Triple Hedgehog Pathway Inhibition for Treatment of Basal Cell Carcinoma

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Potential Significance of Combined Hedgehog inhibition

1. Increase efficacy
2. Shorter time to response, greater patient acceptability
3. Prevent resistance

Background

Locally advanced basal cell carcinomas (laBCCs) are often unamendable to surgery and radiotherapy. Considerations include risk of disfiguration and functional impairment when operating on tumours of extensive size, hazardous locations or with neurovascular invasions and on patients with multiple recurrences, especially in basal cell nevus syndrome (BCNS). Radiotherapy is not readily accessible for all patients, it can be contraindicated due to previous exposures and in patients with conditions that predisposes to skin cancers.

Vismodegib is the first-in-class, oral selective Hedgehog (Hh) pathway inhibitor for the treatment of locally advanced and metastatic BCCs, approved by the Food and Drug Administration (FDA) in 2012. Vismodegib selectively binds to SMO and inactivates the migration of SMO into the primary cilium. [1] Sonidegib is a similar small molecular SMO inhibitor was approved by the FDA in 2015. [2]

Vismodegib monotherapy is limited by intolerable side effects, high cost and resistance.

Vismodegib monotherapy achieves an objective response rate of 43-66.7% in laBCCs with 9.5- 24.5 months of median progression-free survival. [1,3,4] The common side effects include muscle spasms (64%), alopecia (62%), alteration in taste (54%), unintentional weight loss (33%), muscle weakness (28%) anorexia (25%), loss of taste (22%), diarrhoea (17%), nausea (17%) and fatigue (16%). [3] Although non-life-threatening and often temporary, these side effects are poorly tolerated, leading to high drop-out rate of at least 28-36%. [3,4] Vismodegib costs $7 500 USD per month, or $250 USD per capsule. An average 10-month cost of treatment costs $75 000 USD. [5] Furthermore the median duration of response lasts less than two years in laBCCs before resistance occurs. [3] Mutations have occurred at the level of SMO, downstream of SMO and through synergistic non-canonical activation of the Hh pathway. [6,7] Vismodegib-resistant tumours are also resistant to sonidegib, due to the class effect. [2,8] Experiments on novel combined histone deacetylases and Hh pathway inhibitions are underway to overcome SMO mutations in vismodegib-resistant tumours. [7] However, the drug development process is slow.

Novel use of existing drugs provides a timely and economical treatment option with proven safety profile.

Itraconazole, a common azole antifungal agent, was discovered to also inhibit the translocation of Smoothened (SMO) in a mechanism distinct from the existing SMO antagonists. [9,10] The cost of the is less than 2% of vismodegib. After one month of use in vismodegib-naïve patients, itraconazole, resulted in a 45% reduction in tumour activity, measured by glioma-associated oncogene (GLI) messenger RNA expression. [9] This is inferior to vismodegib monotherapy, which is associated with a 90% decrease. [11] The results of the phase II itraconazole study suggest itraconazole use as an adjunct with vismodegib. Its safety was demonstrated by a phase Ib, open-label, parallel pharmacokinetic study, where no drug-drug interaction was associated with 200mg of itraconazole ingested two hours prior to vismodegib. [12]

Imiquimod, independent of its Toll-like receptor 7/8 activities, was shown to inhibit the Hh pathway downstream. This can potentially clear resistant tumour cells downstream of SMO. [13]

Multi-focal inhibition has been shown to work more efficaciously than a single pathway inhibition when treating melanocytic tumor. [14]

We tested this hypothesis of multi-focal inhibition in laBCC.

Presentation

A 71-year-old man with a history of non-melanoma skin cancer presented with a non-healing plaque around his right lower eyelid and medial canthus measuring 3.2x1.8cm. (Figure 1A) The tumor had been present for several years, but recently became symptomatic, causing intermittent irritation of the eye and occasional bleeding.

On examination, the tumor appeared indurated and scar-like, with irregular borders extending to the caruncle and lower lacrimal. A punch biopsy showed basal cell carcinoma (BCC) with an aggressive growth pattern.

Conventional treatments were inappropriate

- Morbidity risk from surgery is particularly high as his contralateral eye was completely without vision.
- Sole caregiver for his wife with severe dementia, making it difficult to attend radiotherapy.
- No radiation oncology facilities nearby

Combined Hedgehog Inhibition

Vismodegib PO 150mg daily
+ Itraconazole PO 100mg daily
2 months into this therapy…
+ Imiquimod 5% cream daily*

* To avoid eye irritation, we waited until the tumor regressed near the eye before introducing imiquimod. Imiquimod was ceased after two week when patient became intolerant to the crusting. (Figure 1B)

Result

- Complete clinical and histological clearance at 4 months. (Figure 1C)
- Side effects: muscle cramps, dysgeusia and mild hair thinning, attributed to vismodegib. No drug-interactions noted.
- No changes on renal and liver functions.

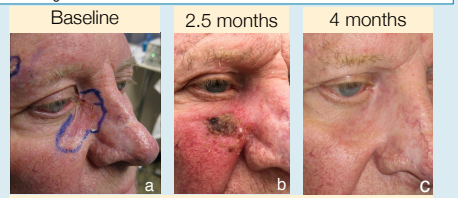

Figure 1: Clinical photo taken at baseline, 2.5 months and 4 months

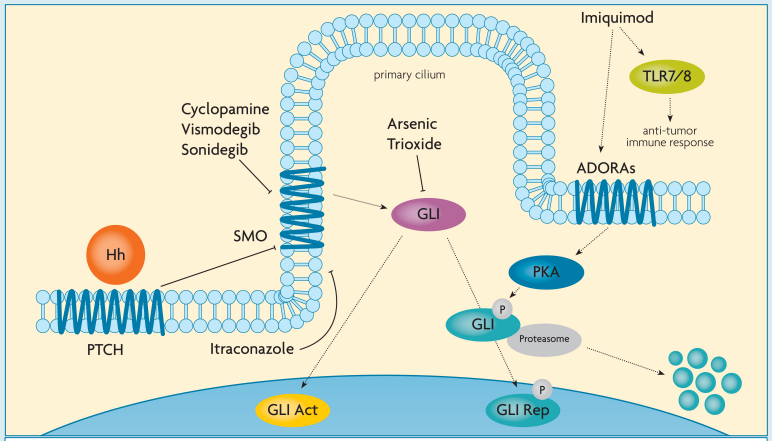

Figure 2: Diagram of a cell showing the Hedgehog (Hh) pathway.

When active during embryogenesis, Smoothened (SMO), a seven-pass transmembrane protein, migrates from the intracellular endosome into the primary cilium, which activates the GLI-mediated transcription of Hh-target genes in the nucleus.

After birth the Hh pathway becomes dormant. Without, Hh ligand stimulation, PATCHED (PTCH1), a 12-pass transmembrane Sonic hedgehog receptor protein, blocks the translocation of SMO into the primary cilium. Without SMO, the GLI factors repress the target gene transcription in the cell nucleus.

Aberrant activation of the Hh signalling pathway is a key driver in the pathogenesis of BCCs. Most BCCs are caused by a loss-of-function mutation of PTCH1 (80-90%), or a gain of function mutation of SMO (~10%).

Both vismodegib and itraconazole inhibit SMO translocation, but through independent pathways.

Imiquimod activates adenosine receptors (ADORA), causing protein kinase A (PKA)-mediated phosphorylation and repression of GLI . As imiquimod acts downstream of SMO, it may be beneficial for mutations at the level or downstream of SMO.

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