

Old drug, New Target: Itraconazole and Basal cell Carcinoma

Mina Zarei¹, Keyvan Nouri¹

¹University of Miami, Miller School of Medicine, Florida, USA

Non-melanoma skin cancers (NMSCs) are the most common type of human cancer, with basal cell carcinomas (BCC) representing the majority of these cancers [1]. The World Health Organization (WHO) estimates 2–3 million cases of NMSC per year [2]; however, NMSCs are not routinely reported to cancer registries and their incidence might be underestimated. One study of NMSC occurrence in the US revealed that in 2006, 3.5 million cases were diagnosed among 2.2 million people [3]. BCC originates from the basal cells of the epidermis and has a multifactorial development. Some of the established risk factors include ultraviolet (UV) radiation, ionizing radiation, arsenic, and immune suppression [1]. The most commonly employed treatment options for BCCs include surgical methods such as Mohs micrographic surgery, surgical excision, electrodesiccation and curettage, cryosurgery, and non-surgical methods such as radiotherapy, topical imiquimod, topical fluorouracil, and photodynamic therapy [1]. However, treatment of BCC is currently challenging in patients who are not eligible for surgery or radiotherapy. Although non-surgical options such as vismodegib are available for these individuals, developing tolerance to this medication and recurrence of the tumor is a matter that needs to be addressed.

Molecular and genetic studies have shown that almost all BCCs contain genetic alterations in the Hedgehog (Hh) signaling pathway. These alterations cause inhibition of patched homologue 1 (PTCH1), and activation of smoothened homologue (SMO), which results in BCC [4]. These genes are the major targets of UV radiation for BCC induction and frequently display characteristic UV-induced mutations.

Vismodegib is a first-in-class, small-molecule systemic inhibitor of the Hh intracellular signaling pathway that binds to SMO and leads to inhibition of an aberrant activation of the Hh pathway. In January 2012, vismodegib was approved by United States Food and Drug Administration (FDA) for the treatment of adult patients with symptomatic metastatic BCC, or locally advanced BCC inappropriate for surgery or radiotherapy [5]. However, some patients

develop resistance to vismodegib. In a retrospective study by Chang *et al.* of treated patients, 21% developed at least 1 tumor regrowth while undergoing continuous vismodegib treatment [6]. The mechanism of this resistance is not clear; however, it is possible that some tumor cells develop mutations in the SMO protein resulting in decreased binding of the drug. Another reason of tumor regrowth could be compensatory amplification of genes downstream from SMO such as Gli in some of the tumor cells [6].

Therefore, there is a need to find a novel treatment as a replacement for vismodegib in the BCC patients who develop resistance. It requires approximately 10 years and \$800 million to develop a new medication that can be approved and used in clinical setting [7]. One potential way to by-pass the time-consuming and costly process of drug development is to repurpose the medications that have been previously approved for an alternate clinical indication.

In 2010, Kim *et al.* from Stanford University screened a library of ~2400 FDA-approved or post-phase I drugs for activity in inhibition of Hh signaling [8]. In this screening, itraconazole was identified as a potent inhibitor of Hh pathway activity. This antifungal is commonly used in clinical practice as an orally delivered systemic treatment that can be sustained for months. They also found that itraconazole was by far the most potent inhibitor of Hh pathway activity among other azoles and its mechanism of action was shown to be clearly distinct from its inhibitory effect on fungal ergosterol synthesis.

Recently, Kim *et al.* continued their effort to evaluate the effect of itraconazole on the Hh pathway and on tumor size in human BCC tumors [9]. In this study, patients were recruited with one 4 mm in diameter BCC tumor into two cohorts to either receive oral itraconazole 200 mg twice per day for one month or 100 mg twice per day for an average of 2.3 months. The primary outcome of this study was change in biomarkers including Ki67 tumor proliferation and Hh pathway activity. Secondary outcome included change in tumor size. Itraconazole reduced cell proliferation by 45%, Hh pathway activity by

Conflict of Interest:
None declared

This article has been peer reviewed.

Article Submitted on: 11th
July 2014

Article Accepted on: 16th
September 2014

Funding Sources: None
declared

Correspondence to: Dr
Mina Zarei

Address: University of
Miami, Miller School of
Medicine, Florida, USA

Email Address:
m.zarei@med.miami.edu

Cite this article: Zarei M.
Old drug, new target:
itraconazole and basal
cell carcinoma. *J Pioneer
Med Sci* 2015; 5(1):21-22

65%, and reduced tumor area by 24%. Based on the results, itraconazole can reduce BCC tumor size via inhibition of the Hh signaling pathway after one month of treatment. However, larger trials with longer duration of itraconazole administration are required to measure the clinical efficacy of itraconazole. In this study, itraconazole treatment was associated with two adverse events (grade 2 fatigue and grade 4 congestive heart failure). Itraconazole does not have the adverse reactions related to Hh pathway inhibition including hair loss, muscle cramps and weight loss which might be related to less Hh inhibition by this medication compared to vismodegib.

Since Kim *et al.* evaluated the effect of 200 mg itraconazole for only one month, it is not possible to directly compare the results of their study with vismodegib. Based on the available evidence, itraconazole seems to have less clinical utility compared to vismodegib as first-line treatment, since itraconazole reduces Hh pathway by 65% after one month in contrast to a 90% reduction by vismodegib [9, 10]. Itraconazole could be effective as second line therapy, because itraconazole acts on SMO at a site distinct from vismodegib [6]. Further studies such as double-blinded randomized controlled trial should be designed to compare itraconazole and vismodegib to each other.

Kim and colleagues have also initiated a trial of combination itraconazole and arsenic trioxide (FDA approved for acute promyelocytic leukemia) in patients with metastatic BCC for whom vismodegib has failed [9]. Further research is needed to obtain drugs targeting downstream components of the Hh pathway (e.g. Gli) or to exploit combinatorial therapies in order to overcome potential drug resistance.

REFERENCES

5. Kwasniak L, Garcia-Zuazaga J. Basal cell carcinoma: evidence-based medicine and review of treatment modalities. *Int J Dermatol* 2011; 50:645–58.
6. World Health Organization (2011) Skin Cancers. How common is skin cancer? Available from URL: <http://www.who.int/uv/faq/skincancer/en/index1.html> (Accessed 14 August 2014)
7. Rogers HW, Weinstock MA, Harris AR, et al. Incidence estimate of nonmelanoma skin cancer in the United States, 2006. *Arch Dermatol* 2010; 146:283-7.
8. Sekulic A, Migden M, Oro A, et al. Efficacy and safety of vismodegib in advanced basal-cell carcinoma. *N Engl J Med* 2012; 366:2171-9.
9. Meiss F, Zeiser R. Vismodegib. *Recent Results Cancer Res* 2014; 201:405-17.
10. Chang AL, Oro AE. Initial assessment of tumor regrowth after vismodegib in advanced basal cell carcinoma. *Arch Dermatol* 2012; 148:1324-5.
1. DiMasi JA, Hansen RW, Grabowski HG. The price of innovation: new estimates of drug development costs. *J Health Econ* 2003; 22:151–85.
2. Kim J, Tang JY, Gong R, et al. Itraconazole, a commonly used antifungal that inhibits Hedgehog pathway activity and cancer growth. *Cancer Cell* 2010; 17:388-99.
3. Kim DJ, Kim J, Spaunhurst K, et al. Open-label, exploratory phase II trial of oral itraconazole for the treatment of basal cell carcinoma. *J Clin Oncol* 2014; 32:745-51.
4. Tang JY, Mackay-Wiggan JM, Aszterbaum M, et al. Inhibiting the hedgehog pathway in patients with the basal-cell nevus syndrome. *N Engl J Med* 2012; 366:2180-8.