Hedgehog pathway inhibitors for basal cell carcinoma: case reports and review of the literature

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Summary

Sonic Hedgehog inhibitors (SHHis) are a novel treatment for locally advanced and metastatic BCC's not amenable to, or refractory to surgery or radiotherapy. Use can be limited by significant side effects and recurrence.
Two cases of recurrent, infiltrating and metastatic tumours demonstrating excellent responses to SHHis are presented. Case one is a 43-year old man with recurrent, locally advanced, inoperable facial BCC that shows a complete response to vismodegib. Case two is a 58-year old man with metastatic BCC that demonstrates complete resolution of metastatic disease and improvement of local disease with sonidegib.
Both cases demonstrate dramatic and sustained clinical responses to SHHis. Such medications provide hope for such advanced tumours.

KEY WORDS: advanced basal cell carcinoma; sonidegib; vismodegib; hedgehog inhibitors.

Introduction

Basal Cell Carcinoma is the most common cutaneous malignancy (1) and the incidence is rising worldwide (2, 3). The rate of metastatic BCC (mBCC) is very low, estimated between 0.0028-0.55% with locally advanced BCC (laBCC) at around 0.8% of all BCCs(4-6). Metastases arise more frequently with primary tumours that are large, untreated, or aggressive, or with recurrent tumours (5).

During embryonic development, the Hedgehog (Hh) signaling pathway is essential for cell differentiation and proliferation and tissue patterning, as well as playing a role in the maintenance of certain tissues and stem cells in adults (5). There are 3 mammalian Hh ligands and signaling is activated when one of these ligands binds to the extracellular region of the patched 1 (PTCH1) transmembrane receptor, thereby relieving the inhibition that unbound PTCH1 exerts on the smoothened (SMO) transmembrane receptor (5, 6). SMO can then induce Hh pathway-target gene expression through activation of the glioma-associated oncogene (GLI) transcription factors (5, 6).

BCC was first linked to aberrant Hh pathway signaling when mutations in the PTCH1 gene were identified as the driving mutation in patients with Gorlin syndrome, who often have numerous BCCs (5). Subsequently, most spontaneous BCCs were found to have mutations in components of the Hh pathway that promote aberrant signaling, including inactivating mutations in PTCH1 in 85-90% and activating mutations in SMO in 10% (5). One study carried out genomic profiling with whole exome sequencing of 293 BCCs – this showed a high mutation rate with 85% of tumors harbouring mutations in the Hh pathway (6).

Two oral Sonic Hedgehog inhibitors (SHHis), both SMO inhibitors, have been approved by the US FDA: vismodegib in 2012 (for laBCC and mBCC) and sonidegib in 2015 (for laBCC – also approved for use in mBCC by TGA Australia) (5, 7). Vismodegib was approved by the European Medicines Agency in 2013 for laBCC and mBCC. NICE, however, did not approve use of vismodegib in the UK in 2017 stating 'uncertainty in the evidence and because it is not cost effective' (8). Itraconazole, an older anti-fungal drug, has also been shown to inhibit the same pathway, by a different mechanism (9). The drugs have proven efficacy, with a recent meta-analysis confirming overall response rates of 61.9% for vismodegib and 55.2% for sonidegib, and complete response rates showing that a minority of patients can expect complete cure (7). The most common side effects encountered with both drugs were muscle spasms, dysgeusia and alopecia, which can be expected to occur in most patients (7). These led to 25% of patients discontinuing therapy (7). Other potential side effects include nausea, vomiting, weight loss, myalgia and fatigue (7).

Two cases are presented of recurrent, infiltrating and metastatic BCC demonstrating excellent responses to SHHis.

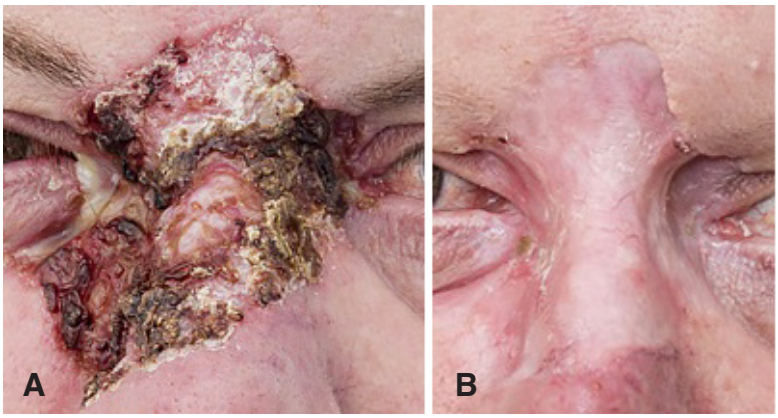

Figure 1A, B - A) Initial presentation. b) Response after 7 months of vismodegib 150mg.

Case one

A 43-year old male smoker had a right medial canthal infiltrative BCC incompletely excised in 1999 and was subsequently lost to follow-up. He re-presented in July 2017 with a two-year history of likely recurrence.
Extensive, infiltrative BCC was noted over the nasal bridge, and involving both medial canthi (Figure 1). CT head and neck demonstrated destruction of the nasal cartilage and demineralisation of nasal bone. MRI of skull base and face demonstrated locally advanced tumour.
Surgical resection would be associated with excessive morbidity, including the loss of one or both eyes, and was therefore contraindicated. Similarly, it was thought that radiotherapy would compromise vision and not be curative as a single modality.
Vismodegib 150 mg daily was commenced in January 2018. Significant regression was noted after 4 weeks, with no side effects reported. After 7 months of vismodegib a complete response was seen (Figure 1B), and treatment discontinued. Mild, tolerable adverse effects including nausea, lethargy, anorexia and abdominal cramps were noted.
After 1 month, a small area of recurrence was noted at the right medial brow and foci at bilateral nasofacial sulci. MRI demonstrated no evidence of recurrence. Vismodegib was recommenced with excision of these small edge recurrences.

Case two

A 58-year old male smoker, with a past history of cirrhosis and peripheral neuropathy, presented with a 5-month history of increasing left sided facial pain and headache, associated with new lumps on the underside of his left mandible. This was on a background of a recurrent nasal BCC requiring extensive surgical resection and adjuvant radiotherapy 5 years prior.
On examination, there was left mandibular tenderness associated with ipsilateral cervical lymphadenopathy. Biopsy of left cheek/masseter revealed infiltrative BCC, with nodal metastases. PET CT confirmed mandibular disease and lung metastases.
Following discussion at the skin cancer MDT, sonidegib 200 mg daily was commenced.
A repeat PET scan, 3 months later, demonstrated resolution of cervical lymphadenopathy and lung metastases, with decreased tumour burden at the left hemimandible (Figure 2). Despite mild side effects initially, including lethargy, muscle cramps and cough,

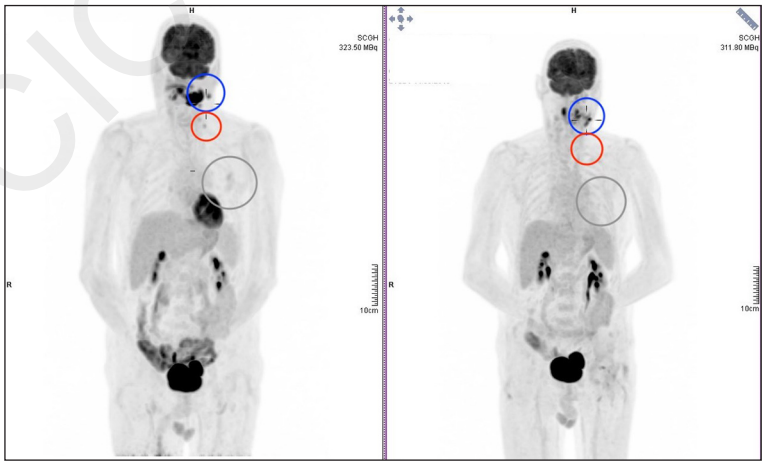

Figure 2 - PET CT demonstrating resolution of lung metastases (grey circle) and cervical lymphadenopathy (red circle), and significant improvement of left hemimandible tumour burden (blue circle) after 3 months of sonidegib.

sonidegib was discontinued after 7 months, secondary to anorexia and significant weight loss. Ongoing PET CT monitoring continues.

Discussion

Historically, laBCC and mBCC have proven difficult to manage, with options limited to surgery or radiotherapy. The introduction of SHHis has greatly improved the therapeutic armory in managing laBCC and mBCC. The two cases highlight clinical situations that, prior SHHis, would have resulted in significantly greater morbidity, if not mortality. Both vismodegib and sonidegib have shown significant clinical improvement in both cases, highlighting efficacy for laBCC (for vismodegib) and mBCC (for sonidegib). Overall survival prior to the introduction of SHHis was 24 months in mBCC (with median survival of 8 months) – this increased to 33.4 months in the ERIVANCE trial (10) with vismodegib.

A recent meta-analysis suggested that vismodegib was statistically superior to sonidegib for mBCC (7). However the most recent update of the BOLT study suggested that sonidegib was similar in both efficacy and survival rate to vismodegib (11). Two year survival for vismodegib and sonidegib were similar in mBCC (62.3% *vs* 69.3% respectively) and for laBCC (85.5% *vs* 93.2% respectively) (10, 11). However, overall response rate for mBCC was lower for sonidegib (10, 11) suggesting that a trial of vismodegib may be beneficial should sonidegib therapy fail. Furthermore, a case report has showed failure of vismodegib treatment for mBCC with brain involvement that improved with a combination of sonidegib and itraconazole (12), highlighting that switching or combining SHHis may merit consideration.

A recent series of 8 cases highlighted similar results (13). These cases were limited by adverse effects and suggested that SHHis are best used for control rather than cure of mBCC (13). Other cases have been presented in the literature, demonstrating encouraging results, especially for vismodegib, for both laBCC and mBCC (14-18).

Both patients tolerated the medications with side effects in keeping with expectations based on published research (muscle spasms, fatigue, nausea) (7, 10, 11). Neither patient suffered from dysgeusia or alopecia, both noted to be common side effects (7). This may be due to shorter treatment duration, as side effects have been shown to be more common in those treated for longer, with 80% vismodegib patients having muscle spasm and alopecia if treated for over 12 months (10). Both patients were treated for under 12 months.

These cases demonstrate the efficacy of both vismodegib and sonidegib at treating laBCC and mBCC respectively.

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