

Optimizing the Pharmacokinetics of Sonidegib in Small Bowel Syndrome and Advanced Basal Cell Carcinoma: Our Solution

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SYNOPSIS

- Basal cell carcinoma (BCC) is the most common cancer worldwide, with an increasing annual incidence^{1,2}
 - In patients with advanced BCC, lesions become extensively locally invasive or metastatic, and traditional first-line surgical treatment may be contraindicated³
- Hedgehog pathway inhibitors (HHIs) represent an alternate treatment option for patients with advanced BCC⁴
 - HHIs block the aberrant Hedgehog pathway activation that allows transcription of glioma-associated oncogene transcription factors and activation of target genes for tumorigenesis and angiogenesis during development of BCC (Figure 1)⁵
 - Most HHIs prevent Hedgehog signaling by binding to and preventing activation of transmembrane protein Smoothed⁵

- Sonidegib is an HHI approved in the US, the EU, Switzerland, and Australia for the treatment of adult patients with locally advanced BCC that has recurred following surgery or radiation therapy or is not amenable to surgery or radiation therapy⁷
 - Recommended dosing is one 200 mg capsule by mouth daily on an empty stomach or ≥ 1 hour before or ≥ 2 hours after a meal⁷
 - Treatment should continue until significant toxicity or disease progression⁷
 - Administration with a high-fat meal increases drug absorption by 7.4- to 7.8-fold⁷
- Use of HHIs, including sonidegib, in patients with dysphagia or impaired gastrointestinal absorption poses unique and challenging management scenarios

OBJECTIVES

- Understand the effects of high-fat foods on sonidegib absorption
- Raise awareness of and improve access to sonidegib for other patients with gastrointestinal absorption issues

METHODS

- An N-of-1 trial was conducted
- The patient was an 83-year-old woman with history of short bowel syndrome and dysphagia
 - She also had a history of multiple keratinocyte carcinomas of the nose and cheek, which were previously treated with Mohs micrographic surgery, radiation, and salvage radiation
- The patient presented to Strasswimmer Mohs Surgery, Delray Beach, FL, USA with a large, surgically unresectable, recurrent, locally advanced BCC lesion on the nasal tip
 - Biopsy of the nose revealed a locally advanced, infiltrative BCC
- Considering patient factors and HHI pharmacology, half of a capsule (100 mg) of sonidegib was prescribed to be taken in 2 tablespoons of vanilla ice cream once daily
 - Due to teratogenicity risk with sonidegib, a family member of no reproductive potential divided the capsule using medical gloves and a razor blade
- Efficacy was assessed via observation of tumor response
- Safety evaluations included monitoring for signs and symptoms of toxicity
 - Electrolytes, liver function, and creatine kinase values were monitored
- Patient provided informed consent for publication

RESULTS

- After 5 weeks of treatment, reduction in tumor size was noted (Image 1)

Image 1. Photographs showing tumor response in patient with BCC following sonidegib treatment

A. The patient upon initial presentation with an infiltrative BCC of the nose



B. Improvement of the patient's infiltrative BCC after 5 weeks of sonidegib treatment



BCC, basal cell carcinoma.

- Around week 5 of treatment, the patient began to experience adverse effects, including mild nausea and muscle cramping of the hands and feet
 - Clinical laboratory parameters remained within normal limits
 - A 5-week medication holiday was subsequently instituted with symptom resolution
- Tumor regrowth was noted after 5 weeks without therapy, so sonidegib was reinstated at the same dose for another 5 weeks
- In total, the patient completed three 5-week sonidegib cycles with 5 weeks of medication holiday between each cycle
- Following the third course of sonidegib, the patient and her family were satisfied with treatment results
 - More than 1 year later, she continues to deny further issues

CONCLUSIONS

- Combining a low dose of sonidegib with ice cream, a high-fat food, helped overcome the patient's gastrointestinal absorption and swallowing issues
- Clinical improvement of BCC was noted after 5 weeks of sonidegib treatment
- Adverse effects included nausea and muscle cramping, though the patient's bloodwork values remained within normal limits for the duration of treatment
- The patient best tolerated a treatment regimen alternating 5 weeks on and 5 weeks off sonidegib

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DISCLOSURES

HG, MC, and JS report nothing to disclose.

Figure 1. Hedgehog signaling pathway⁶

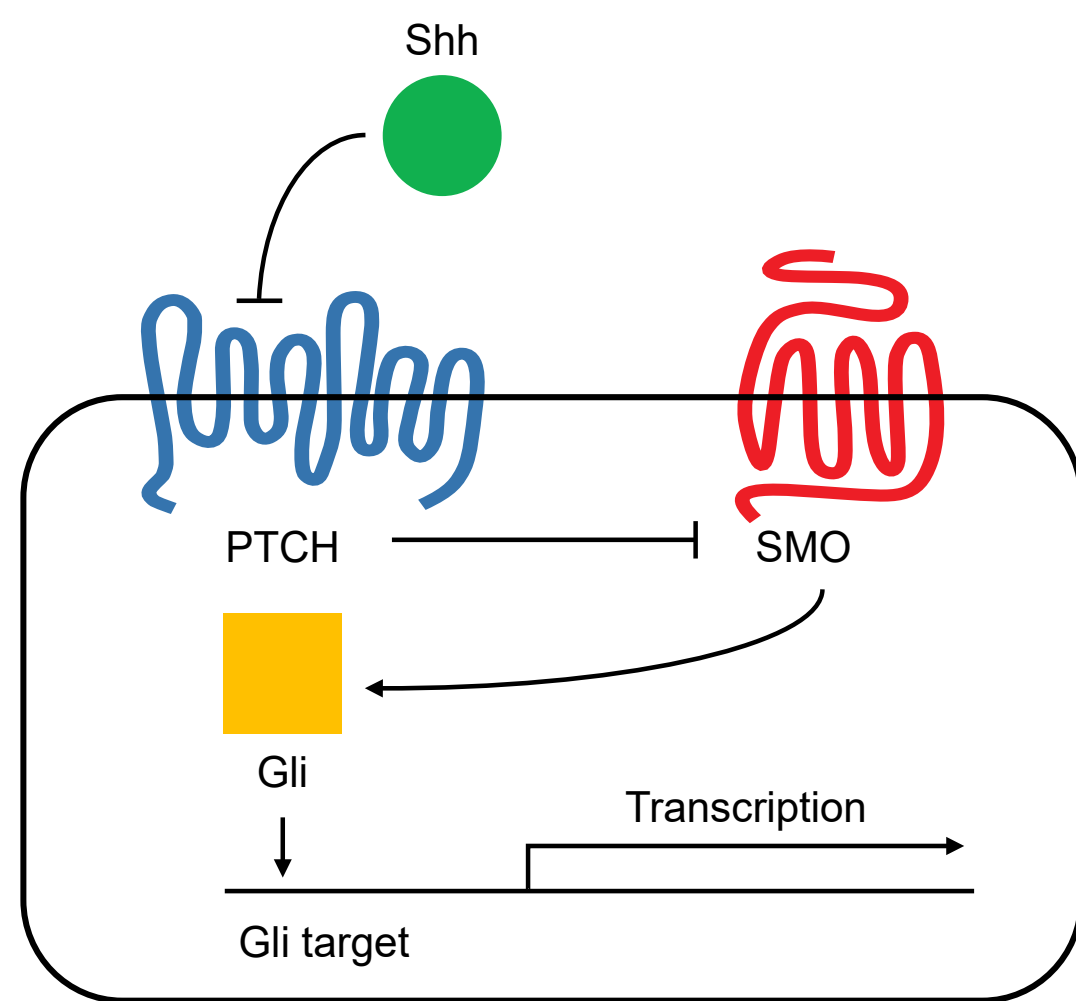


Image source: Jain S, et al. *OncoTargets Ther.* 2017;10:1645–53. Gli, glioma-associated oncogene; PTCH, Patched; Shh, Sonic hedgehog; SMO, Smoothened.