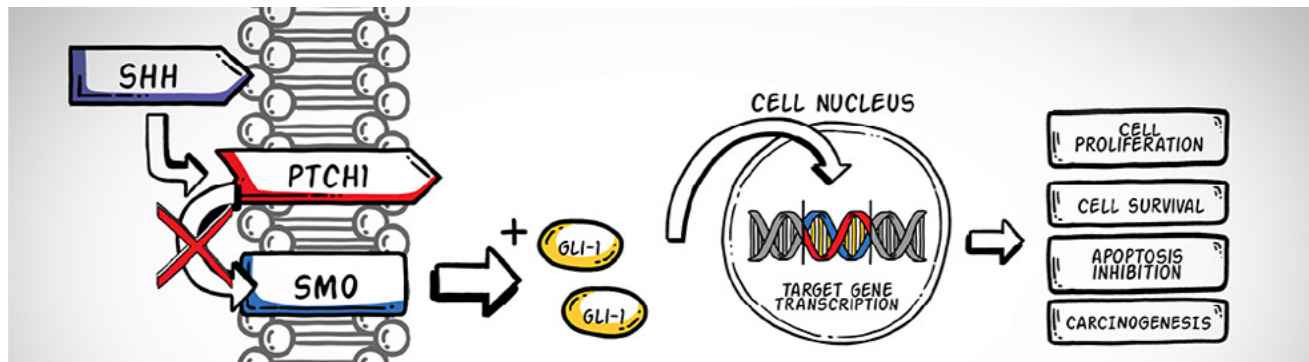


ADVANCED BASAL CELL CARCINOMA: HOW TO NAVIGATE CHALLENGING CLINICAL SCENARIOS WITH SYSTEMIC TREATMENT

CLINICAL INSIGHT

1. Introduction

Basal cell carcinoma (BCC) is the most common of all malignancies, but rarely causes death. The development of BCC results from an interaction between numerous genes and environmental factors. A key pathway in BCC is the highly conserved hedgehog pathway. Among the multiple alterations in BCC, hedgehog pathway alterations, eg, mutations in the patched 1 gene (PTCH1) and the smoothened gene (SMO), are nearly ubiquitous.



2. Systemic Treatment: Hedgehog Pathway

BCC is classified as low risk, high risk, and advanced. A hedgehog, ie, smoothened gene, inhibitor is a key treatment option for patients with advanced disease. Sonidegib and vismodegib are the 2 hedgehog inhibitors currently approved in the United States. These inhibitors bind to smoothened gene, thereby preventing glioma-mediated activation of gene transcription and downstream effects, such as cell proliferation and carcinogenesis. Multidisciplinary care is generally required for the management of patients with advanced BCC.



3. Systemic Treatment: Vismodegib

The safety and efficacy of vismodegib were established in the ERIVANCE and STEVIE studies, which primarily involved patients where surgery was not appropriate. The ERIVANCE study showed that treatment with vismodegib resulted in objective response rates (ORRs) of 60.3% in locally advanced BCC and 48.5% in metastatic BCC at 39 months. In the larger STEVIE study (N=1215), the ORRs were 68.5% and 36.9%, respectively, at 8.6 months. Progression-free survival was 23.2 months and 13.1 months, respectively. The most common adverse events occurring in the majority of patients treated with vismodegib were muscle spasm, alopecia, and dysgeusia. The MIKIE study compared 2 intermittent dosing regimens (not approved by the US FDA) of vismodegib in patients with multiple BCCs amenable to surgery. Results at the end of 72 weeks showed good activity and comparable safety with both intermittent regimens.

4. Systemic Treatment: Sonidegib

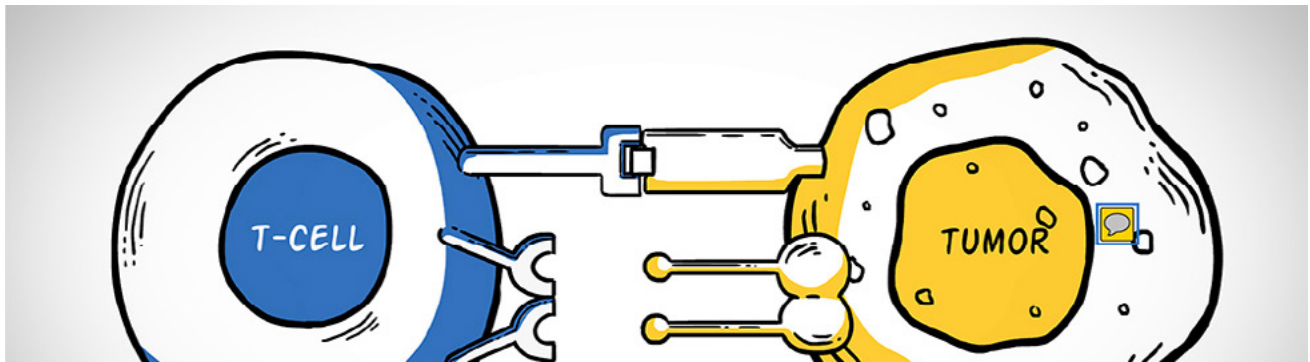
The safety and efficacy of sonidegib were established in the BOLT study, which involved patients with locally advanced BCC not amenable to surgery or radiation therapy or metastatic BCC. In patients with locally advanced BCC and metastatic BCC treated with sonidegib 200 mg/day, the respective ORRs were 43% and 15% at 13.9 months and 56% and 8% at 42 months. As with vismodegib, nearly all patients treated with sonidegib experienced 1 or more adverse events. The most common adverse events were muscle spasm, alopecia, and dysgeusia.

5. Optimizing Hedgehog Inhibitors

A key strategy to optimizing treatment with hedgehog inhibitors is to mitigate the severity of adverse events. It is, therefore, important that patients be educated about common adverse events beginning at treatment initiation. Unfortunately, there is little information from formalized investigation to guide management. Therefore, standard approaches such as hydration and electrolyte replacement to manage muscle spasms and nutrition consultation for dysgeusia and weight loss are important. Similarly, since there are no established guidelines, patients treated with a hedgehog inhibitor should be monitored every 1-3 months as typically done with any anticancer therapy.

6. Emerging Agents

A limitation of hedgehog inhibitor therapy is the development of resistance, often due to alternative mutations in smoothed gene. Various evidence suggests that immunotherapy may play a key role in the treatment of patients who develop resistance to sonidegib or vismodegib. Among this evidence is investigational use of the PD-1 inhibitor nivolumab and early evidence with the investigational PD-1 inhibitor cemiplimab. PD-1 inhibitors are thought to bind to the PD-1 receptor on the surface of the T-cell, thereby preventing the tumor cell from deactivating the T-cell through binding via PD-1L/PD-2L.



7. Case Studies

A key question encountered in the clinical use of hedgehog inhibitors is how long should therapy be continued in patients with locally advanced BCC? This question has not been formally investigated. Based on observations from clinical trials that some patients achieved a complete response and the objective response rate appeared to increase over time, it seems that treatment should be continued as long as the patient tolerates therapy. Thus, close monitoring and implementing strategies to improve patient tolerability and treatment adherence are important. For those patients who no longer tolerate hedgehog inhibitor therapy but experience a good treatment response, as exhibited by tumor shrinkage, local therapy with surgery or radiation therapy may be considered.