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Review Paper

Comparative Analysis of The Efficacy and Tolerability of Sonidegib And Vismodegib In the Treatment of Advanced Skin Cancer

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ABSTRACT

Advanced pores and skin cancers, specifically basal cellular carcinoma (BCC), poses a huge task in medical workout because of its aggressive nature in favorable sufferers. Targeted remedy alternatives that include Hedgehog pathway inhibitors have provided novel treatment methods for patients who can also be unable to go through surgical operation or whose tumors are locally superior or metastatic. These include Sonidegib and Vismodegib, FDA-accepted capsules that act on the Hedgehog signalling pathway and show promise in efficacy. This file gives a comparative evaluation of those capsules in phrases of their efficacy, protection and tolerability inside the remedy of advanced pores and skin most cancers. Sonidegib and Vismodegib are two inhibitors of the Hedgehog pathway; this research compares their efficacy in treating upper skin cancers, particularly basal cellular carcinoma (BCC). Their effectiveness in reducing tumor burden and improving survival and tolerability profiles mainly from scientific studies are evaluated. Their use can be compared and contrasted in scientific practice, as a literature review makes clear.

INTRODUCTION

Skin cancer is one of the common types of cancer worldwide, and basal cell carcinoma (BCC) is the most general type of nonmelanoma skin cancer^[1]. Systemic treatment is necessary for people with advanced or metastatic BCC; however, surgery or local therapies may treat most BCCs. Targeting the hedgehog signaling pathway has emerged as a significant therapy option for advanced BCC,

thanks to the mechanisms of Vismodegib and Sonidegib^[2]. The paper aims to provide a comparison of their efficacy and tolerability in advanced skin cancer treatment, to expose their clinical use and provide suggestions for future treatment strategies. The majority of non-melanoma skin cancers are basal cell carcinomas (BCCs). Localized basal cell carcinomas are often surgically or locally treated. Patients whose BCC

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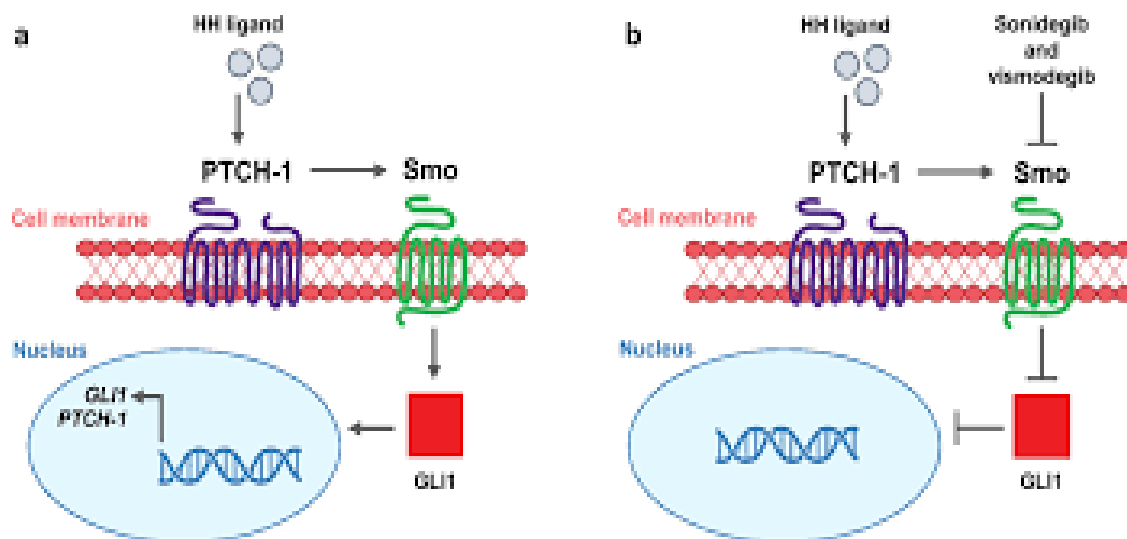
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has progressed to an advanced stage or metastasized must undergo systemic therapy [3]. Hedgehog pathway inhibitors—sonidegib and vismodegib specifically—have markedly shifted

the treatment landscape for advanced BCC owing to their mechanism of action and targeted approach of blocking molecular pathways that promote tumor growth.

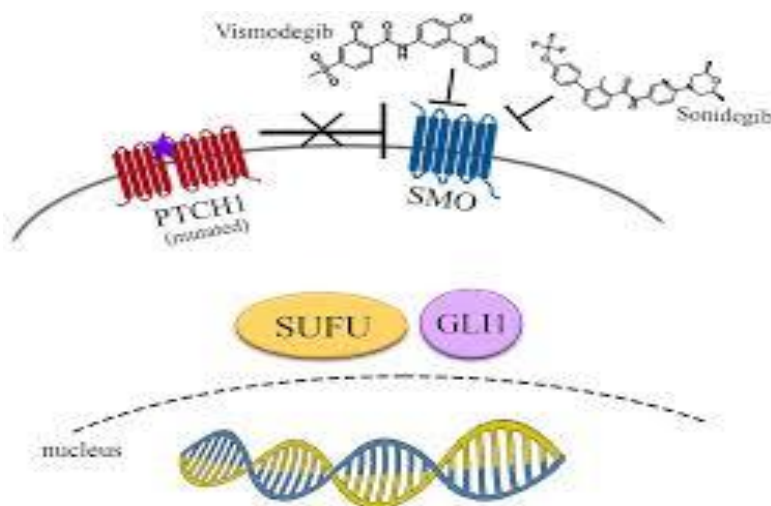


Source: Springer, 2013

The two drugs both target the Smoothed (SMO) BCC is one of the malignancies that exhibits abnormal activation of the Hedgehog signaling system, which involves a receptor. In this comparative review, which is based on data from recently published clinical trials, the effectiveness, safety, and therapeutic uses of various medications are discussed in order to help with therapy options for advanced bladder cancer control malignancy ranks high in the most common cancers globally.

Background on Skin Cancer and the Hedgehog Pathway

Although basal cell carcinoma (BCC) is often relatively mild, it may become aggressive when it has spread or is no longer operable. In such cases, disease management relies on targeted therapies and systemic treatments.



Source: Research gate, 2018

Hedgehog is a pathway involved in controlling development, particularly in terms of cell growth and differentiation in the embryo. Dysregulation of this pathway on the molecular level is associated with numerous cancers in adults and can lead to BCC. namely, cancer and uncontrolled pathway activation are caused by genetic alterations in the Hedgehog pathway, namely in the Patched-1 gene. (PTCH1) gene being notable. Potent SMO inhibitors (Sonidegib and Vismodegib), once administered, prevent further downstream signaling and tumor growth.

Prevalence and Types of Skin Cancer

One particular area of concern for dermatologists is advanced skin cancer — particularly ever-growing skin cancer types, like BCC. Although most basal cell carcinomas (BCC) can be managed locally, the rate of advanced or metastatic BCC is increasing as detection of BCCs improves.

Hedgehog Signalling Pathway

Controlling cell growth and transformation is a key function of the Hedgehog pathway. Pathogenesis of malignancies, including BCC, is often linked to dysregulation of this system [4]. For the treatment of advanced skin cancer, two Hedgehog pathway inhibitors, Vismodegib and Sonidegib, have recently received approval.

Mechanism of Action of Sonidegib and Vismodegib [5-6]

- Vismodegib (Erivedge)

The Hedgehog pathway inhibitor Vismodegib disrupts Smoothed receptor (SMO) function to suppress downstream GLI transcription factor activation and tumor growth. For the treatment of advanced BCC, the FDA authorized Vismodegib in 2012.

- Sonidegib (Odomzo®)

The inhibitor Sonidegib blocks the Hedgehog pathway similarly to Vismodegib but features distinct chemical properties and drug absorption characteristics. FDA authorized Sonidegib's use for advanced BCC treatment in 2015.

Efficacy in the Treatment of Advanced Skin Cancer

- Clinical Trials of Vismodegib

The effectiveness of Vismodegib in reducing tumor size was established in the ERIVANCE BCC study, which was conducted on patients with advanced BCC. The overall response rate reached forty-three percent while progression-free survival achieved 9.5 months [7].

- Clinical Trials of Sonidegib

This jibes with what we saw in the BOLT study, where patients with advanced BCC who took Sonidegib had a 22.1-month progression-free survival rate and an overall response rate of 56% [8]. For some advanced BCC patients, studies show Sonidegib achieves long term therapeutic outcomes beyond Vismodegib capabilities.

- Comparative Efficacy

Studies evaluating use of both medications together show that effectiveness for tumor reduction is equal. Between vismodegib and sonidegib, we see varying results with sonidegib generally achieving longer sustained responses and better progression free survival. Importantly, for patients who cannot have surgery due to the location of their tumor or other health concerns, these therapeutic medicines provide a beneficial alternative to surgery [9].

Tolerability and Safety Profile [10-11]

- Adverse Effects of Vismodegib



Sonidegib, like Vismodegib, produces dysgeusia with muscle spasms and alopecia. Although limited clinical data exist, Sonidegib appears to have a superior tolerability profile of muscle spasms relative to Vismodegib.

- Adverse Effects of Sonidegib

Like Vismodegib, Sonidegib causes dysgeusia, alopecia, and muscle spasms. On this parameter, Sonidegib has a potentially better overall tolerability profile, as muscle spasms are less frequent with Sonidegib than Vismodegib.

Comparative Safety

While sonidegib has side effects similar to those of Vismodegib, it has different rates of occurrence and impact. Sonidegib is preferred in patients with muscle related side effects due to its lower risk of muscle spasm and better gastrointestinal tolerability than Vismodegib^[12].

Clinical Application and Patient Selection [13,14,15,16]

- Choosing Between Sonidegib and Vismodegib

Treatments are chosen by clinicians based on a holistic assessment involving assessment of tumor size, comorbidities, and selection of a side effect tolerance level. However, patients with a history of muscle spasm typically respond well to Sonidegib, Patients with advanced basal cell carcinoma (BCC) in localized parts of the body have shown improved responses to Vismodegib.

- Long-Term Management

These drugs will exhibit teratogenic properties, which will necessitate comprehensive monitoring, as well as potential side effects and tumour responses, throughout their extended therapeutic period. Supportive care interventions, such as

muscle relaxants, can improve patient quality of life and treatment compliance.

Mechanism of Action and Clinical Efficacy:

Vismodegib and sonidegib both directly inhibit this critical Hedgehog signalling pathway, which is foundational to cellular growth and differentiation. Abnormal pathway activation is characteristic of BCC tumor development and progression. Blocking Smoothed (SMO) protein function during Hedgehog signal transduction inhibits tumour growth (Basset, 2015).

Vismodegib:

The FDA originally authorized vismodegib, an inhibitor of the Hedgehog pathway, for the treatment of laBCC and mBCC. The landmark ERIVANCE BCC trial established its efficacy for advanced BCC, showing a DCR and ORR of 68% and 30% respectively. For patients lacking many other therapeutic alternatives, this rendered vismodegib a therapeutic option worth considering.

Sonidegib:

Sonidegib, another SMO inhibitor, was given due to the BOLT trial. This trial reported an ORR of 56% and a DCR of 94% in patients with laBCC. Although the ORR appeared to be higher than that of Vismodegib, direct comparisons between trials are difficult because of differences in patient populations and study designs. Yet sonidegib demonstrates a strong therapeutic activity in laBCC, with the results of the BOLT trial suggesting it may be an excellent treatment option.

Comparative Efficacy Considerations^[17,18]:

While the drugs share many similarities in their science, there are some distinct differences in the findings when these drugs are compared together. Short action times and strong therapeutic effects



could make sonidegib attractive to patients who need stronger, quicker treatment responses. Treatment selection should be informed by disease severity assessment and the individual patient characteristics.

Duration of Response: Both drugs can produce long-lasting effects can be produced by both medications, but resistance can develop over time. It is important to monitor the course of the illness and consider alternative treatments.

Subgroup Analysis: Clinical trial subgroup analyses of both drugs to determine their efficacy in specific patients, such as those who have had prior radiotherapy, or specific genetic mutations. However, these analyses can provide a foundation for treatment optimisation and perhaps patient selection.

Long-Term Outcomes: These studies need sustained follow up for establishing the impact of these medications in terms of overall survival and durability of response.

Tolerability and Adverse Events:

Their quality of life is significantly affected by the many side effects linked to hedgehog pathway inhibitor drugs. For patients making choices in this area, knowing the tolerability profiles of Vismodegib and Sonidegib is just as crucial ^[19].

Common Adverse Events ^[20]:

Similar adverse event profiles are shared by both medications, such as:

- Myalgia (muscle cramps and spasms)
- Alopecia (hair loss)
- Dysgeusia, or disturbance of taste
- Weariness
- Experiencing nausea and vomiting
- Loss of appetite and weight

Differences in Tolerability ^[21-22]:

Adverse events, however similar in spectrum, can differ in frequency and severity.

Muscle Spasms and Cramps: Some of the most common and annoying side effects. Research has shown that Vismodegib can cause more serious and frequent muscle spasms and also force patients to increase the dose (Trémolières, 2018) or stop therapy altogether.

Other Adverse Events: Reportedly, Vismodegib can cause more alopecia than Sonidegib, while Sonidegib can incur a marginally increased risk of some GI side effects like nausea and vomiting. But these negative effects are more or less the same for both drugs (Gupta, 2018).

Management of Adverse Events: Adverse events should be managed proactively. This includes patient education, dose modifications, supportive care.

Key Tolerability Considerations ^[23-24]:

- An unfavourable incident may have a significant impact on the quality of life of patients. These need management that is proactive and ongoing evaluation.
- Tolerability: The key to treatment adherence is tolerability. According to Skidmore (2017), patients that suffer from adverse occasions can often cause cessation for care.
- Physiological Variation: Every human being has a unique tolerance level. Age, co-morbidities, and concurrent medications can affect the frequency and severity of adverse events.

Clinical Decision-Making:

Clinicians also need to consider individual patient features, degree of disease severity and tolerability



issues in choosing between Sonidegib and Vismodegib.

- **Patient Preferences:** Consider the patient's preferences for tolerability and treatment goals when making decisions.
- **Cost and Access:** The cost and availability of these medications may also affect treatment decisions.
- **Monitoring and Follow-Up:** Routine monitoring for adverse events and disease progression is required in both medications ^[25].

Sonidegib and vismodegib treat advanced BCC. Although both medications target the same pathway and have similar adverse event profiles, they differ in tolerability and efficacy ^[26]. More research and collection of practical data are necessary to better understand their relative efficacy. The specifics of each medication and each patient's circumstances can help clinicians design treatment plans to improve treatment outcomes and patients' quality of life with advanced skin cancer ^[27].

CONCLUSION

In the absence of surgical options for patients with advanced BCC, sonidegib and vismodegib offer systemic therapy. Although their efficacy in reducing tumors is similar, sonidegib also may be superior regarding tolerability and prolonged progression-free survival. Both drugs, however, require careful consideration of patient factors and side effects. Prospective studies must seek to refine the safety profile of these agents, as well as combination therapies with other agents to improve upon efficacy ^[28].

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CONFLICT OF INTEREST

The authors claim no conflict of interest

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