Basal cell carcinoma (BCC) is the most common human cancer detected in Western populations and poses significant health expenditure. Most BCCs are slow growing and managed with topical, photodynamic, radiation therapy or the "gold standard" of surgical excision. The use of Hedgehog pathway inhibitors is a major advancement in the treatment of locally advanced (laBCC) and metastatic BCC (mBCC), which accounts for one to 10 percent and 0.0028-0.5 percent of all BCCs, respectively.

Most BCCs arise from the loss of patched homologue 1 (PTCH1) inhibition of the Smoothened (SMO) homologue. This results in an aberrant activation of the GLI transcription factors in the hedgehog-signaling pathway downstream, leading to unregulated oncogenesis. Local mutation of the PTCH1 membrane receptor gene causes individual BCC development, while germ line mutation in PTCH1, which occurs in the autosomal dominant basal cell nevus syndrome (BCNS) or Gorlin Syndrome, can result in thousands of BCCs over one’s lifetime. Understanding this disease pathophysiology is essential for development of targeted therapeutics.

There are currently two FDA-approved oral hedgehog inhibitors, both of which act on the same receptor to inhibit the transmembrane protein, SMO. Vismodegib, 150mg daily (Erivedge, Genentech), was approved in 2012 as the first available treatment for laBCC and mBCC. In 2015, the second drug of its class, sonidegib, 200mg capsule once daily (Odomzo, Novartis), was approved. More targeted therapies are under investigation.

The side effects and resistance of SMO inhibitors can be factors that limit their optimal efficacy. This is well documented in the pivotal studies of ERIVANCE and STEVIE for vismodegib and BOLT for sonidegib. Despite being categorized as mild-to-moderate according to the trial definitions, the common side effects cause a relatively high rate of discontinuation (28.2 percent in vismodegib and 27.8 percent in sonidegib). These adverse effects can be subdivided into common class effects, drug-specific effects and rare associations. Pregnancy precaution, pharmacokinetic interactions, and treatment resistance are also important considerations that need to be discussed with patients prior to treatment initiation and reviewed during and after the treatment course.

**MUSCLE CRAMP/SPASM**

Muscle spasm is the most commonly reported side effect of the SMO inhibitors, experienced by 66.4 percent and 49 percent of vismodegib and sonidegib users, respectively. From basic science study, we understand that SMO inhibitors also independently activate the non-canonical hedgehog pathway, which activates the calcium channels of cell membranes to induce muscle spasms. Clinicians can suggest a combination of exercise, massage, and acupuncture to alleviate the musculoskeletal pain. Thermal compresses and transcutaneous electrical nerve stimulation have also shown benefits in non-controlled settings. We explain to our patients that pain is a subjective experience and we encourage them to try these non-pharmacological methods from registered providers to find their individualized ideal regimen.

For patients who have exhausted the lifestyle measures, a two-week trial of amlodipine 10mg daily can be prescribed, if there are no contraindications. In one small prospective cohort study, amlodipine reduced the frequency of the muscle cramps as early as two weeks, but not the severity or duration.

As the muscle cramps take around two to three months to develop and typically resolve one month after drug cessation, pulse therapy with one-month treatment followed by a one-month break can be recommended.
ALOPECIA

Following muscle spasms, alopecia is the second most commonly reported side effect, occurring in 61 percent and 43 percent of vismodegib and sonidegib-treated patients, respectively.9 Hair loss tends to become noticeable in the fifth month after taking vismodegib.10 More information is available for vismodegib because it is a well-established drug, but a similar outcome can be expected with sonidegib.

Hedgehog inhibitors hinder the normal hair cycle but they do not destroy the hair follicle.13 This non-scarring etiology is consistent with telogen effluvium, where the telogen count is significantly increased compared to the anagen hair count on biopsy, with preserved follicular density and architecture.14

When warning patients about hair loss, it is important to assure that hair typically regrows within months after drug cessation. Permanent alopecia with minimal regrowth after one year of drug cessation is extremely rare, but has been reported in a single instance.15 Curiously, the observation of hypertrichosis on extremities has also been documented in a minority of patients. The pathophysiology is unknown.

There are no miracle treatments for hair loss, unfortunately. Sun protection and avoidance of chemicals/physical irritants support baseline hair and scalp health.16 Minoxidil reduces telogen arrest and extends the anagen growth phase. The topical foam is readily available. Oral minoxidil 1mg daily is more effective than the topical form in our clinical experience and exerts minimal systemic effect, such as hypotension.17 Larger confirmatory studies are needed.

Interestingly, hair regrowth while on continuous treatment could be a warning sign of drug resistance. When this occurs, the clinician and patients may need to plan an alternative treatment.18

DYSGEUSIA

Dysgeusia (a change in taste sensation) affects 57 percent and 38 percent of vismodegib and sonidegib patients, respectively.5 The median time of first onset ranges from the thirtieth day to six months in vismodegib-treated patients.16,19 While mostly the taste change is mild, 23 percent and seven percent of the vismodegib and sonidegib patients have “grade 2” dysgeusia, causing unpleasant or loss of taste with resultant dietary changes.20,21

Dysgeusia is a class effect of all modifiers of the Sonic hedgehog pathway, which signals for the differentiation of the precursor taste cells into cells that detect sweet, salt, and bitter tastes.22 Vismodegib treated mice are associated with smaller taste cell size, reduced taste-sensing expression, slower growth rate, as well as weight loss likely attributed to the reduced oral intake.22

“Interestingly, hair regrowth while on continuous treatment could be a warning sign of drug resistance. When this occurs, the clinician and patients may need to plan an alternative treatment.”

Fortunately, taste buds have a limited lifespan of 10-16 days.22 Patients can be assured that new taste buds will emerge after treatment cessation. Some self-care strategies we recommend include smaller and more frequent meals, food at room temperature, stronger seasoning, adjusting the salt/sugar level to taste, increasing chewing time for salivary production, avoidance of metallic plates and cutlery, increasing water intake between foods, and maintenance of oral hygiene.23

A mild decline in zinc level has been observed in patients after taking vismodegib.19 When facing a patient concerned they are losing their taste, periodic monitoring of zinc levels and supplementation of 140mg/day zinc gluconate may be helpful to optimize gustation.24 Finally, the intermittent therapy proposed for muscle spasms also works for dysgeusia, as both of these side effects are usually quick to resolve after drug cessation.

WEIGHT LOSS

Weight loss is reported in 33.4 percent of vismodegib patients and 27 percent of sonidegib patients.5 For some patients, weight loss is a desired “side-effect” rather than an adverse-effect. The weight loss is an independent side effect, and it may be compounded by dysgeusia. This risk should be explained to all patients before starting therapy.

When initiating vismodegib, it is recommend that patients’ nutritional status and weight are monitored. Dietitian review, regarding high protein, high calorie diet, and fortified supplements, such as nutritional shakes, are recommended for malnourished patients and patients who experience significant undesired weight loss. An increased vigilance is recommended for high-risk populations, such as the elderly.

FATIGUE

Fatigue is experienced in 20.1 percent and 29 percent of vismodegib and sonidegib patients, respectively.5 The pathophysiology is likely multifactorial. Clinicians should review and optimize for any medical and psychological co-morbid-
ities, social stressors, sleep disturbances, or nutritional deficiencies that could be contributing to fatigue.

Regular aerobic and strength exercise can improve endurance and functional capacity.\textsuperscript{25} Clinicians can also refer patients for cognitive behavioral therapies or supportive-expressive therapies that are designed for fatigue management.\textsuperscript{26} Wellbeing and mindfulness programs include sleep hygiene, acupuncture, massage, pilates, yoga, and meditation.\textsuperscript{25,27} Like pain, fatigue is also a subjective experience requiring individualized management combining various lifestyle strategies.

**PREGNANCY AND FERTILITY PRECAUTIONS**

The hedgehog regulatory pathway is essential for embryogenesis. Based on animal studies, both vismodegib and sonidegib are embryotoxic and teratogenic.\textsuperscript{28,29} There is no controlled human data.

Pregnancy, breast-feeding and blood donation are contraindicated. Negative bHCG must be determined for all women of reproductive age prior to initiating treatment. Double protection using a chemical and physical barrier is recommended. After drug cessation, contraception needs to continue for at least seven months for vismodegib and 20 months for sonidegib according to their package inserts. As the drug is present in semen, even male patients need to use barrier contraception with spermicide and avoid sperm donation for two to six months after treatment with vismodegib and sonidegib, respectively. Vasectomy does not obviate this requirement.

It has been reported that 32.9 percent of premenopausal women experience amenorrhea whilst taking vismodegib.\textsuperscript{30} Amenorrhea, associated with high FSH and low estrogen suggests functional ovarian decline.\textsuperscript{31} Animal studies show that fertility can be permanently impaired when using SMO inhibitors.

Open discussion of fertility and pregnancy risks is recommended. For patients with BCNS who could be on SMO inhibitors long-term, referral to fertility preservation specialists should be offered. With endocrine markers and menopause-associated changes, such as bone density, genital atrophy, and dyslipidemia should be monitored periodically with long-term treatment.\textsuperscript{31}

**CREATINE KINASE ELEVATION**

Myositis or myopathies associated with creatine kinase (CK) elevation are the most common grade 3-4 serious adverse effects and the dose-limiting factor in sonidegib, experienced by six percent of the patients on the 200mg daily dose.\textsuperscript{21} Fortunately, the CK level is unaffected in vismodegib because of its unique pharmacokinetics associated with its high-affinity binding to the acute phase protein, a-1-acid glycoprotein.\textsuperscript{32,33}

Before treatment and at each visit, patients should be counseled to promptly return if they experience muscle weakness, muscle ache and/or dark urine. For sonidegib, CK and creatinine should be measured at baseline and monitored according to response. Sonidegib should be withheld if CK rises above 2.5 times the upper limit of normal. Encouragement of fluid intake is important for prevention and treatment. Symptoms can be managed with magnesium supplementation, simple analgesia, and muscle relaxants. Renal function is typically preserved and rhabdomyolysis is rare. When the CK normalizes, pulse therapy or alternatives to sonidegib should be considered, taking into account the severity of the CK derangement verses that of the BCC and patient’s general health.

**DRUG INTERACTIONS AND FOOD**

The liver metabolizes both vismodegib and sonidegib. Liver function tests can be monitored periodically, especially in patients on polypharmacy, although this is not a compulsory requirement according to the product inserts.\textsuperscript{34-36} Sonidegib is primarily metabolized via the cytochrome P450 (CYP) 3A pathway. The sonidegib plasma concentration is lowered with concurrent use of P450 (CYP) 3A inducers. Hence, sonidegib should not be combined with itraconazole, a common antifungal agent with hedgehog inhibitory effects against BCCs. Concomitant administration of strong P450 (CYP) 3A inhibitors, which can increase sonidegib levels, are also contraindicated.\textsuperscript{34} Furthermore, exposure to sonidegib increases when it is administered with lipid-rich foods, hence it should be taken on an empty stomach.

In contrast, vismodegib has no reported drug or food interactions nor need for dose modification according to the package insert.\textsuperscript{35} Due to its high protein affinity, it has a theoretical potential to displace other protein-bound medications, such as warfarin. Monitoring for INR elevation after initiating vismodegib is recommended.\textsuperscript{37}

Clinicians should revisit their patient’s comprehensive medical and drug history. The SMO inhibitors should be monitored closely in patients with a history of myositis, liver and renal derangements. Regular review and rationalization of the patient’s prescription and over-the-counter medications is
important to prevent drug interactions. The baseline workup should include weight, blood tests (renal function, CK, liver function test and in women of reproductive age, bHCG) and biopsies for histological confirmation of the lesion type.

**GASTROINTESTINAL EFFECTS**

Gastrointestinal side effects are non-specific and common adverse effect of many drugs. Nausea was reported in 16 percent and diarrhea was reported in 17 percent of the patients treated with vismodegib in the STEVIE study. In the BOLT trial on sonidegib, nausea and vomiting occurred in 35 percent and 7.9 percent patients, respectively, and 30.4 percent of the study patients reported diarrhea. Most of these complaints are mild. General symptoms require generalized management. There are various antiemetic classes for the treatment of emesis in general, such as anti-dopaminergic, serotonin receptor antagonist, antihistamine, phenothiazine and glucocorticoid medications. However, these are rarely needed for the mild symptoms and patients can try simple measures such as taking ginger as a natural emetic, avoiding pungent odors and fatty foods and eating small meals. When vomiting or diarrhea occurs, fluids should be replenished orally, rarely the symptoms are severe enough for intravenous supplementation.

**RARE SIDE EFFECTS**

Rare side effects of new drugs are often recognized through post-market surveillance. Reports should be interpreted with caution, as they could be a side effect or simply an association.

**SQUAMOUS CELL CARCINOMA**

People with basal cell carcinoma often share similar risk factors for squamous cell carcinoma (SCC). There are increasing case reports of SCC relapse and development in patients treated with vismodegib. The associated may be explained by a dual function of PTCH1 noted in mice studies, promoting SCC growth whilst inhibiting BCCs.

As sonidegib was released after vismodegib, its associated with SCC is yet to be determined, with three documented patients with new SCCs. Nonetheless, unexpected growth of an existing or new lesion should be promptly biopsied.

**SPINY HYPERKERATOSIS**

There is one case report of trichodysplasia spinulosa-like lesions in an immunocompetent patient treated with vismodegib, which resolved following cessation of the medication. This could be managed with keratolytics, pulsed vismodegib therapy or the trial of another SMO inhibitor. Assuming this is not associated with TS polyomavirus infection, a new diagnosis of ‘spiny follicular papules’ has been suggested for this drug-induced phenomenon.

**RESISTANCE**

An ongoing challenge is the development of drug resistance. Hedgehog signaling can be resurrected via mutations in SMO itself, downstream mutations in the hedgehog pathway or synergistic non-canonical activation of the hedgehog pathway.

As vismodegib and sonidegib work on the same receptor on SMO, resistance to one confers resistance to the other. There are other hedgehog pathway inhibitors that work on different receptors or different parts of the pathway but their efficacy is either not a great or studies have not shown similar efficacy. Given there are no effective alternatives, a limited response duration is still beneficial in relieving patient disease burden. With vismodegib, the median duration of response lasts 22.7 and 10.0 months in patients with aBCC and mBCC, respectively. For sonidegib, this is likely to be at least 17.7 months and 10.2 months, as a longer follow-up study is required for the newer agent.

Patients need to understand that SMO inhibition may not be a permanent cure. Setting a realistic expectation is especially important for BCNS patients who require lifelong BCC suppression. When discussing options beyond the SMO inhibitors, clinicians should weigh the temporary benefits against their side effects, keeping in mind the larger picture of patients’ quality of life and general prognosis.

**TAKE HOME MESSAGE**

SMO inhibition is the first medically effective option in the management of locally advanced and metastatic BCC. Although mild in nature, their side effects of muscle cramps, alopecia, dysgeusia, weight loss, and fatigue can affect patients’ quality of life and lead to premature treatment discontinuation and poor compliance. Strict con-
tracheal measures should be followed during and in the specified period after drug cessation. To maximize patient compliance, pre-treatment counseling should highlight the transient nature of many of the common side effects and patient should be encouraged to explore lifestyle modifications ameliorate these symptoms.

Regular follow up of treatment response, side effects, and patient concerns is ideal practice. Blood tests for renal, liver function, and CK is an inexpensive and relatively accessible way to objectively ensure systemic safety. Solutions for side effects and resistance continue to be explored by research and combination therapy. Off-label pulse therapy is most effective if muscle spasm and dysgeusia is the patient’s main concern, as these effects are quick to resolve upon drug cessation.

Involvement of patients in the treatment planning process, keeping in mind their general prognosis and quality of life is recommended when intolerable side effects or resistance occurs. ■

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