Hedgehog Inhibitors are Effective Treatment for Basal Cell Cancer Recurrence

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Case Report

ABSTRACT

The hedgehog signaling pathway is one of the major regulators of cell growth and differentiation during embryogenesis. Mutation of some component of hedgehog pathway is common in cancers, especially in basal cell carcinoma (BCC) and Medulloblastoma. Hedgehog inhibitors have recently emerged as a novel treatment for BCC with specific indications and overall clinical benefit. BCC is one of the most common cancers in the United States, comprising approximately 80% of non-melanoma skin cancers. We present a case of an 88 year old female diagnosed with advanced extensive recurrent BCC of scalp whose lesions improved significantly after treatment with Vismodegib despite years of prior neglect.

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INTRODUCTION

The Hedgehog pathway plays an essential role in cell growth and differentiation in the developing embryo. Although it is typically silenced in postembryonic life and adult tissues, it may be activated to stimulate tissue repair or cell proliferation. Abnormal activation may lead to cancer, including basal cell carcinoma (BCC). Hedgehog pathway inhibitors target the Hedgehog signaling pathway, blocking the activities of the Hedgehog-ligand cell surface receptors. Hedgehog pathway inhibitors may be used to treat basal cell carcinoma that has spread to other parts of the body [1].

BCC is one of the most common cancers in the United States, comprising approximately 80% of non-melanoma skin cancers. It is seen mostly in fair skinned population. The mainstay treatment for localized BCC is surgery, but the options for metastatic, recurrent or advanced disease is limited. Hedgehog inhibitors have emerged recently as a novel treatment for these entities and appear to have high response rates, durable responses and potentially progression free survival benefits- all good measures of overall clinical benefit. Two medication currently in use from this group are: Vismodegib and Sonidegib.

CASE PRESENTATION

Our patient is an 88 year old female with hypertension who was diagnosed with localized basal cell carcinoma of the scalp on biopsy some 10 years ago. She was successfully treated with surgical excision and skin grafting at that time and was disease free for several years. Seven years later she started to have ulcerated skin lesions on scalp that was treated as an infection with antibiotics. She was non-compliant and was lost to follow up repeatedly. Ten years after the surgery, the patient returned to our clinic with progressive, recurrent, biopsy proven BCC in the same area of scalp (Figure 1).

![Image](image_url)

*Figure 1: Lesion before treatment*

She was somewhat confused and slow to comprehend, but with no gross neurologic deficits. Calvaria had disappeared over a large area of parietal and occipital regions and brain tissue was palpable in the same oval area (10 by 7 cm) under the skin lesion. There was no lymphadenopathy or hepatosplenomegaly.
She was anemic with hemoglobin of 11 mg/dl. Magnetic resonance imaging of brain showed intact brain parenchyma but destruction of Calvaria in the parietal and occipital areas. Computed tomography of abdomen and pelvis showed no signs of distant metastases.

Since she was not a candidate for surgical treatment, we started her on Vismodegib. Patients ulcerated beefy lesions significantly improved after 4 months of treatment (Figure 2).

![Figure 2: Lesion after treatment](image)

She did develop shortness of breath and was found to have pulmonary emboli with multiple clots about 2 months post treatment. Anticoagulation was successful and symptoms resolved. Her BCC has continued to improve on Vismodegib.

**DISCUSSION**

The hedgehog pathway is critical in embryogenesis and is always activated. It is significantly less present and less commonly activated in adults. It is believed to play a role in regulating adult stem cell function, especially maintenance and regeneration of adult tissue.

The hedgehog signaling pathway can cause basal cell proliferation and tumor growth. Signaling in this pathway is initiated by the cell surface receptor smoothened homolog (SMO). In adults, this pathway normally is inhibited by another cell surface receptor, the patched homolog 1 (PTCH1). Binding of the hedgehog ligand to PTCH1 prevents its degradation and increases its effect. (Figure 3)
In mammals, there are three hedgehog genes: Sonic, Indian, and Desert Hedgehog. These genes code for a secreted protein, or ligand, the best studied of which is Sonic. Normally, the Sonic hedgehog ligand is not present and therefore not active. In the resting state, patched homolog (PTCH) receptor prevents activation of the hedgehog pathway by inhibiting Smoothened (SMO). When Sonic (the ligand) is present, it binds to the PTCH receptor on the cell surface and causes the PTCH receptor to move into the cell and be degraded. When PTCH is degraded, SMO moves from the inside of the cell to the cell surface. This releases control on SMO and activates the hedgehog signaling pathway which in return causes transcription of target genes responsible for cell proliferation, differentiation, and tissue maintenance [2].

Two mechanisms have been identified by which the hedgehog pathway may be involved in the pathogenesis of basal cell carcinoma. Mutations of PTCH1 may prevent inhibition of SMO activation of the hedgehog pathway, or mutations of SMO may result in constitutive activation of the pathway.

Vismodegib (150 mg as a single oral daily dose) is a small-molecule inhibitor of SMO, which thus blocks activation of the hedgehog pathway. The approval of vismodegib on January 30, 2012, represents the first Hedgehog signaling pathway targeting agent to gain FDA approval. Sonidegib belongs to a class of biphenyl carboxamides and was discovered as an SMO antagonist using a high-throughput screen in vitro. In 2015 FDA has approved it in the 200 mg capsule form [3].
Both drugs are approved for use in locally advanced BCC, with vismodegib also approved for metastatic BCC. The most extensive data on the safety and efficacy of vismodegib in basal cell carcinoma comes from a pre-planned interim (STEVIE) analysis of an international, open-label trial. The objective response rate in those with locally advanced disease was 67 percent; 34 percent complete and 33 percent partial. In those with metastatic disease, the objective response rate was 38 percent; 7 percent complete, 31 percent partial. The median progression-free survival for the entire study population was 20 months; 24.5 months in those with locally advanced disease and 13.1 months in those with metastatic disease [4].

Treatment side effects include muscle cramps, weight loss, fatigue, loss of appetite and may be associated with the development of cutaneous squamous cell carcinoma. Challenges regarding vismodegib use include the recurrence of BCC after drug discontinuation and the development of acquired resistance. Resistance to hedgehog inhibitors has been attributed to mutations in SMO or activation of the RAS/MAPK (mitogen-activated protein kinase) pathway. New research into dual inhibition aims to overcome this resistance and provide a more lasting response [5].

Vismodegib can cause embryo fetal death or severe birth defects when administered to a pregnant woman and therefore is a category D medicine. It is embryotoxic, fetotoxic and teratogenic in animals. Teratogenic effects included severe midline defects, missing digits and other irreversible malformations.

Our patient is a unique one. She ignored her lesions for years and acquired a destructive extensive form that is hard to come by in this day and age. Regardless, the treatment with hedgehog inhibitors was helpful and effective. Pulmonary emboli happened after treatment, but we cannot be sure if it was a side effect of medication or a natural happening in an elderly cancer patient with sedentary life style. If there are more reports of pulmonary emboli, this should be evaluated further.

CONCLUSION

For patients with locally advanced recurring basal cell carcinoma that is not amenable to treatment with surgery; treatment with an inhibitor of the hedgehog signaling pathway is beneficial.

DECLARATION OF CONFLICTING INTEREST

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