Vismodegib in the Treatment of Advanced BCC

Abstract:
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Abstract
Basal-cell carcinoma (BCC) is the most commonly diagnosed malignancy, comprising over 80% of non-melanoma skin cancers. Surgical excision is adequate treatment for most BCCs. Options are however limited for the minority of patients presenting with locally advanced inoperable or metastatic BCC. The Hedgehog signalling pathway is a critical driver in the pathogenesis of both sporadic and hereditary BCC. On 31st January 2012, based on a phase II clinical trial the US Food and Drug Administration approved Vismodegib (Erivedge®, Roche) a first-in-class, small-molecule oral Hedgehog-inhibitor for the treatment of locally advanced inoperable and metastatic BCC. We present our experience treating the first Irish patient with this agent.

Case Report
A fifty two year old man was referred with a 14-year history of a slowly enlarging interscapular lesion, (Figure 1). The patients past history included peptic ulcer disease and a 30-pack year history of cigarettes smoking. A biopsy of the lesion revealed an invasive, ulcerated basosquamous cell carcinoma. Given the extensive nature of the tumour site an MRI scan was performed showing a lesion extending from the skin involving spinal muscles bilaterally and abutting the spinous processes from C7-T2. Complete staging with CT thorax, abdomen and pelvis documented no metastatic disease. The multidisciplinary team outcome concluded that down-staging with vismodegib would be appropriate given disease extent. A successful application was made for compassionate use of the drug. The patient received the approved daily dose of 150mg. Within two weeks there was dramatic improvement. At 16 weeks multiple scouting biopsies revealed florid inflammatory and giant cell reactivity but no evidence of malignancy. During treatment he reported muscle spasms, dysgeusia, alopecia and anorexia consistent with the known adverse effects of this agent. An MRI at 22weeks showed healing at the level of the deep fascial planes. The area of ulceration had almost completely healed at week 26 of vismodegib, at which point he developed two nodules within the boundaries of his original tumour (Figure 2). Biopsies revealed nodular BCC. The patient is now being assessed for surgical excision.

Discussion
Most BCCs are cured by surgery alone. Patients who present with locally advanced or metastatic disease at diagnosis represent a minority and have limited treatment options. Overall survival estimates for patients with metastatic disease are poor ranging from 8 months to 3.6 years. The pathogenesis of BCC is well understood and most cases of both sporadic BCC and Basal Cell Naevus Syndrome involve activated and aberrant Hedgehog pathway signalling. This pathway is fundamental in the development of embryonic cells and is important in the maintenance of adult cell homeostasis. Irregular activation results in a number of signals and modifications of secreted ligands, culminating in the deactivation of Smoothened (SMO), which normally acts as an inhibitor of downstream Gli-proteins. Persistent stimulation of these proteins upregulate target genes important in cell differentiation and survival. Vismodegib inhibits SMO and demonstrated efficacy in phase II trials with response rates of 43% and 30% reported in patients with locally advanced and metastatic disease, respectively. Consistent with other targeted agents e.g. vemurafenib in the treatment of BRAF-mutated melanoma, acquired resistance to vismodegib appears rapidly with a median duration of response of 7.6 months. Indeed, our patient developed resistance at 6 months. The mechanism of vismodegib resistance remains unclear but may involve alternate pathway activation or acquired mutations. The histology of recurrent BCC in our patient differed from original biopsies and such histological variation has been reported. This concept will be important in future research to aid understanding of acquired resistance.

In the phase II study over 40% of patients with locally advanced BCC discontinued treatment before progression of disease. The reasons for discontinuation were not collected, however adverse effects specifically muscle cramps and dysgeusia as experienced by our patient have been implicated. The underlying pathogenesis and optimal treatments of toxicities are unknown. The clinical impact and position of Vismodegib in treating metastatic/inoperable BCC and down-staging borderline inoperable BCC continues to evolve. Our patient experienced moderate toxicity from this agent and will now proceed to surgery with potentially improved surgical outcome.

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References


