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


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

Vismodegib monotherapy achieves an objective response rate of 43-68.7% in iBCCs with 0.5-24.8 months of median progression-free survival. 11,12 The common side effects include muscle spasms (64%), asthenia (62%), alopecia (58%), Pringle’s sign (36%) and proteinuria (26%). 11

Vismodegib resistant tumours are also resistant to sonidegib, due to the class effect. 11,13 Experiments on novel combined histone deacetylase and hedgehog pathway inhibitors are underway to overcome SMO meditated resistance. However, the drug development process is slow.

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

Imiquimod, a common azole antifungal agent, was discovered to also inhibit the transactivation of Smoothened (SMO) in a mechanism distinct from the existing SMO antagonist. 14 The cost of the less than 2% of vismodegib. After one month of use in vismodegib-naive patients, four patients, resulted in a 45% reduction in tumour activity measured by glomerular-association oncogene (GLI) messenger RNA expression. 15 This is inferior to vismodegib monotherapy, which is associated with a 50% decrease. 11 The results of the phase II isctime study suggest Imiquimod 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 250mg of Imiquimod ingested two hours prior to vismodegib. 15

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 down the SMO. 15

Multi-focal inhibition has been shown to work more efficaciously than a single pathway inhibition when treating melanocytic tumor. 14 We hypothesized this multi-focal inhibition in iBCC.

Presentation

A 77-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 3.5x2.8 cm. (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 irritated and scaly like, with irregular borders extending to the canalicule 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.


Result

The result showed that clinical and histological clearance at 4 months. (Figure 1C)

- Side effects: muscle cramps, dysgeusia and mild hair thinning, attributed to Imiquimod. Weight loss, anorexia.
- No changes on renal and liver function.

Figure 1: Clinical photographs 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. 16

After birth the Hh pathway becomes dormant. Without, Hh ligand stimulation, PATCHED (PTCH), a 12-pass transmembrane Sonic hedgehog receptor protein, blocks the translation 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 PTCH (80-90%), or a gain of function mutation of SMO (10%).

Both vismodegib and Imiquimod inhibit SMO translation, but through independent pathways.

Imiquimod activates adenose 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 of downstream of SMO.

Multiple targets: Hh-GLI, EGFR, VEGF, STAT3, JAK2

Figure 3: Graph of effect on SMO by Imiquimod, Sonidegib, and vismodegib. Imiquimod has the effect on SMO by acting on SMO, which is the downstream of Hh pathway.

Figure 4: The effect of Imiquimod on SMO expression in BCC cell line. The expression of SMO is decreased after Imiquimod treatment.

Reference