Management of Cutaneous and Extracutaneous Side Effects of Smoothened Inhibitor Therapy for Advanced Basal Cell Carcinoma

Shalini V. Mohan and Anne Lynn S. Chang

Abstract

Smoothened inhibitors represent the first class of targeted drugs approved for use in advanced and metastatic basal cell carcinoma. For many patients with limited treatment options, this drug class has led to significant clinical improvements, but is not without side effects. In this review, we outline the basic mechanism of smoothened inhibitors and the most commonly observed cutaneous and extracutaneous side effects. We also highlight possible mechanisms for these adverse events and current management strategies. Clin Cancer Res; 21(12): 2677–83. ©2015 AACR.

Introduction

Smoothened inhibitors (SI) are a class of drugs newly approved by the FDA for use in advanced basal cell carcinomas (BCC). Because BCCs are the most common human malignancy worldwide, with an age-adjusted incidence of 1,000 to 1,500 per 100,000 adults in the United States (1), the ability to suppress their growth in a targeted fashion is a highly significant step forward in cutaneous oncology. Smoothened (SMO) is a 7-transmembrane protein in the hedgehog (Hh) signaling pathway that when aberrantly activated can function as an oncogene by promoting unregulated activation of the Hh pathway (2–4). The Hh signaling pathway is responsible for midline embryonic development and is generally silenced in adults except for activity in hair follicles and taste buds (5–11). Aberrant activation of this pathway results in tumorigenesis and is associated with BCCs and medulloblastoma (2–4, 6, 7). SIs block Hh signaling, leading to suppression of tumor growth and tumor regression (12–17). Although there are many potential targets within this pathway, most compounds in clinical development that block Hh signaling target SMO, including vismodegib (GDC-0449), which is already commercially available (18). Other SIs currently being studied in clinical trials include sonidegib (LDE225), saridegib (IPI-926), and BMS-833923 (XL139; refs. 12–15, 17).

A number of cutaneous and extracutaneous side effects of SIs have been reported (12, 14–17, 19), although few studies have been conducted on the mechanisms of the clinical side effects in humans. Nevertheless, data on the function of the Hh pathway from preclinical animal models and the limited clinical trials in humans lend insight into how SIs may exert their toxicities (8, 20–31). While data are still being collected on side effects specific to individual SIs, several side effects, such as hair loss, muscle spasms, and gastrointestinal (GI) and taste disturbances, are common to several SIs and are likely class effects. Adverse effects (AE) may be significant enough to lead to drug discontinuation (15, 16, 32), and therefore the ability to adequately manage these AEs is crucial to treatment adherence and patient quality of life. The significance of these side effects and lack of effective treatment options for these drug toxicities are illustrated in the pivotal phase II study of vismodegib, in which 12% of advanced BCC patients discontinued treatment due to an AE (16), and more recently in an international study with a 30-month follow-up in which 22.1% of advanced BCC patients discontinued treatment due to an AE (32). To date, there is no evidence that SI-induced cutaneous or extracutaneous side effects correlate with drug response, unlike other targeted therapies such as EGFR inhibitors, for which an acne-like rash is associated with tumor response (33).

Although not discussed in this review, SIs are potent teratogens that lead to severe midline defects in the developing fetus and are not to be used in females of childbearing potential or male partners of females of childbearing potential who do not agree to use two forms of reliable contraception (34).

Because of dose effects of drug toxicities, this review considers the rates of side effects based on phase II and/or FDA-approved dose whenever possible. Long-term data on AEs are still being collected as more patients are exposed to SIs, but high-quality data are available for some of these drugs through phase I and II clinical trials (12–17, 19, 35). The side effects discussed here were selected on the basis of literature reports and incidence and are not meant to be comprehensive.

Cutaneous Adverse Effects of Smoothened Inhibitors

Hair loss

Approximately 15% to 60% of patients treated with SIs experienced alopecia within 2 to 4 months of initiating SI therapy; exact rates depend on the specific SI (Table 1; refs. 12–17, 21, 30, 35–43). Alopecia is reported more frequently with
vismodegib than other SIs, with up to 58% and 63% of patients affected in phase I and II trials, respectively (16, 19, 35, 43). A phase II study of sonidegib revealed an alopecia incidence rate of 43% at the 200-mg daily dosage (12, 13). SI-related alopecia is reported to affect eyebrows, eyelashes, and body hair, although our clinical observations have shown that some patients with hair loss in one anatomical area may have spared hair loss in other locations. In humans, the Hh pathway is reported to maintain bulge cell phenotype and is likely needed for normal hair follicle regeneration (30). SI-related alopecia is reversible following discontinuation of the drug, with patients seeing evidence of regrowth after 4 to 6 weeks (42).

**Hypersensitivity reaction**

Two cases of patients experiencing drug hypersensitivity reactions following treatment with vismodegib were recently reported (Table 1; refs. 41, 42). One report describes a 77-year-old woman being treated with vismodegib for numerous and recurrent BCCs who developed on-target side effects in addition to sudden onset of fevers, chills, myalgia, and fatigue 3 weeks after drug initiation (41). Treatment was discontinued, and laboratory testing revealed elevated liver function and hypereosinophilia. These laboratory values normalized 10 days after discontinuation of vismodegib (42). The patient was not exposed to any other medications or drugs during treatment with vismodegib. A skin biopsy confirmed superficial and deep perivascular dermatitis with eosinophils, consistent with a cutaneous drug eruption. The patient was treated with topical steroids and did not need to discontinue vismodegib. The exact incidence of dermal hypersensitivity reaction in patients being treated with vismodegib is unclear and likely to be <20% as rash was not one of the common side effects in the phase II study that led to FDA approval (16).

**Squamous cell carcinoma and keratoacanthoma**

One potential concern with the use of targeted therapies is the possibility that abrogation of one pathway may lead to activation of another. A recently published case report describes patients without a history of squamous cell carcinoma (SCC) who developed keratoacanthoma (a low-grade variant of SCC originating from hair follicles) immediately after initiation of vismodegib for locally advanced BCC (1aBCC: Table 1; ref. 36). Other reports have described patients who developed cutaneous SCC following vismodegib treatment, both as new tumors and as lesions within the existing 1aBCC tumor bed (37–40). In a recent international study of 104 patients receiving vismodegib for advanced BCC, 11% developed SCC (32).

The etiology of this connection may be multifactorial and can be thought of on both a cellular and clinical level. On a cellular level, SMO inhibition may select for tumor cells that are not driven by the Hh pathway, including SCCs (18, 40). On a clinical level, UV light exposure is a common risk factor for both BCC and SCC (44); therefore, individuals exposed to high levels of UV may develop both types of skin cancer. In addition, patients receiving SIs may have more frequent or more complete skin examinations, which may lead to a detection bias. Although no data from randomized trials currently exist to support this hypothesis, long-term outcomes studies are under way that may help to answer this question. Because of the possibility of new-onset SCCs after initiation of SIs, total-body skin examinations with a low threshold to biopsy new suspicious lesions appears prudent.

**Extracutaneous Adverse Effects of Smoothened Inhibitors**

**Gastrointestinal toxicity (nausea, vomiting, diarrhea, and constipation)**

Nausea and vomiting were the most common GI toxicities, affecting up to one-third of patients receiving vismodegib, sonidegib, or saridegib (Table 2; refs. 12–16, 35). On the basis of data from 198 patients enrolled in phase I and II trials of vismodegib, 95% of patients experienced grade 1 or 2 GI disturbances, including nausea, vomiting, diarrhea, constipation, and pain (45). Grade 3 or 4 GI irritation was reported in 10% of patients (45). In a phase II trial of sonidegib, 33% of patients treated with the 200-mg daily dosage experienced nausea (12, 13). Only 3 of 28 patients exposed to varying doses of BMS-833923 in a phase I study reported nausea (17). No formal studies to date have examined the efficacy of currently available antiemetics for SI-induced nausea or vomiting. Anecdotally, medications such as ondansetron or metoclopramide have been used and can provide significant relief. SI-related diarrhea and constipation can be reduced or resolved with loperamide or stool softeners, respectively, although no formal studies have been conducted to identify the agents that are most effective in reducing or eliminating these side effects.

The Hh pathway is highly expressed in the GI epithelium and plays an important role in function and repair (5). In animal models, paracrine Hh signaling has been demonstrated from the stomach to the colon and has been found to be important in modulating villus core smooth muscle (23). Disruption of this pathway through SIs may explain the GI side effects of nausea, vomiting, diarrhea, and constipation (27).

**Amenorrhea**

Amenorrhea or menstrual irregularity has been reported in women of childbearing potential taking vismodegib (Table 2; refs. 35, 46). For instance, in an expanded access study of vismodegib, 4 of 8 women of childbearing age experienced irregular menses or amenorrhea while on vismodegib (35). In this small number of patients, there were no clear differences in weight loss or hormonal birth control use between those who did or did not experience menstrual irregularity. Strasswimmer and colleagues reported a case of a 34-year-old patient who developed amenorrhea one month after starting vismodegib and resumed menses 5 weeks after discontinuation (46). After hormonal evaluation, this patient’s amenorrhea was attributed to blockade of follicle-stimulating hormone-receptor–dependent signal transduction at the level of the ovaries. While the exact mechanism of amenorrhea remains to be further clarified, an alternative hypothesis might involve SI effects on the uterus—the exogenous hormone-induced menses of a patient treated in our practice with a prior bilateral oophorectomy ceased after initiation of SI therapy. To date, we are not aware of any cases in which menstrual cycles did not resume after vismodegib cessation.

**Dysgeusia**

Taste disturbance or dysgeusia was reported within the first 1 to 2 months following SI initiation in 16.7% to 70.6% of patients,
Management of Side Effects of SMO Inhibitor Therapy for aBCC

Table 1. Cutaneous side effects of SIs organized by reported time to clinical onset

<table>
<thead>
<tr>
<th>Observed side effect</th>
<th>Incidence</th>
<th>Average time to onset of symptoms</th>
<th>Reported severity (grade)</th>
<th>Reported or hypothesized mechanism</th>
<th>Management options (level IV evidence)</th>
<th>Selected references</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hair loss</td>
<td>Vismodegib: 58%-63%&lt;sup&gt;a&lt;/sup&gt; 2-4 mo&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1/2&lt;sup&gt;2,4&lt;/sup&gt;</td>
<td>Inhibition of hair follicle regeneration: Rittie et al., 2009 (30) Chiang et al., 1999 (21)</td>
<td>No known effective treatment to date, reversible after discontinuation</td>
<td>Vismodegib: Sekulic et al., 2012 (18) Dirix et al., 2012 (43) Chang et al., 2014 (35) Sonidegib: Migden et al., 2014 (12), Dummer et al., 2014 (13), Rodon et al., 2014 (15) Saridegib: Jimeno et al., 2013 (4) BMS-833923: Siu et al., 2010 (17)&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Hair loss</td>
<td>Sonidegib: 16.7%-43%&lt;sup&gt;c&lt;/sup&gt; 2 mo&lt;sup&gt;d&lt;/sup&gt;</td>
<td>3/4&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
<td>No known effective treatment to date, reversible after discontinuation</td>
<td>Sonidegib: Migden et al., 2014 (12), Dummer et al., 2014 (13), Rodon et al., 2014 (15) BMS-833923: Siu et al., 2010 (17)&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
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<tr>
<td></td>
<td>Saridegib: 22%&lt;sup&gt;f&lt;/sup&gt; BMS-833923: 15%&lt;sup&gt;g&lt;/sup&gt;</td>
<td></td>
<td></td>
<td>No known effective treatment to date, reversible after discontinuation</td>
<td>Saridegib: Jimeno et al., 2013 (4) BMS-833923: Siu et al., 2010 (17)&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>SCC</td>
<td>Vismodegib: 11% 1 mo-8 y 3</td>
<td>1/2&lt;sup&gt;2,4&lt;/sup&gt;</td>
<td>Unclear if advanced BCC patients have increased risk of SCC versus detection bias from increased monitoring while receiving SIs versus SI drug effect</td>
<td>Excision, regular full-body skin examination for surveillance</td>
<td>Vismodegib: Lam et al., 2014 (41) Kwong et al., 2014 (42)&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Keratoacanthoma</td>
<td>Not well characterized 2-7 wks 3</td>
<td>3&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Promotion of squamous differentiation</td>
<td>Surgical excision and regular full-body skin checks</td>
<td>Vismodegib: Aasi et al., 2013 (36)&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
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</table>

NOTE: The side effect profile is pooled from published literature in human trials for SIs, including vismodegib (GDC0449), sonidegib (LDE225), saridegib (IPI-926), and BMS-833923 (XL139). Shaded rows indicate a side effect observed with more than 1 SI.

<sup>a</sup>Levels of evidence: level II: prospective comparative studies, systematic review of level II studies or level I studies with inconsistent results; level III: case-control studies, retrospective comparative studies, systematic review of level III studies; level IV: case series with no comparison group, retrospective case series.

<sup>b</sup>Vismodegib at 150-mg daily dose.

<sup>c</sup>Sonidegib at 200-mg daily dose.

<sup>d</sup>Saridegib at 160-mg daily dose.

<sup>e</sup>BMS-833923 based on phase I study of 28 patients at 30 to 540 mg daily, as AE rates at individual doses not provided.

<sup>f</sup>Based on a phase II study of vismodegib (GDC0449).

<sup>g</sup>Based on a phase II study of vismodegib (GDC0449).

Depending on the particular SI used (Table 2; refs. 12–17, 20, 25, 29, 31, 35, 46–49). While not formally studied, dysgeusia’s contribution to lack of appetite has been suggested by clinical observation. Grade 2 dysgeusia includes altered taste with change in diet (per Common Terminology Criteria for Adverse Events version 4; ref. 50), potentially leading to weight loss, an adverse event also associated with SIs (12, 13, 16, 35). Sonidegib and saridegib had the lowest reported dysgeusia incidence rates with 16.7 to 38% and 27.8%, respectively (12, 17, 35, 44). In our clinical experience and as reported in the Basal Cell Nevus Network patient support group newsletter, patients experience a metallic or bland taste associated with most food and beverages (51). Patient-reported suggestions for coping with SI-related dysgeusia include consumption of spicy, sweet, cold, or acidic foods and use of baking soda as a mouth rinse before eating (51).

Data from preclinical animal models provide evidence to suggest that dysgeusia is an on-target effect of HH pathway inhibition (20, 22, 24, 26). Sonic HH (Shh)-responsive cells maintain the taste buds and filiform and fungiform papillae, all of which play a role in taste (20, 22, 24, 26). Inhibition of Shh signaling through SIs likely leads to disruption of these structures, thus accounting for the dysgeusia observed in patients treated with SIs.

**Myopathy (including symptoms of muscle spasms and muscle pain; myalgia)**

Myopathy is one of the most common AEs of SIs (12–14, 16, 35, 44), with up to 71% of patients treated with vismodegib, 50% of patients treated with sonidegib, 33% of patients treated with saridegib, and 44% of patients treated with BMS-833923 having reported muscle spasms (Table 2; refs. 12–14, 16, 17, 35, 44). Clinically, myopathy is often one of the first AEs to be reported (35). Many of our patients on vismodegib indicated myopathy can significantly affect their quality of life and may even lead patients to discontinue treatment with SIs. There is little evidence to suggest that a correlation exists between the symptoms of myopathy and elevated creatine kinase (CK) levels. Oral muscle relaxants (e.g., cyclobenzaprine) may transiently decrease the severity or number of muscle spasms; however, future studies are needed.
### Table 2. Extracutaneous side effects of SIs organized by reported time to clinical onset

<table>
<thead>
<tr>
<th>Observed side effect</th>
<th>Incidence</th>
<th>Average time to onset of symptoms</th>
<th>Reported severity (grade)</th>
<th>Reported mechanism</th>
<th>Management options (level IV evidence)*</th>
<th>Selected references</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>Vismodegib: 15.1%–29.6%&lt;sup&gt;a&lt;/sup&gt;  Sonidegib: 16.7%–33%&lt;sup&gt;c&lt;/sup&gt;  Saridegib: 33%&lt;sup&gt;d&lt;/sup&gt;  BMS-833923: 11%&lt;sup&gt;e&lt;/sup&gt;</td>
<td>1–3 mo&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2/2&lt;sup&gt;c&lt;/sup&gt;  3/4&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Impaired GI motility</td>
<td>Antihemetic (e.g., ondansetron), appetite stimulant (e.g., megestrol, dronabinol), H2 antagonists</td>
<td>Vismodegib: Chang et al., 2014 (16)  Migden et al., 2014 (12)  Dummer et al., 2014 (13)  Rodon et al., 2014 (15)  Saridegib: Jimeno et al., 2013 (34)  BMS-833923: Siu et al., 2010 (17)</td>
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<tr>
<td>Amenorrhea or irregular menses</td>
<td>Vismodegib: up to 50%&lt;sup&gt;e&lt;/sup&gt;  Sonidegib: 16.7%&lt;sup&gt;c&lt;/sup&gt;  Saridegib: 27.8%&lt;sup&gt;c&lt;/sup&gt;  BMS-833923: 44%&lt;sup&gt;s&lt;/sup&gt;</td>
<td>1 mo&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1</td>
<td>Mechanism unclear, could be target effects on uterus</td>
<td>May resolve upon discontinuation of vismodegib</td>
<td>Vismodegib: Chang et al., 2014 (35)  Strasswimmer et al., 2014 (46)</td>
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<tr>
<td>Dysgeusia</td>
<td>Vismodegib: 5%–70.6%&lt;sup&gt;b&lt;/sup&gt;  Sonidegib: 33.1%–50%&lt;sup&gt;c&lt;/sup&gt;  Saridegib: 33%&lt;sup&gt;d&lt;/sup&gt;  BMS-833923: 44%&lt;sup&gt;s&lt;/sup&gt;</td>
<td>1–2 mo&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1&lt;sup&gt;2/3&lt;/sup&gt;  3/4&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Inhibition of lingual papillae development in animal model: Liu et al., 2004 (49)  Castells et al., 2014 (20)</td>
<td>Supportive care (e.g., strongly flavored food, baking soda mouth rinse, etc.)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>Vismodegib: Sekulic et al., 2012 (16)  Chang et al., 2014 (35)  Sonidegib: Migden et al., 2014 (12)  Dummer et al., 2014 (13)  Rodon et al., 2014 (15)  Saridegib: Jimeno et al., 2013 (34)  BMS-833923: Siu et al., 2010 (17)</td>
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<tr>
<td>Muscle spasm</td>
<td>Vismodegib: 68%–70.6%&lt;sup&gt;b&lt;/sup&gt;  Sonidegib: 33.1%–50%&lt;sup&gt;c&lt;/sup&gt;  Saridegib: 33%&lt;sup&gt;d&lt;/sup&gt;  BMS-833923: 44%&lt;sup&gt;s&lt;/sup&gt;</td>
<td>1–2 mo&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1&lt;sup&gt;2/3&lt;/sup&gt;  3/4&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Inhibition of muscle repair in animal model: Li et al., 2004 (25)  Straface et al., 2009 (31)  Piccioni et al., 2014 (29)</td>
<td>Muscle relaxant (e.g., cyclobenzaprine), levocarnitine&lt;sup&gt;g&lt;/sup&gt;</td>
<td>Vismodegib: Sekulic et al., 2012 (16)  Chang et al., 2014 (35)  Sonidegib: Migden et al., 2014 (12)  Dummer et al., 2014 (13)  Rodon et al., 2014 (15)  Saridegib: Jimeno et al., 2013 (34)  BMS-833923: Siu et al., 2010 (17)</td>
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<td>Elevated CK&lt;sup&gt;s&lt;/sup&gt;</td>
<td>Sonidegib: 16.7%–29%&lt;sup&gt;c&lt;/sup&gt;  Saridegib: 11%&lt;sup&gt;c&lt;/sup&gt;  BMS-833923: 11%&lt;sup&gt;s&lt;/sup&gt;</td>
<td>6–8 wks&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2–4</td>
<td>Inhibition of Hh-regulated skeletal muscle repair</td>
<td>Monitor for rhabdomyolysis, avoid overexertion and concomitant medications that may exacerbate</td>
<td>Sonidegib: Migden et al., 2014 (12)  Dummer et al., 2014 (13)  Rodon et al., 2014 (15)</td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>Vismodegib: 1%–26.5%&lt;sup&gt;b&lt;/sup&gt;  Saridegib: up to 88.9%&lt;sup&gt;e&lt;/sup&gt;</td>
<td>1–3 mo&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2–4</td>
<td>Drug-drug interaction, direct hepatocellular damage, impaired hepatocyte regeneration</td>
<td>Consider removing any interacting concomitant medications</td>
<td>Vismodegib: Ventarola and Silverstein, 2014 (47)  Ash and Jolly, 2014 (48)  Saridegib: Jimeno et al., 2013 (34)</td>
</tr>
<tr>
<td>Weight loss</td>
<td>Vismodegib: 16%–46%&lt;sup&gt;b&lt;/sup&gt;  Sonidegib: 16.7%–27%&lt;sup&gt;c&lt;/sup&gt;</td>
<td>4–10 mo&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1&lt;sup&gt;2/3&lt;/sup&gt;  3/4&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Likely multifactorial, including decreased dietary intake due to GI side effects</td>
<td>Appetite stimulant, calorie-dense dietary supplements</td>
<td>Vismodegib: Sekulic et al., 2012 (16)  Chang et al., 2014 (35)  Sonidegib: Migden et al., 2014 (12)  Dummer et al., 2014 (13)  Rodon et al., 2014 (15)</td>
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<sup>b</sup>Vismodegib at 150-mg daily dose.

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<sup>d</sup>Saridegib at 160-mg daily dose.

<sup>e</sup>BMS-833923 based on phase I study of 28 patients at 30 to 540 mg daily, as AE rates at individual doses not provided.

<sup>f</sup>Based on McNabb, 2013 (51).

<sup>g</sup>L-carnitine benefit is currently being evaluated in a clinical trial (NCT01893892).

<sup>h</sup>Elevated CK<sup>g</sup> is a laboratory parameter not assessed in vismodegib clinical trials; therefore, the incidence rate is unknown because physicians and patients cannot spontaneously report CK levels.

Based on a phase II study of vismodegib (35).
needed to identify the best method of treating this common side effect. Levocarnitine, an amino acid derivative that is commercially available as a supplement, is currently being tested in a randomized, double-blind, placebo-controlled trial in patients with vismodegib-associated muscle spasms (NCT01893892) based on anecdotal patient reports of decreased muscle spasm frequency and severity while taking this agent.

The mechanism of myopathy in humans taking SIs has not been established. In animal models, activation of the Shh pathway promotes regeneration of myofibers (25, 29, 31); therefore, inhibition of the pathway with SIs may impede muscle repair.

Elevated creatine kinase

Currently, the incidence of CK elevations appears to vary with the different SIs. Assessment of CK levels was not included in vismodegib clinical trial protocols; therefore, the incidence of elevated CK in these studies is unclear. Vismodegib does not require monitoring of CK levels based on the package insert (3); however, patients with risk factors for CK elevation may be considered for monitoring, as elevated CK has been reported with vismodegib treatment (52, 53). For instance, our clinical experience in patients taking multiple medications suggests that CK elevation may occur in rare instances and is reversible upon discontinuation of vismodegib. In contrast, studies of sonidegib included CK monitoring, which has been shown to result in grade 2 to 4 CK elevation in up to 29% of patients (Table 2), with or without clinical symptoms, in a dose-dependent fashion (12, 13). The incidence of CK elevation in patients exposed to saridegib or BMS-833923 in phase I studies was not reported (14). CK monitoring may be considered in individuals with risk factors for rhabdomyolysis, such as alcohol abuse, concomitant medications (including HMG-CoA reductase inhibitors, itraconazole, cyclosporine, colchicine, and erythromycin), overexertion, or muscular dystrophy (54, 55), although evidence-based guidelines currently do not exist for this practice.

Although there is no clear association between muscle spasm or myalgia symptoms and CK elevations, it could be hypothesized that CK elevation may result from impaired repair of cellular damage, as discussed in the section on myopathy (29, 31).

Hepatotoxicity

Hepatotoxicity in the form of transaminitis or cholestasis has been reported in patients being treated with SIs (Table 2; refs. 12–17, 20, 25, 29, 31, 35, 46–49). For vismodegib, the rate of occurrence did not exceed 30% (47, 48). Similar effects were seen with saridegib in patients with solid tumors, in whom the major dose-limiting toxicity was transient and reversible grade 3 alanine aminotransferase and/or aspartate aminotransferase elevation at the phase II dose of 160 mg/day (1 of 18 patients; 6%; ref. 14). Some of the reported cases of hepatotoxicity occurring in patients being treated with SIs may be due to concomitant use of medications that may also contribute and thus enhance this side effect. For instance, elevated liver enzymes and cholestasis were reported in an individual on vismodegib therapy after starting a nonsteroidal anti-inflammatory drug for muscle spasms (48). Postmarketing data for vismodegib based on a summary from the FDA Adverse Events Reporting System spanning January 2012 to January 2013 revealed 15 cases of hepatotoxicity, including elevated liver enzymes or bilirubin, hepatitis, and hepatocellular damage (47). These cases included patients taking vismodegib with other known hepatotoxic drugs, such as erlotinib and acetaminophen (56, 57). Although additional data are needed to provide guidance on laboratory monitoring for patients on SI therapy, periodic laboratory monitoring may be considered in those taking potentially hepatotoxic medications.

The Hh pathway is important in the hepatic repair response following chronic liver injury in human liver cells (28); therefore, inhibition of Hh signaling may prevent repair of adult liver injuries. However, the specific mechanism of SI-associated hepatotoxicity has not been reported.

Weight loss

Weight loss associated with SI treatment may be multifactorial in origin, including decreased oral intake from dysgeusia, GI toxicity, and/or advanced BCC. Compared with other toxicities, weight loss has a later onset with vismodegib, with a reported median time to onset of 175 days after initiation (35). Because of the late onset and the relatively short follow-up times in many clinical trials, the true incidence of weight loss may be under-reported. For instance, in an expanded access study of vismodegib with a median exposure time of 5 months, approximately 20% of patients experienced grade 1 or 2 weight loss, whereas in a phase II study with median exposure time of 10 months, approximately 46% of patients experienced grade 1 to 4 weight loss (Table 2; refs. 16, 35). Similarly, a phase II study of sonidegib showed that 27% of patients receiving the 200-mg once-daily dosage experienced weight loss (Table 2; refs. 12, 13).

Management of weight loss depends on the severity of the side effect. For moderate to severe weight loss, high calorie nutritional supplements and consultation with an oncologic nutritionist may be of benefit. In our patients, oral megestrol acetate or dronabinol has helped to stimulate appetite but formal studies are needed to determine the optimal strategies to combat or reduce the weight loss side effect.

Discussion

Because the SI drug class is new, long-term data on AEs and their management are forthcoming. Studies directed at managing side effects are underway and more are needed. Multidisciplinary care to manage toxicities, including regular skin cancer surveillance by a dermatologist, is crucial. Given the potential long-term nature of SI treatment, with responsive metastatic BCC patients dosed indefinitely until tumor progression, the ability to successfully manage side effects is critical for patient adherence and quality of life.

Disclosure of Potential Conflicts of Interest

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References

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