Vismodegib: A smoothened inhibitor for the treatment of advanced basal cell carcinoma

Suruchi Aditya, Aditya Rattan[1]

Department of Pharmacology, Dr. Harvansh Singh Judge Institute of Dental Sciences, Chandigarh, [1]Department of cardiology, Heartline, SCO-58, Panchkula, Haryana, India

ABSTRACT

Incidence of basal cell carcinoma (BCC), the most common skin cancer in humans, is rising. Surgery is the mainstay of treatment but there is no standard of care for locally advanced or metastatic disease. Hedgehog signaling proteins are critical for cell growth and differentiation during embryogenesis; Hh pathway is silenced in adults. Dysregulated or aberrant Hh signaling has been implicated in the pathogenesis of BCC. This hyperactive pathway can be inhibited by use of smoothened inhibitors such as vismodegib. Food and drug administration approved this oral, once-daily medication in 2012 to treat adults with metastatic BCC or locally advanced, recurrent BCC after surgery and also for patients with locally advanced BCC who are not candidates for surgery or radiation treatment. Clinical studies have shown it to be highly efficacious and the most common adverse effects include, muscle spasms, alopecia and dysgeusia. Use of targeted biologic modifiers, exemplified by Hh directed therapeutics offer a new hope to patients with high-surgical morbidity or inoperable tumors.

Key words: Basal cell carcinoma, hedgehog signaling pathways, vismodegib

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Address for correspondence:
Dr. Suruchi Aditya, Department of Pharmacology, Dr. Harvansh Singh Judge Institute of Dental Sciences, Sector 25, Chandigarh, India.
E-mail: suruchiaditya@rediffmail.com

INTRODUCTION

Basal cell carcinoma (BCC) is the most common cutaneous tumor accounting for approximately, 70% of all malignant diseases of the skin. The incidence has increased dramatically over the years, and the number of women under 40 years diagnosed with BCC has more than doubled in the last 30 years. Compared to Caucasians, incidence in Asians is low.[1,2] Once metastasized, BCC is highly malignant and associated with poor prognosis.

Risk-factors for development of metastatic basal cell carcinoma (mBCC) include, age, male sex, skin photo-type (I, II), frequent sun exposure and sunburn, severe actinic damage, history of radiotherapy, number of tumors already present, tumor size >1 cm, truncal tumor, family history of skin tumors, low DNA repair capacity, glutathione S-transferase and cytochrome P450 polymorphism, tumor necrosis factor microsatellite polymorphism and Patched (*Ptch*) gene polymorphism.[3]

Choice of treatment is based on the type, size, location, and depth of penetration of the tumor, age and general health of the patient, and the likely cosmetic outcome of specific treatments. Most cases are treated with surgery. Patients with locally advanced basal cell carcinoma (laBCC) (inoperable or unresectable lesions, where surgery may result in substantial morbidity and/or deformity or presence of contraindication to surgery) currently have limited non-surgical treatment options available. Therefore, there is need for new and non-disfiguring treatments.

HISTORY

Cyclopamine, a steroidal alkaloid, extracted from the corn lily, was found to be an inhibitor of the hedgehog (Hh) pathway. Attention was drawn to this plant after it was noticed that sheep that fed on the flowers while they were pregnant gave birth to deformed offspring, with only one eye and brain malformations.

Vismodegib (GDC-0449) was discovered by high-throughput screening of a library of small-molecule compounds and subsequent optimization through medicinal chemistry. Chemically, vismodegib is 2-chloro-N-(4-chloro-3-(pyridin-2-yl) phenyl)-4-(methylsulfonyl) benzamide. The molecular formula is $C_{19}H_{14}Cl_2N_2O_3S$. The molecular weight is 421.30 g/mol [Figure 1].

MECHANISM OF ACTION

What is Hh signaling pathway?

The Hh signaling pathway is a key regulator of cell proliferation, differentiation, apoptosis and self-renewal in the developing embryo. Post-developmentally, Hh signaling pathway is inactive in all the normal cells, with the exception of hair, skin and stem cells.[4]

Three short acting polypeptide Hh ligand homologues that are secreted signaling proteins are: Sonic Hedgehogs (SHh), Indian Hh and Desert Hh. In the active state, the signaling pathway is initiated by binding of SHh to its receptor, *Ptch* – a 12-transmembrane receptor, which diminishes inhibitory effect of *Ptch* on smoothened (*Smo*), another 7-transmembrane protein, which is then localized into primary cilium. There, *Smo* activates an intracellular cascade that results in activation and nuclear translocation of *Gli* family transcription factors (*Gli* 1-3), *sufu* (suppressor of fused, a tumor suppressor gene), *Hhip, Ptch*1, and so on. They induce transcription of SHh target genes like *Gli* 1, (a reliable marker of SHh signaling activating genes) that promote cellular proliferation, cellular survival, stemness and cell fate determination in a variety of organs, involving the activation of cyclins and cyclin-dependent kinases.[2] In the absence of Hh ligand, *Ptch* exerts inhibitory effect on signal transducer *Smo* and no downstream signaling occurs. *Gli* 2 is phosphorylated and cleaved into a truncated peptide that represses the transcription of SHh target genes.

Mutations in *Ptch* that result in continuous *Smo* activation are the most common alterations found in BCC, followed by mutations in p53 and Cyclin-dependent kinase inhibitor 2A (CDKN2A).[5]

Vismodegib is a selective Hh pathway inhibitor that blocks Hh signaling by binding to *Smo* and inhibiting activation of downstream Hh target genes [Figure 2].

PHARMACOKINETICS

Oral bioavailability of vismodegib is 31.8%. The volume of distribution ranges from 16.4 L to 26.6 L; plasma protein binding is very high (>99%). Vismodegib binds to both albumin and alpha-1-acid glycoprotein (AAG) and binding to AAG is saturable. Metabolic pathways of vismodegib in humans include oxidation, glucuronidation, and pyridine ring cleavage. Vismodegib and its metabolites are eliminated primarily by the hepatic route. The elimination half-life (t½) of vismodegib is 4 days after continuous once-daily dosing.

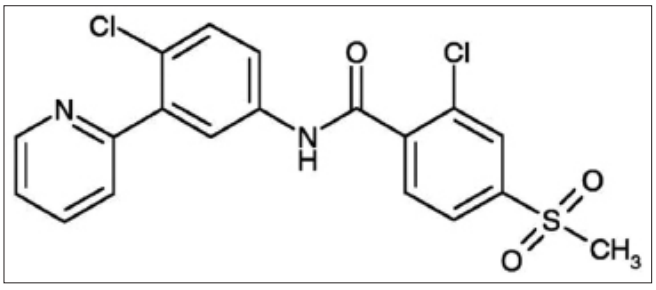

Figure 1: Molecular structure of vismodegib

CLINICAL EXPERIENCE WITH VISMODEGIB

In the phase I study involving 33 patients with laBCC or mBCC, there were two complete responders (objective response with no residual BCC on sampling tumor biopsy), and 16 partial responders (a 50% reduction in palpable or visible tumor). The overall response rate (ORR) among the 18 patients with mBCC was 50% (95% confidence interval [CI], 29-71) and in patients with laBCC was 60% (95% CI, 33-83).[6] The most common adverse events included fatigue, weight loss, muscle spasms, hyponatremia and dysgeusia with only one patient being withdrawn from study due to adverse events.

The phase II ERIVANCE BCC (Efficacy and safety of the Hh pathway inhibitor vismodegib in patients with advanced BCC) study evaluated vismodegib in 104 patients considered unsuitable for surgery. 43% patients with laBCC (95% CI: 31-56; $P < 0.001$) experienced substantial shrinkage of tumors or healed visible lesions whereas 30% (95% CI: 16-48; $P = 0.001$) experienced mBCC tumor shrinkage; the ORR for laBCC and mBCC was 60% and 46% respectively. The median duration of progression free survival was 9.5 months.[7]

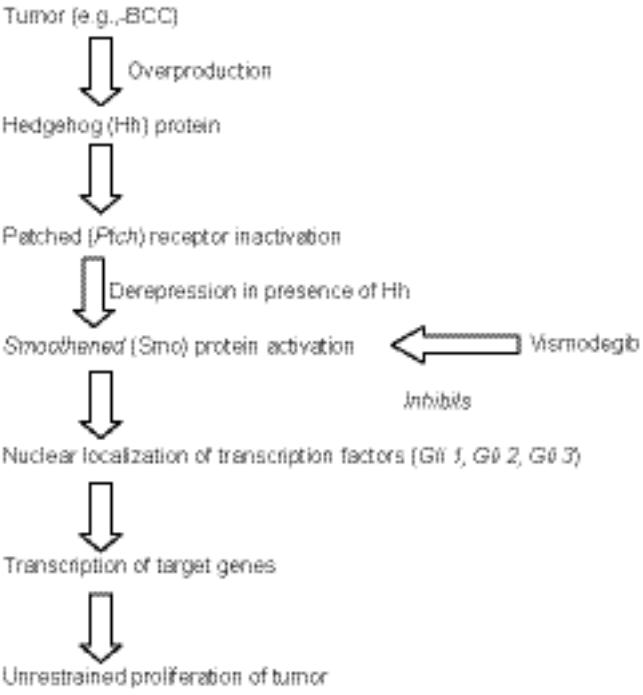

Figure 2: Site and mechanism of action of vismodegib. Binding of vismodegib to smoothened inhibits downstream signaling, preventing proliferation of tumor cells

In another phase II randomized placebo-controlled trial involving 41 basal cell nevus syndrome patients, 24 patients developed 0.07 new BCCs per month in vismodegib group versus 1.74 BCCs per month in the placebo group ($P < 0.001$). Additionally, existing BCCs decreased by 24 cm in the vismodegib group compared to 3 cm in the control group ($P = 0.006$).[8]

INDICATION

Vismodegib, 150 mg once daily, is a novel oral S*mo* antagonist, approved by Food and drug administration (FDA) in 2012, for the treatment of adults with mBCC or laBCC that has recurred following surgery or patients unsuitable for surgery or radiation. It represents a breakthrough in the management of advanced BCC, especially, for patients 'with high surgical morbidity and inoperable tumors.

The median duration of treatment in trials has been 10.2 months (range: 0.7-18.7 months). The drug is continued until disease progression or unacceptable toxicity.

Vismodegib may be highly useful in the neoadjuvant treatment of advanced BCC, for example with patients taking it for 3 months or so to shrink their tumor and then undergoing surgery (medical debulking). Prior to adopting this approach, however, it will be important to rigorously assess whether any potential tumor cells remain in clinically regressed regions, as there could be an increased risk of recurrence if surgical excision leaves some of these cells behind.

Currently, the drug has limited distribution and is available only through contracted specialty pharmacies and it is unavailable in India.

ADVERSE EFFECTS, PRECAUTIONS AND CONTRAINDICATIONS

The most common adverse events observed in clinical trials have been muscle spasms, hair loss, dysgeusia, weight loss, fatigue, nausea, decreased appetite, and diarrhea.

As it is a substrate of the efflux transporter P-glycoprotein (P-gp), co-administration with drugs that inhibit P-gp (e.g., clarithromycin, erythromycin, and azithromycin) can increase its systemic exposure. Malformations, pilomatricoma, toxicities in bone, and growing incisor teeth were observed in pre-clinical studies in rats. Skeletal growth complications may limit its use in children. Blood donations should be avoided for 7 months after its last dose.

Because of its teratogenicity, vismodegib carries a black box warning about embryo fetal death and severe birth defects and it is a pregnancy category D medication. Female patients of reproductive potential should be instructed to use a highly effective form of contraception (failure rate of less than 1%) while taking vismodegib and for at least 7 months after the last dose of vismodegib. Male patients should be instructed to use condoms with spermicide, for at least 2 months after the last dose of vismodegib.

THE PROBLEM OF RESISTANCE

Mutations leading to development of resistance to drugs that target *Smo* can diminish their effectiveness. After an initial dramatic response to therapy in a patient, resistant disease emerged after 3 months with relapse at multiple sites. Tumor biopsies revealed that this mutation retained *Smo* activity but interfered with vismodegib binding, preventing the drug effect. Whether this mutation arose in the setting of vismodegib therapy or was present subclinically remains to be clarified.[6] Other mechanisms of resistance include amplification of Hh signaling molecules downstream of *Smo* (*Gli* 2), amplification of Hh target genes, and up regulation of signaling pathways which interact with Hh, such as PI3K.[9] Hh inhibitors which act at the level of the *Gli* transcription factors may prove effective in the setting of resistance to a *Smo* inhibitor. In cancers where Hh is not the sole driver of tumor growth, Hh antagonists may need to be combined with other inhibitors (e.g., geftinib). Long-term safety is yet another issue that needs to be ascertained.

FUTURE PERSPECTIVES

Robotnikinin is the first reported inhibitor of SHh protein, which functions to bind to *Ptch* and remove its inhibition on *Smo*, allowing for constitutive cellular signaling. It acts upstream of S*mo.* BMS 833923 and saridegib (IPI-926) are inhibitors of *Smo,* like vismodegib. Gli-antagonists, GANT-58, GANT-61, and JK 184(used for research only) are *Gli* inhibitors that work downstream from *Smo* to inhibit pathway signaling and could provide a method of treatment for patients with different mutations in SHh proteins, including those who develop resistance to *Smo* inhibitors.[4]

Until now, patients of BCC with Gorlin syndrome or ionizing radiation damage had little choice but to undergo multiple surgical procedures. For these patients and for those with BCC tumors that are large, advanced, refractory to treatment, or recurrent, vismodegib represents an important therapeutic advancement. Given the ability of vismodegib to cause impressive tumor shrinkage, it may be highly useful in a neoadjuvant setting for "medical debulking" prior to surgery; a smaller tumor would mean a smaller surgical scar. Hh antagonists cause tumor regression by intrinsic inhibition of Hh pathway, decrease in cancer stem cell population, a paracrine effect on tumor stromal cells and an improvement in therapeutic efficacy of cytotoxic drugs by diminishing the desmoplastic fibrotic stromal responses.

CONCLUSION

Incidence of BCC, the most common human malignancy is increasing. Advanced BCC can be disfiguring or debilitating and can lead to significant morbidity. Mutations that activate Hh intercellular signaling pathway genes have been implicated in the pathogenesis of BCC. Vismodegib is a first-in-class FDA approved Hh antagonist that offers a new hope in the treatment of advanced BCC.

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