilium in Hh signaling,¹⁰⁻¹² co-receptors of Hh molecules,¹³⁻¹⁵ potential molecules mediating PTCH1-mediated SMO suppression,¹⁶ and ways for Gli transcription factor regulation.¹⁷⁻²⁰ This pathway is referred to as canonical signaling. In addition, Gli transcription factors can be also activated in the noncanonical fashion by KRAS, TGF β , PI3K, and PKC (Figure 1). Any mutation in these pathways may lead to abnormal fetal development as well as malignant disease in adults.

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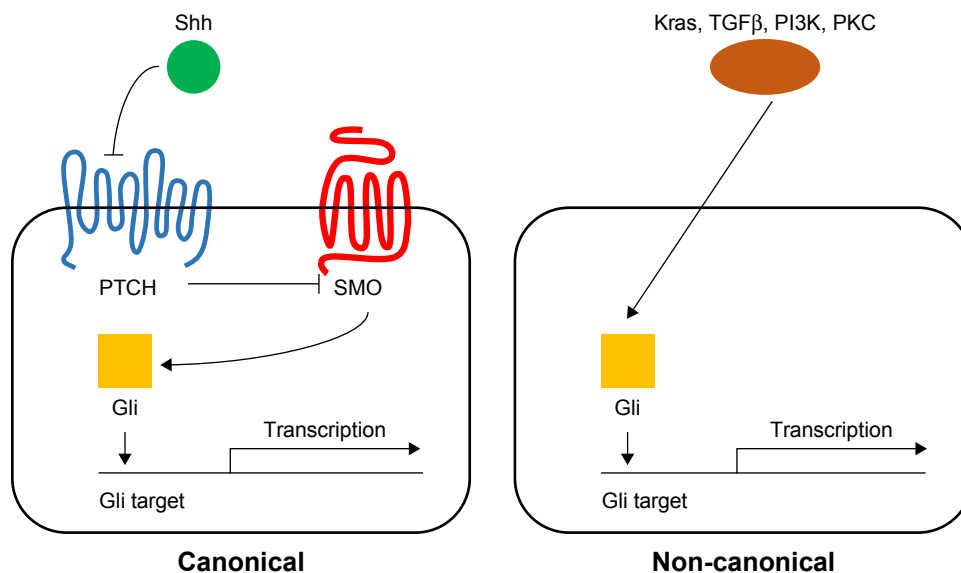


Figure 1 Canonical Hh signaling and noncanonical Hh signaling.
Abbreviations: Hh, Hedgehog; PTCH, patched; Shh, Sonic hedgehog; SMO, smoothened.

Since its connection to human cancer development, numerous compounds have been discovered to have inhibitory effects on Hh signaling. As of yet, two compounds (vismodegib and sonidegib) have been approved by the US Food and Drug Administration (FDA) to treat basal cell carcinomas (BCCs). In this review, we will focus on sonidegib: its discovery, mechanism of action, and clinical utility for advanced BCCs (aBCCs).

The Hh pathway in cancer development

The Hh signaling pathway was first linked to cancer development when it was found that mutations in PTCH1 are linked to a rare and hereditary form of BCC, basal cell nevus syndrome (BCNS), also known as Gorlin syndrome.^{21,22} Gorlin syndrome has two major phenotypes: developmental defects and an increased risk of developing cancers that are associated with Hh signaling mutations, including BCC, medulloblastoma, rhabdomyosarcoma, and meningioma.

The majority of BCCs and other Gorlin syndrome associated cancers, including rhabdomyosarcomas, meningiomas, and medulloblastomas, have mutations in PTCH1, SMO, and other Hh pathway molecules or an elevation in Hh target gene expression. Based on these findings, it has been suggested that Hh signaling plays several roles in cancer development: as a tumor driver, tumor promoter, tumor metastasis promoter, or cancer stem cell promoter. As previously discussed, activating mutations of Hh signaling can drive the development of BCCs, medulloblastomas,

rhabdomyosarcomas, gastrointestinal stromal-like tumors, and Barrett's esophagus.²³ In small cell lung cancer (SCLC), Hh signaling can promote cancer development but cannot drive tumor formation. In pancreatic cancers, inhibiting Hh signaling can prevent tumor invasion and metastasis. Finally, Hh signaling can regulate cancer stem cell numbers as well as the tumor microenvironment, creating conditions that promote tumor growth. This role of Hh signaling can be found in leukemia and liver cancer, and is often responsible for the recurrence of cancer through resistance to chemotherapy and radiotherapy.^{24–33} Dysregulation of any component of the Hh pathway leading to its aberrant activation can result in malignant conditions through these mechanisms.

BCC

BCC is the most common form of skin cancer and among the most commonly diagnosed forms of cancer in the USA, with over one million cases per year.³⁴ Although it has a low risk for metastasis, it is a slow growing tumor that causes morbidity via its proximity to critical facial structures. It also has a tendency to relapse, occur in multiple locations, and invade and destroy local tissues.

Classification of BCCs is dependent on prognostic factors including tumor size, histological characteristics, tumor location, margins, and recurrence. Usually, superficial BCC is treatable with nonsurgical techniques including photodynamic therapy and topical imiquimod or 5-fluorouracil treatment, or by surgical techniques including

electrodessication, Mohs micrographic surgery, excisional surgery, cryosurgery, or laser surgery. However, invasion of the BCC into surrounding muscle, bone, or cartilage results in locally advanced BCC. Unfortunately, these tumors are incurable, or not treatable by surgery or radiotherapy. Successful treatment is dependent on tumor progression, a history of previous treatments, and any medical contraindications. Cytotoxic chemotherapy has not been approved for treatment of nonresectable BCC, and these patients can only benefit from palliative care. Metastatic BCC (mBCC) is extremely rare, with an incidence of up to 0.55% of cases. It commonly affects the regional lymph nodes, lungs, and liver. The prognosis of mBCC is very poor, with a mean survival between 8 months and 3.6 years. Both locally advanced BCC (laBCC) and mBCC can be collectively referred to as aBCC. Unfortunately, treatment of aBCC was nonexistent until the recent development of Hedgehog pathway inhibitors (HPIs).

There are a number of small molecules targeting SMO, with potent activity to treat Hh-driven aBCC. Although several compounds are shown to target Gli transcription factors or the Hh molecules, their specificity and potency to treat aBCC have not been demonstrated in clinical trials. Currently, seven small molecule inhibitors are under clinical trial or have been approved to target SMO in the treatment of Hh-driven cancers. These SMO inhibitors include cyclopamine derivatives IPI-926 (saridegib), GDC-0449 (vismodegib), BMS833923 (XL-139), PF04449913 (glasdegib), LY2940680 (taladegib), LEQ506, TAK-441, and LDE-225 (NVP-LDE225, sonidegib).^{8,35–37}

Discovery, modifications, and mechanism of action of sonidegib

Sonidegib, marketed as Odomzo by Novartis, was approved by the FDA in July 2015 as a 200 mg oral pill for treatment of

recurrent aBCC, or aBCC in patients who are not eligible for surgery or radiation therapy. It is currently being investigated for use in the treatment of other cancer types.

Sonidegib belongs to a class of biphenyl carboxamides and was discovered as an SMO antagonist using a high-throughput screen *in vitro*.³⁸ A structure–activity relationship study was performed using variations in three regions of the originally identified molecule, compound 1, which is the core structure of sonidegib (Figure 2A). First, modification to region A with a nitrogen in the pyridine moiety and the addition of *cis*-dimethyl groups on the morpholine ring helped to mitigate the risk of widespread toxicity by reducing electron density. Next, the addition of a methyl group in region B increases the potency to inhibit SMO. Furthermore, a modification to region C with $-\text{OCF}_3$ at the R₄ position yielded 5 m (NVP-LDE225; Figure 2B), with the most favorable pharmaceutical properties, ADMET (absorption, distribution, metabolism, excretion, and toxicity) properties, and pharmacokinetics.

Sonidegib interacts with SMO in the drug-binding pocket, where it acts as an antagonist, preventing downstream activation of Hh pathway signaling (Figure 3).^{39–42} Based on the recently reported SMO structure, there are numerous residues in the drug-binding pocket interacting with a SMO antagonist. It was reported that residues from the extracellular tips of helices I, II, V, and VII interact with LY2940680. The most notable interaction is between R400 of helix V and the compound via the phthalazine ring. Several structured water molecules in the ligand pocket are also critical for the interactions, including R400, H470, D473, E518, and N521 side chains. Mutations within the pocket, including Q476 and D473, prevent sonidegib binding. Other mutations, including S533 and W535, cause conformational changes in SMO, blocking sonidegib from accessing the drug-binding

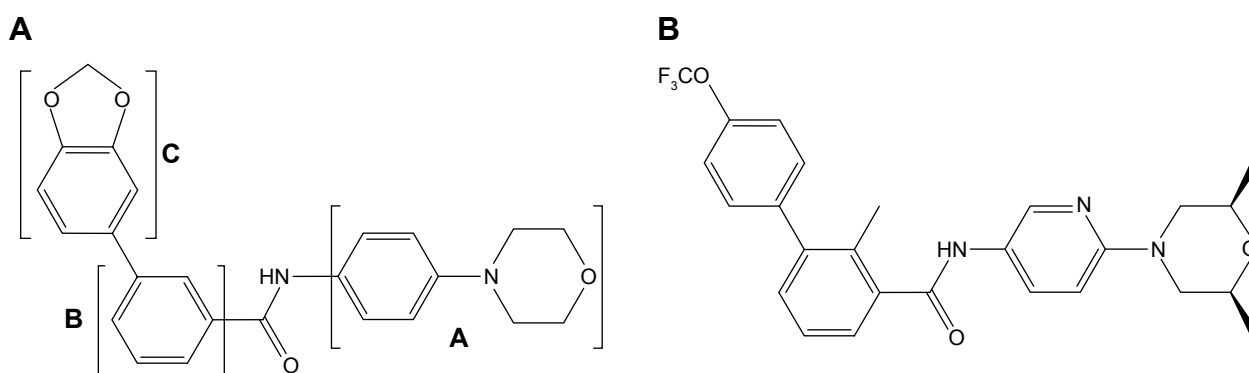


Figure 2 Generation of Sonidegib.

Notes: (A) The structure of compound #1 from a cell-based screening. (B) The structure of sonidegib, which has high biological potency.

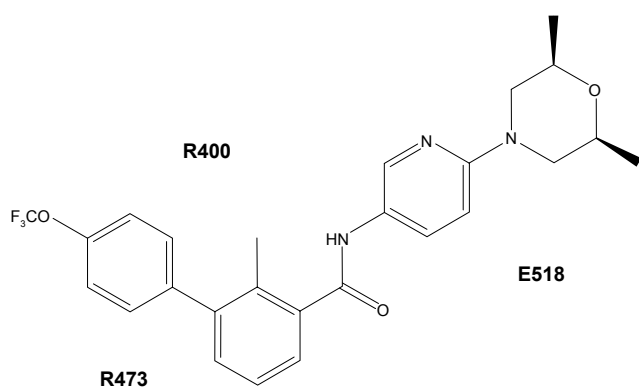


Figure 3 Sonidegib interacts with the drug-binding pocket of SMO, which mainly consists of three amino acids: arginine (R) 473, arginine (R) 400, and glutamic acid (E) 518.

Abbreviation: SMO, smoothened.

pocket.⁴² These mutations have been found to confer resistance to sonidegib.⁴³

Metabolic profiles and pharmacokinetics of sonidegib

Sonidegib has a unique metabolic profile. While the T_{max} for sonidegib in blood and plasma is only 2–3 h, the T_{max} for its main metabolite M48 is 60 h, suggesting that sonidegib is slowly metabolized by the body. The $T_{1/2}$ for sonidegib is over 14 days.⁴⁴ Similarly, the T_{max} for vismodegib is ~2 h with $T_{1/2}$ in the plasma around 7–14 days.^{45,46} Vismodegib is also a slowly metabolized compound, with the major metabolite M1 appearing 24 h after administration.

Sonidegib has multiple pharmacokinetic properties that make it an effective therapeutic agent.⁴⁷ It is highly bound to plasma proteins (over 99%) in humans. It shows between 69% and 102% oral bioavailability when given in solution. Sonidegib also shows high tissue penetration and favorable blood–brain barrier penetration, making it a viable treatment for medulloblastoma. It did not show cytochrome P450 inhibition or induction, minimizing its potential to interact with the metabolism of other drugs. In screens against a panel of receptors, channels, transporters, kinases, and proteases, no activity was identified, limiting its potential for off-target effects.³⁸

Sonidegib has a pH-dependent solubility, with a low solubility at high pH.^{38,48} A Phase I study in Asian patients showed that they have a lower maximum tolerated dose (MTD) due to more severe creatinine kinase (CK) elevation.⁴⁹ Thus, dosing considerations should be taken when treating individuals of East Asian descent as compared to the Western population.

Clinical trials with sonidegib

Sonidegib was approved for the treatment of aBCC following the demonstration of its efficacy in the Phase II BOLT (BCC outcomes with LDE225 treatment) clinical trials.⁵⁰ Since then, additional clinical trials have been completed to assess the efficacy of sonidegib in aBCC treatment.⁵¹ The BOLT study included long-term follow-up data of patients treated with sonidegib. This was a multicenter, randomized, double-blind study in which patients took either 200 or 800 mg sonidegib daily. Over 50% of patients saw objective responses in the 200 mg study arm, whereas the response with the 800 mg study arm was lower. Out of the 94 patients who had laBCC and responded to the drug, 18 progressed or died, while more than half had a response for >6 months. More importantly, 80% of patients with mBCC showed and maintained an objective response. Long-term follow-up of patients in this study showed that 200 mg sonidegib has a better treatment profile over 800 mg, and it maintains extended efficacy in the treatment of aBCC.

Sonidegib efficacy has also been studied to determine the objective response rate, progression-free survival, and time to tumor response. Exposure-safety analysis was performed at doses ranging from 100 to 3,000 mg once daily and 250–750 mg twice daily. Both responders and nonresponders showed similar plasma concentration levels, but there was no correlation between the dosage and probability of tumor response. Similarly, increasing exposure did not show an improvement in progression-free survival nor in time to tumor response.⁵² Thus, patients who fail to respond to lower doses may not benefit from an increase in dose. These results, consistent with other studies, suggest that a 200 mg dose of sonidegib can be used to achieve clinical efficacy and avoid potential adverse events associated with drug toxicity.

Interestingly, the adaptive immune response is promoted in patients with aBCC treated with sonidegib or vismodegib. Immunological markers, including Ber-Ep4, BCL-2, CD4, CD8, and HLA-DR-class II, were measured in aBCC after treatment with vismodegib (n=22) or sonidegib (n=1). Following 4 weeks of treatment, Ber-EP4 and BCL-2 expression in tumors decreased, while HLA expression was upregulated on residual tumor cells, leading to the recruitment of CD8⁺ cytotoxic T cells into the tumor mass. Analysis with quantitative polymerase chain reaction revealed that expression of immune response-regulating genes was altered, which is consistent with our previous study that the Hh pathway is responsible for suppressing the immune response, and SMO antagonists relieve the suppression.^{52,53} Although this study was severely

limited by the low number of patients treated with sonidegib, the result supports the role of Hh signaling for the immune suppressive microenvironment as well as the possibility to combine immune modifiers with Hh signaling inhibition to achieve extended tumor control.

Although sonidegib has been shown to be effective in the treatment of aBCC, its use in patients previously treated with vismodegib will not be effective. The majority of patients who were treated with sonidegib following resistance to vismodegib experienced progressive disease; these patients were found to have SMO mutations that prevented the antagonist effects of SMO antagonists.⁴³

One method to detect tumor shrinkage after sonidegib treatment is the use of noninvasive imaging technologies reflectance confocal microscopy and high-definition optical coherence tomography. In patients who showed complete response, pseudocystic structures, or areas of necrosis and fibrosis were observed by these noninvasive techniques.⁵⁴ The treatment effect can be observed without exposing the patients to radiation over multiple occasions. However, residual tumor cells were often found in some cases. Thus, caution should be taken, as always, when using imaging as a tool for guiding treatment. It should be used in concert with other tools to determine the best course of action for the patient.

These studies consistently show sonidegib efficacy in the treatment of aBCC. Sonidegib shows strong promise in the long-term treatment of aBCC, especially when combined with other therapies, including immune modifiers.

There are significant interests in shifting toward the application of sonidegib in the treatment of other cancers renal cell carcinoma, lung cancer, myeloid leukemia, pancreatic cancer, medulloblastoma, ovarian cancer, and lymphoma. Most of the studies, however, were performed in mouse models.

Sonidegib has been shown to be efficacious in the treatment of SCLC. The Hh pathway has been linked to tumor initiation in SCLC. A Phase I study determined the MTD of sonidegib for the treatment of SCLC in combination with etoposide/cisplatin chemotherapy agents. Patients received up to six, 21-day cycles of etoposide/cisplatin with 400 or 800 mg daily sonidegib. A total of 800 mg was determined to be the MTD, with 79% of patients showing partial response.⁵⁵ Interestingly, a high efficacy is observed when a higher dose of sonidegib is used.

Together, these studies show the potential for sonidegib to treat aBCC and possibly other cancer types. There is evidence to indicate that sonidegib treatment along with other agents could be more efficacious. While sonidegib is an effective

drug, its safety profile must be evaluated for each potential treatment indication.

Safety, tolerability, and adverse effects of sonidegib

The BOLT study first assessed the safety and tolerability of sonidegib in the treatment of aBCC.⁵⁰ In aBCC treatment with sonidegib, almost all patients experienced at least one adverse event. The most commonly observed adverse events in patients receiving sonidegib (200 or 800 mg) include (from most common to least common): muscle spasms, alopecia, dysgeusia, nausea, increased CK, fatigue, decreased weight, diarrhea, decreased appetite, myalgia, and vomiting (Table 1). Adverse events leading to dose interruptions, reductions, or treatment discontinuation were less frequent with the 200 mg/day dose in comparison with the 800 mg dose. Grade 1/2 muscle spasms, dysgeusia, nausea, and alopecia were the most common causes of discontinuation. CK elevation was the most common grade 3/4 event, occurring in 6% of patients taking the 200 mg dose; women show a lower risk of CK abnormality than men.⁵² Furthermore, CK elevations were observed at low doses in Japanese patients, which resulted in their lower MTD of sonidegib.^{48,49} Serious adverse events, including rhabdomyolysis and very high CK, were very rarely associated with sonidegib. None of the deaths in the study were associated with sonidegib treatment.^{50,51}

Around 70% of patients taking 200 mg sonidegib were able to stay on treatment for at least 8 months. Despite seeing tumor response, many patients discontinued treatment, citing severe discomfort. However, over half of those who discontinued experienced only grade 1/2 adverse events. Many of these patients did not feel the need to suffer through treatment after already seeing benefits.⁵³ Management strategies for adverse events combined with improved patient education regarding treatment plans may lead to increased patient acceptance and tolerance of sonidegib therapy.

Adverse events associated with treatment are linked to the inhibition of the Hh pathway in normal tissues. Although adverse events may be mild, the long-term experience can cause patients to experience decreased quality of life, treatment interruption, and discontinuation before achieving any therapeutic benefit. These adverse events may have a significant impact on the clinical outcome of the patient. Improved knowledge of the mechanisms and management of adverse events will help physicians to better guide their treatments with appropriate prevention or intervention.

Table 1 Summary of smoothened antagonists

Name	LDE225	GDC0499	IPI-926	PF-04449913	TAK-441	BMS833923/ XL-139	LY-2940680	LEQ506
Drug name	Sonidegib/ Odomzo	Vismodegib/ Erivedge	Saridegib	Glasdegib			Taladegib	
CAS number	956697-53-3	879085-55-9	1037210-93-7	1095173-27-5	1186231-83-3	1059734-66-5	1258861-20-9	1204975-42-7
MW	485.5	421.3	504.3	374.4	576.2	473.2	512.5	432.56
NCT number	NCT02111187; NCT02195973; NCT02086513; NCT02151864; NCT02138929; NCT02086552; NCT02358161; NCT02129101	NCT02639117; NCT02337517; NCT01835626; NCT02956889; NCT02694224; NCT01601184; NCT02648048; NCT02690948; NCT02593760; NCT02436408; NCT02781389; NCT02091141; NCT02073838; NCT02523014; NCT01878617; NCT02465060; NCT02693535; NCT02788201	NCT01383538	NCT01841333; NCT02367456; NCT02038777; NCT01546038; NCT02226172	1204073	NCT01218477	NCT02784795; NCT02530437	NCT1106508
Recommended dose	400 mg qd	150 mg qd	160 mg qd	100 mg qd	MTD 1,600 mg qd	100 mg qd	200 mg qd	250 mg bid
Binding to SMO	Drug-binding pocket	Drug-binding pocket	Drug-binding pocket	Drug-binding pocket	Not determined (possibly not in the pocket)	Not known	Drug-binding pocket	Not known (possibly not in the pocket)
Adverse events	Muscle spasms; alopecia; dysgeusia; nausea; creatine kinase elevation; vomiting/ weight loss/ diarrhea	Muscle spasms; weight loss; alopecia; fatigue; low appetite; diarrhea	Liver function abnormality; fatigue; muscle spasms; vomiting/ nausea; rash; diarrhea	Dysgeusia; fatigue; low appetite; dizziness; dehydration; diarrhea	Hyponatremia; fatigue; dysgeusia; alopecia; muscle spasms	Not available	Not available	Not available
Single agent (S) or combined therapy (C)	S, C	S, C	C	S, C	S	S	S, C	S

Abbreviations: MTD, maximum tolerated dose; SMO, smoothened; CAS, Chemical Abstracts Service; MW, molecular weight; NCT, National Clinical Trial; bid, twice daily; qd, once daily.

Muscle spasms can be relieved by passive stretching, heating, cryotherapy, exercise, electrical stimulation, splinting, and changing sitting or sleeping positions. Pharmacologic treatments include calcium channel blockers, nerve stabilizers, or magnesium supplements. A number of other pharmaceuticals have been recommended, especially for cases in which muscle spasms spread to the abdomen. Almost 40% of patients taking 200 mg sonidegib experience dysgeusia, often leading to weight loss. Delta-9-tetrahydrocannabinol showed promise in improving taste sensation and appetite. Consulting with a dietician can be beneficial for these patients and has been shown to decrease the onset

of dysgeusia. Hair loss (alopecia) in these patients can affect their psychosocial well-being, leading to problems such as depression.

Sonidegib and other Hh signaling inhibitors block follicles from starting the anagen growth phase after shedding of hair in telogen, leading to extended, or in some cases, permanent hair loss. Minoxidil and dihydrotestosterone inhibitors may help promote hair growth. Weight loss can be associated with the disease process or the treatment itself. It usually begins at least 6 months following the beginning of treatment. Again, dieticians and supplementation can be helpful in these cases.

Fatigue is often a result of the culmination of other adverse events, including the muscle spasms and decreased appetite. Pharmacologic interventions may help, but physical activity, psychosocial intervention, sleep therapy, and nutritional supplementation may also help. Nausea is one of the earliest reported adverse events. Sonidegib was reported to be a moderate to high emetogenic agent. Serotonin inhibitors, antipsychotics, and other pharmaceutical agents can be provided for their antiemetic effects. In addition to regular monitoring of CK levels before and during treatment, health care providers should watch for symptoms of rhabdomyolysis, including muscle pain, tenderness, and weakness.⁵⁶ Despite the multitude of adverse events patients may experience, application of these strategies can improve patient tolerance of treatment.

In the treatment of SCLC with sonidegib, the adverse events are markedly different from those seen in aBCC. This may be the result of a higher recommended dose of sonidegib used to treat SCLC (800 mg) versus aBCC (200 mg). SCLC patients often experience grade 3/4 toxicities including anemia, neutropenia, CK elevation, fatigue, and nausea. The toxicity of sonidegib led to discontinuation of treatment in one patient.⁵⁵

The safety profile of sonidegib in cancers besides aBCC has not been thoroughly studied as of yet. As more of these studies move toward human trials, we can expect to see further evaluation of safety and tolerability, which will likely vary among different cancer types. However, the safety studies done in aBCC patients illustrate that although the drug is effective, it does have significant related adverse events. Many patients discontinue due to the long-term grade 1/2 events they experience, indicating lower patient quality of life, acceptability, and adherence. Nevertheless, the benefit of the drug is much greater than the potential side effects, and through patient education and management strategies, adverse events can be minimized and treatment can be continued further to improve the outcomes.

Other SMO inhibitors

Vismodegib is a first-in-class HPI that was approved by the FDA in 2012 for the treatment of aBCC, and it is currently being studied for use in other cancers, including colorectal cancer, pancreatic cancer, and medulloblastoma. Vismodegib acts in the same drug-binding pocket as sonidegib. In its Phase I study, about half of the patients treated with vismodegib showed tumor response. Patients in the Phase II study showed lower tumor response and many experienced serious adverse events.³⁷ However, over 50% of patients experience

refractory aBCC and a portion of initial responders develop resistance. In these patients, resistance to sonidegib is also predicted.⁴³ Adverse events associated with vismodegib treatment include grade 3 fatigue, hyponatremia, muscle spasms, and atrial fibrillation. Although vismodegib is fairly efficacious and has a similar safety profile to that of sonidegib, it seems to have more severe adverse events.

Cyclopamine was among the first SMO antagonists to be developed. It functions as an inverse agonist of SMO. However, it exhibits poor oral solubility and has many off-target adverse effects, making it a poor candidate for use in human cancer treatment. IPI-262, BMS-833923, Taladegib, PF-04449913, TAK-441, and LEQ506 are being investigated in clinical trials for treatment of aBCC.³⁷ In a study comparing the pharmacologic properties of these drugs, there was a significant variation in their inhibiting potencies as well as their ability to be used in a topical application. For example, LEQ-506 and TAK-441 are favorable in the treatment of minimally invasive BCC due to their properties in a topical formulation and their low side effects. In contrast, sonidegib and vismodegib have stronger side effects, limiting their use in less invasive BCCs.⁵⁷ The development of these SMO inhibitors promises the coming of therapies that will offer diverse properties in terms of treatment indications, clinical efficacy, and safety profiles.^{58–60}

Perspectives

The evaluation of sonidegib's clinical efficacy and its safety profile indicate its promise for treatment of aBCC and possibly for other cancer types. A large proportion of patients see clinical benefits with only mild to moderate adverse events. Despite the rare serious adverse events, the complete response rate (~30%) is fairly low for a tumor type driven mostly by mutations in the PTCH1 gene. The response rate for mBCC is even worse (<5%). There are a number of reasons for the different responses from BCC patients. First, the genetic mutations underlying the Hh signaling activation in the BCCs were not known at the time of clinical trials. For gene mutations in SMO or SUFU, which may contribute to ~20% of tumors, sonidegib and vismodegib will not be effective. Second, the response of patients to drugs varies significantly; detailed analysis of the biomarkers following the treatment may reveal additional mechanisms as to why some patients respond better than others. Third, while Hh signaling is the single most important pathway for BCC development, other signaling pathways do play important roles, such as p53 gene mutations. Fourth, drug resistance occurs frequently following treatment with SMO antagonists such as vismodegib.

The resistance may be from mutations of SMO itself or other important players such as PI3K signaling.

Thus, there is still a lot of work needed for better treatment of BCCs using SMO inhibitors. Patient education and management strategies can significantly improve a patient's way of life during treatment. When developing treatment plans, an important consideration is the propensity of patients to develop resistance. While a large proportion of patients show resistance, evaluating tumor response regularly will allow a physician to determine whether sonidegib is the appropriate treatment. Furthermore, genotyping patient tumors could identify patients with mutations leading to resistant tumors and help to avoid unnecessary treatment with a SMO inhibitor.

Sonidegib may have a strong role as an adjunct therapy in the treatment of other cancers. With its observed potentiating effects in multiple cancer types, the approval of additional clinical applications for sonidegib can be anticipated. Nevertheless, although sonidegib is a potent HPI, it will not be effective in suppressing noncanonical Hh signaling since these signaling events bypass SMO-dependent signaling (Figure 1). Growing evidence suggests that certain cancer types, including pancreatic cancer, may exhibit aberrant noncanonical pathway activation. Thus, we may see benefit from the development of a common downstream Hh signaling molecule antagonist, such as inhibitors for the Gli transcription factors.

Acknowledgments

Current research in the laboratory of J Xie is supported by grants from the National Cancer Institute CA155086, Riley Children's Foundation, Jeff Gordon Children's Research Foundation, and Wells Center for Pediatric Research. The authors take this opportunity to thank all the investigators in this field for their works.

Disclosure

The authors report no other conflicts of interest in this work.

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