Vismodegib for Basal Cell Carcinoma and Beyond: What Dermatologists Need to Know

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CLINICAL REVIEW

Basal cell carcinoma (BCC) is the most common cutaneous malignancy. Although indolent, BCCs can be locally aggressive if untreated. Dysregulated hedgehog (Hh) signaling leads to uncontrolled proliferation in BCC. Vismodegib is a small-molecule antagonist of the Hh pathway that binds to smoothened (SMO), a transmembrane protein, and causes inhibition of an aberrant activation of the Hh pathway. Vismodegib is the first drug approved by the US Food and Drug Administration (FDA) for the management of locally advanced or metastatic BCC.

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Hh Pathway in BCC

In embryonic development, the Hh signaling pathway is crucial across a broad spectrum of species, including humans. Various members of the Hh family have been recognized, all working as secreted regulatory proteins. The name of the Hh signaling pathway is derived from a polypeptide ligand called hedgehog found in some fruit flies. Mutations in the gene led to fruit fly larvae that had a spiky hairy pattern of denticles similar to hedgehogs, leading to the name of this molecule. The transmembrane protein smoothened (SMO) is the main component of the Hh signaling pathway and initiates a signaling cascade that in turn leads to an increased expression of target genes, such as GLI1. Patched (PTCH), also a...

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transmembrane protein and a cell-surface receptor for the secreted Hh ligand, suppresses the signaling capacity of SMO. Upon binding of the Hh ligand to the SMO receptor, the suppression of SMO is relieved and a signal is propagated, evoking a cellular response. Molecular and genetic studies have reported that genetic alterations in the Hh signaling pathway are almost universally present in all BCCs, leading to an aberrant activation of the pathway and an uncontrolled proliferation of the basal cells. Frequently, these alterations have been shown to cause loss of function of PTCH homologue 1, which usually acts to inhibit the SMO homologue signaling activity.

Because of the potential importance of Hh signaling in other solid malignancies and the failure of topical inhibition of SMO, subsequent studies on the development of Hh pathway inhibitors have mostly focused on the systemic approach. A multitude of Hh pathway inhibitors have been developed thus far, such as SANTI-SANT4, GDC-0449, IPI-926, BMS-833923 (XL139), HhAntag-691, and MK-4101. Many of these inhibitors have been clinically investigated.

**Systemic SMO Inhibitor: Vismodegib**

Vismodegib was the earliest systemic SMO inhibitor to fulfill early clinical evaluation and the first drug to receive FDA approval for the management of advanced or metastatic BCC. Vismodegib is a small-molecule SMO inhibitor used for the management of selected locally advanced BCC and metastatic BCC in adults. Although there is a possibility of recurrence following drug withdrawal, vismodegib constitutes a new therapeutic strategy presenting positive benefits to patients. It may provide superior improvement over sunsinitib, which has shown efficacy in a few patients; however, the efficacy and tolerance of sunsinitib have been shown to be limited.

**Adverse Effects of Vismodegib Therapy**

Adverse events with vismodegib use have been reported in 98% of patients (N=491); most of these were mild to moderate. However, the frequency of adverse events could prove to be a therapeutic challenge for patients requiring extended treatment. The most frequently reported reversible side effects were muscle spasms (64%), alopecia (62%), weight loss (33%), fatigue (28%), decreased appetite (25%), diarrhea (17%), nausea (16%), dysgeusia (54%), and ageusia (22%). In clinical trials, amenorrhea was noticed in 30% (3/10) of females with reproductive potential. Apart from alopecia and possibly amenorrhea, these side effects are reversible. Alkeraye et al reported 3 clinical cases of persistent alopecia following the use of vismodegib. Amenorrhea is a possible side effect of unknown reversibility.

Vismodegib is a pregnancy category D medication. Severe birth defects, including craniofacial abnormalities, retardations in normal growth, open perineum, and absence of digital fusion at a corresponding 20% of the recommended daily dose, were found in rat studies. Embryo-fetal death was noted when rats were exposed to concentrations comparable to the recommended human dose.

Hepatic events with the use of vismodegib have been reported. The use of vismodegib in randomized controlled trials resulted in elevation of both alanine aminotransferase and aspartate aminotransferase levels compared with placebo. Moreover, severe hepatotoxicity with vismodegib has been reported. A study conducted by Edwards et al concluded that the use of vismodegib in patients with severe liver disease must include thorough risk-benefit assessment, with caution in using other concomitant hepatotoxic medications.

Rare adverse events also have been reported in the literature, including vismodegib-induced pancreatitis in a 79-year-old patient treated for locally advanced, recurrent BCC that was cleared following cessation of therapy. Additionally, atypical fibroxanthoma was observed in an 83-year-old patient after 30 days of treatment with vismodegib for multiple BCCs. The development of other secondary malignancies, such as squamous cell carcinoma, melanoma, keratoacanthomas, and pilomatrixomas, during or after the long-term use of vismodegib also have been described.

**Use of Vismodegib for Adnexal Skin Tumors**

The role of the sonic Hh–PTCH pathway in the pathogenesis of adnexal tumors varies in the literature. Some studies propose the involvement of this pathway in the formation of adnexal tumors such as trichoblastoma, trichoepithelioma, and cylindroma, as in BCC. Various lines of evidence support this involvement. Firstly, in mice, the spontaneous generation of numerous BCCs, trichoblastomas, trichoepitheliomas, and cylindromas has been observed following constitutive activation of the sonic Hh–PTCH pathway. Second, in trichoepitheliomas, there have been positive results in molecular research into the tumor suppressor gene PTCH homologue 1, whose mutations cause constitutive activation of the sonic Hh–PTCH pathway. Third, GLI1 and SOX9 transcription factors associated with the signaling pathway of sonic Hh–PTCH appear to have increased levels in adnexal carcinomas. Lepesant et al reported a notable clinical response to vismodegib in trichoblastic carcinoma. Baur et al reported successful treatment of multiple familial trichoepitheliomas with vismodegib. Nonetheless, more studies are required to assess the efficacy and reliability of vismodegib in the management of adnexal tumors.

**Recommended Dose of Vismodegib Therapy**

The vismodegib dosage that is approved by the FDA is 150 mg/d until disease progression or the development of intolerable side effects. Higher dosing regimens were evaluated with 270 mg/d and 540 mg/d. No added
therapeutic benefit was noted with the increase in the dose, and no dose-limiting toxic effects were observed.

**Management of Vismodegib Side Effects**

Managing patient expectations is a crucial step in improving dysgeusia. The experience of dysgeusia varies among patients; thus, patients should be instructed to adjust their diets according to their level of dysgeusia, which can be achieved by changing ingredients or dressings used with their diet. This step has been proven to be effective in overcoming vismodegib-related dysgeusia. Also, fluid taste distortion may lead to dehyrdration and an increase in creatine level. Thus, patients should be encouraged to monitor fluid intake. Moreover, a treatment hiatus of 2 to 8 months results in near-complete improvement of taste distortion.

For muscle spasms, quinine, treatment break for 1 month, gentle exercise of affected areas, or muscle relaxants such as baclofen and temazepam all are effective methods. For vismodegib-related alopecia, managing patient expectations is key; patients should be aware that hair may take 6 to 12 months or even longer to regrow. In addition, shaving less frequently helps improve alopecia.

For gastrointestinal disorders, loperamide with or without codeine phosphate is effective in resolving diarrhea, and metoclopramide is mostly adequate in treating nausea. Another adverse event is weight loss; weight loss of 5% or more of total body weight prompts dietetic referral. If weight loss persists, a treatment break might be needed to regain weight.

Overall, treatment breaks are sufficient to resolve adverse events caused by vismodegib and do not compromise efficacy of treatment. The duration of a treatment break should be considered before initiation. In one clinical trial, a longer treatment break was associated with fewer adverse effects without affecting the efficacy of treatment.

**Conclusion**

Vismodegib provides an effective alternative to surgical intervention in the management of BCC. However, patients must be monitored vigilantly, as adverse events are common (≥90%).

**REFERENCES**


