Lack of Response to Vismodegib in a Patient with Advanced Basal Cell Carcinoma: A Case Report

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Abstract

Purpose: Basal cell carcinoma (BCC), the most common type of skin cancer in humans, rarely progresses to locally advanced or metastatic BCC. The size, extent, and location of the lesion should be carefully considered when selecting a treatment option for patients with BCC.

Methods: Moreover, clinicians should review the potential for significant deformity and anticipated morbidity, when considering radiation therapy and surgery for treatment.

Vismodegib, the first approved oral therapy for advanced BCC, is a treatment option that clinicians might consider for patients with BCC lesions that exhibit the clinical characteristics as described above.

Results: In this manuscript, we reviewed the mechanism of action, clinical efficacy, and safety of vismodegib and consider the possible causes for a lack of response to the drug.

Conclusion: The therapeutic response to these tumors may be limited by the challenge of acquired resistance against smoothened antagonists.

Keywords

Basal cell carcinoma (BCC); High-risk BCC; Locally advanced BCC; Metastatic BCC; Hedgehog pathway inhibitors

Background

Basal cell carcinoma (BCC) of the skin is the most frequently occurring form of all cancers; more than one out of every three new cancer cases is a skin cancer case, and the vast majority are BCCs. Moreover, the annual incidence of BCC continues to increase worldwide. Most cases are treated and resolved with local therapies, cryotherapy, and surgery [1]. Locally advanced BCC is rare, and it cannot be controlled with surgery or radiation therapy, after which, metastatic BCC may occur and may be associated with significant morbidity and mortality.

These tumours are often disfiguring. Moreover, the high incidence of BCC affects the quality of life of patients owing to pain or bleeding. However, recent developments after 20 years of exhaustive study may eliminate the need for excessively disfiguring or morbid surgery; these developments resulted in the use of vismodegib, on the basis of the discovery of the hedgehog (Hh) signalling pathway and its role in the pathogenesis of BCCs [2]. Unfortunately, the emergence of resistance mutations (SMO mutations) against drugs is a key factor limiting the effectiveness and clinical efficacy of inhibitors used during Monotherapy.

Case Description

A 76-year-old woman presented with a large, 8 × 14 cm ulcerated lesion in the retro-auricular zone, with an extension to the right parieto-occipital region (Figure 1A). The lesion had progressed over a period of 7 years with invasion of the bones and cerebellum. Treatment of this lesion with surgery and radiotherapy failed to eradicate the cancer. Skin findings showed BCC with keratosis differentiation. Biopsy of the right parieto-occipital bone has confirmed the infiltration of bone tissue by basal cell carcinoma and acute osteomyelitis with gram-positive bacterial colonies. Immunohistochemistry analysis confirmed negative expression of CD56 and Cd117 (C-Kitt). The patient had no previous history of family-related skin cancer, and did not have other suspicious lesions during clinical examination. Total body computed tomography scans and positron emission tomography imaging revealed involvement of the underlying bones and cerebellum but showed no signs of metastasis. The findings from magnetic resonance imaging suggested extensive tumor involvement in the cells of the subcutaneous tissue from the right temporal area to the deep right sub-occipital area and neck, with involvement of the skull base, right portion of C1, and extension to the right epidural area at the C1 level of spinal canal, and lack of marrow involvement. Complete staging included the thorax and the abdomen and there was no documented metastatic disease from BCC. The patient treatment was started with vismodegib on 15 September 2015, and a standard dose of 150 mg/day was administered orally. It was the only medication prescribed to the patient at the time and she was evaluated for the effect of treatment, 4 to 16 weeks after the initiation of treatment. Minimal improvement was observed with a small decrease in tumor size, signs of healing in the periphery (Figures 1B and 1C), and minimal side effects including constipation and fatigue. Six months after the initiation of treatment, the patient experienced a significant progression of the lesions. In addition, she developed a unilateral facial paralysis (Figure 1D). Presently, vismodegib treatment has been discontinued and the patient has only been receiving palliative treatment.

Discussion

Most BCCs are treated with surgery alone. However, a small group of patients present with locally advanced or metastatic BCC and they have very few treatment options. Overall survival estimates for patients with metastatic disease are poor ranging from 8 months to 3.6 years.

In advanced BCC, the hedgehog-signalling pathway is upregulated, leading to basal cell proliferation [3]. This pathway is necessary in the development of embryonic cells and it is a requisite in the maintenance of homeostasis in adult stem cells. Aberrant activation leads to the propagation of a number of signals and the modification of secreted ligands, resulting in the activation of smoothened (SMO),...
which normally acts as an inhibitor of downstream glycoproteins. Persistent stimulation of these proteins results in the up regulation of target genes important for cell differentiation and survival [4,5].

Vismodegib is a targeted inhibitor of SMO, which decreases the activity of the hedgehog-signalling pathway and subsequently reduces basal cell proliferation [2]. A durable reduction in the size of unresectable, metastatic, and potentially disfiguring or invasive BCC has been a direct clinical benefit of treatment with vismodegib. The identification of immunohistochemistry markers associated with different drug responses (complete, stable, partial response, or lack of response with progression of the disease) is required. For example, the association between CD56 expression and the lack of response to vismodegib might be explained by the cross-talk between the hedgehog and CD56 signalling pathways [6,7].

The hedgehog-signalling pathway has several potential points of cross-talk with intracellular pathways including the RAS/RAF/mitogen-activated protein kinase (MEK)/extracellular signal-regulated kinase (ERK), phosphoinositide 3-kinase (PI3K)/AKT/mTOR, and epidermal growth factor receptor (EGFR) pathways [3]. These three signalling pathways have been reported to be downstream for the CD56 activation pathway. These points of cross-talk may lead to the activation of the hedgehog-signalling pathway despite SMO inhibition in advanced BCC, with stronger expression and activity of CD56 resulting in a decreased response to vismodegib treatment [7].

In the present case, both CD56 and Cd117 (C-Kitt) showed negative expression.

Presently, we know that the aberrant activation of hedgehog-signaling pathway is involved in multiple aspects of transformation including the persistence of the cancer stem cell phenotype. However, till date, hedgehog-signalling inhibitors, mainly those targeting SMO (such as vismodegib, BMS-833923), have shown good efficacy as Monotherapy in patients with advanced BCC. This lack of response could be attributed to many factors that primarily include a lack of patient stratification in early trials and cross-talk between hedgehog-signalling and SMO [8].

Moreover, there are other pathways about oncogenic signalling that can modulate therapeutic response and the knowledge of hedgehog pathway activation mechanisms in cancer stem cells from most tumour subtypes of BCC is limited [9-11]. It is wise to note that tumour recurrence was reported in most cases after the cessation of treatment. Many side effects have been reported; however, in our patient the side effects were minimal [12].

In conclusion, the population of patients who develop resistance to treatment with an SMO inhibitor is likely to increase as more patients with BCCs are treated with SMO inhibitors. This can explain the poor response of our patient treated with vismodegib. Given the advanced state of disease in many patients, timely initiation of other treatments besides trials of different SMO inhibitors can be critical.

Finally, we consider the present case important for publication as similar cases, albeit few have been reported in the journals until now.

**Conflict of Interest Statement**

The authors declare that they have no competing interests.

**Ethics**

This manuscript followed the procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000.

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**Figure 1:** The lesion (A) at the beginning of treatment; (B) after 4 weeks of treatment; (C) after 4 months of treatment; and (D) after 6 months of treatment (unresponsive).
References


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