SHORT COMMUNICATION

Neoadjuvant Hedgehog Inhibitors for Locally Advanced Basal Cell Carcinoma: Insights from Two Real-world Cases

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Basal cell carcinoma (BCC) is the most common cancer worldwide, with an average lifetime risk of about 30% in individuals with fair skin (1, 2). The gold-standard treatment for BCC is surgical excision with adequate margins, and most lesions are considered easy to treat (1). Radiotherapy represents a valid alternative for patients who are not surgical candidates or when radical surgery is infeasible or would result in poor aesthetic or functional outcomes (1). However, untreated lesions, or those with repeated treatment failures or recurrences, may progress to locally advanced BCC (laBCC), leading to extensive tissue destruction in adjacent anatomical areas. LaBCC is defined as a tumour that is difficult or impossible to manage with standard surgery or radiotherapy (1). The main pathogenetic driver of BCC is activation of the Hedgehog pathway, with loss-of-function mutations of PTCH1 identified in nearly 90% of sporadic BCCs and activating mutations of SMO in about 10% of cases (2).

In recent years, 2 Hedgehog inhibitors (HHIs), vismodegib and sonidegib, have shown significant anti-tumour activity, revolutionizing the management of laBCC (2). However, although reports on the neoadjuvant use of HHIs are steadily increasing (3–7), such evidence remains insufficient to establish a standard of care. The treatment of laBCC continues to be a complex challenge, requiring a multidisciplinary and individualized strategy to achieve durable complete tumour remission. We present 2 cases of laBCC that achieved complete remission with neoadjuvant HHI therapy followed by surgery, the second of which also required radiotherapy.

CASE REPORTS

Case 1. A 67-year-old male patient with no comorbidities gradually developed a large exophytic tumour on the left posterior shoulder over 5 years, with chronic bleeding leading to anaemia (**Fig. 1**A). No prior treatment had been performed. CT scan excluded deep tissue invasion. Histology confirmed the diagnosis of nodular BCC. To minimize functional and cosmetic impairment after surgery, the multidisciplinary tumour board recommended neoadjuvant HHI therapy. Treatment with vismodegib 150 mg daily was initiated and continued for 7 months, achieving near-complete tumour shrinkage (Fig. 1B). Adverse events included grade 1 muscle cramps, which began after 2 months but did not worsen. The patient subsequently underwent radical excision with direct suture of the defect. Complete clinical and histopathological remission was achieved and maintained after 4 years of follow-up. Functional and cosmetic outcomes were excellent (Fig. 1C).

Case 2. A 64-year-old male patient was referred to our centre with a large untreated lesion in the left temple region, measuring approximately 10 cm in diameter, which he reported had grown rapidly over the past year (**Fig. 2**A). Two incisional biopsies confirmed the diagnosis of nodular BCC. After multidisciplinary discussion, treatment with sonidegib 200 mg daily was initiated. Three months later, the dose was reduced to 1 tablet every other day due to adverse events (grade 2 muscle spasms and dysgeusia). Therapy was continued for 9 additional months, achieving a partial response with an approximately 70% reduction in lesion diameter (Fig. 2B). Sonidegib was then discontinued, and the patient underwent radical excision of the residual nodule, with complete clinical and histological remission. The surgical defect (maximum diameter 3 cm) was reconstructed with a full-thickness skin graft. However, 3 months post-surgery, numerous pigmented papules appeared at the periphery of the excision site, dermoscopically consistent with local recurrence (Fig. 2C). The multidisciplinary board recommended radiotherapy. Volumetric modulated arc therapy (VMAT) with 6 MV photons was delivered to a total dose

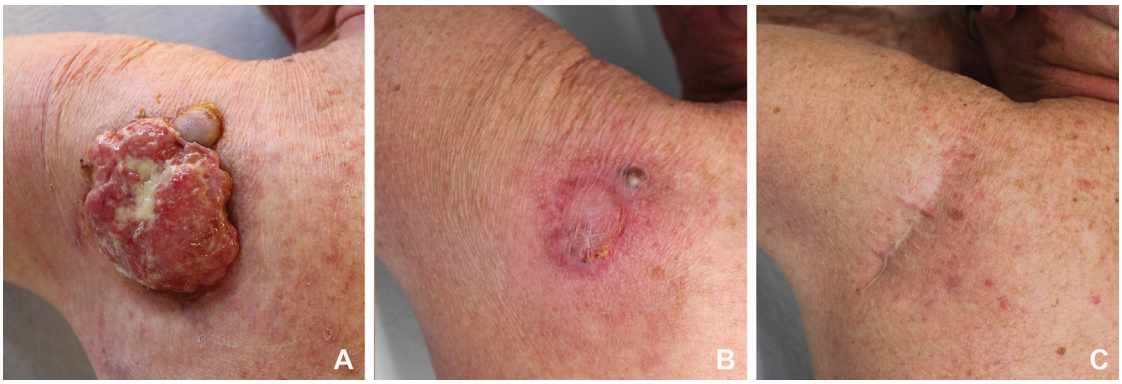

Fig. 1. Case 1: locally advanced basal cell carcinoma of the left posterior shoulder of a 67-year-old man before and after treatment. (A) Clinical presentation at baseline. (B) Tumour reduction after 7 months of vismodegib treatment. (C) 4 years after radical surgery.

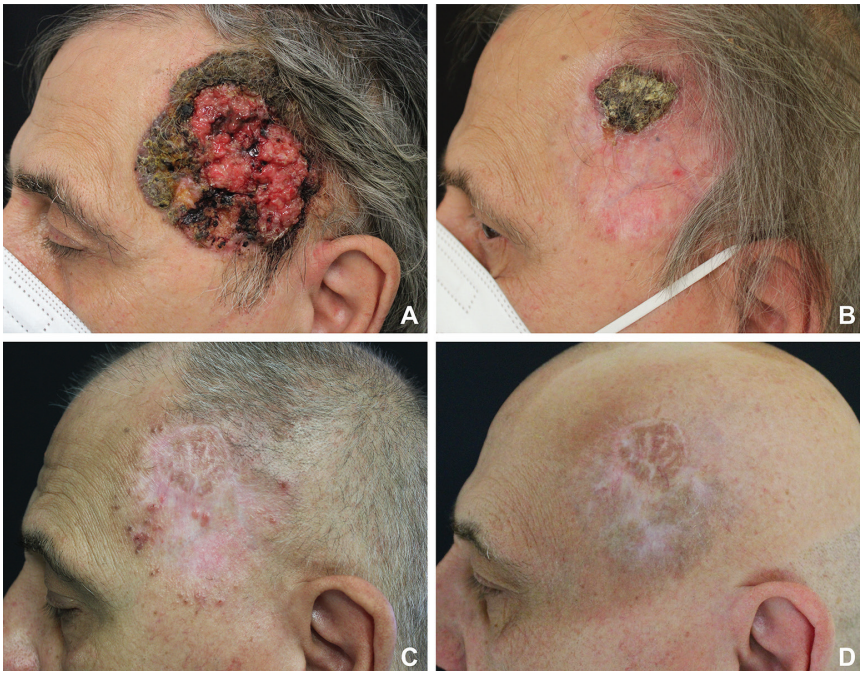

Fig. 2. Case 2: sequential treatment of locally advanced basal cell carcinoma of the left temple of a 64-year-old man. (A) Clinical presentation at baseline. (B) Tumour reduction after 12 months of sonidegib. (C) Local recurrence. (D) 1 year after VMAT radiotherapy, total dose 70 Gy.

of 70 Gy in 35 fractions of 2 Gy each, achieving complete clinical and dermoscopic remission, maintained after 1 year of follow-up, with an acceptable cosmetic result (Fig. 2D).

DISCUSSION

Radical surgery is the first-line treatment for BCC, but when BCC becomes locally advanced, surgery may be impractical or excessively invasive, leading to significant morbidity and severe impairment of quality of life (1). Sonidegib and vismodegib offer an effective pharmacological option (1, 2), representing a major innovation in the management of laBCC. However, complete response (CR) with HHI monotherapy was achieved in only 21.2% of patients treated with sonidegib and 22.2% with vismodegib in the respective registration trials (8), while in a recently published real-life registry, overall CR with HHI was reported in 39% of 452 patients, with a recurrence rate of 45% after treatment discontinuation (9).

In laBCC partially responsive to HHI therapy, tumour shrinkage may facilitate surgery, rendering a previously inoperable tumour resectable or reducing scarring, with improved functional and cosmetic outcomes. In both of our cases, neoadjuvant HHI therapy proved effective in making surgery easier and less destructive. The efficacy of neoadjuvant vismodegib has been investigated in the VISMONEO trial, where 55 patients with histologically confirmed facial BCC, either inoperable or operable with potential functional or major aesthetic sequelae, received vismodegib before surgery, leading to downstaging of the surgical procedure in 80% of cases (3). A recent case report with literature review identified 47 patients with periorbital BCC treated with neoadjuvant vismodegib followed by surgery, showing promising results (4). Conversely, although the efficacy of sonidegib is well established (10), evidence supporting its neoadjuvant use is less robust, being limited to a few studies (5–7), with the first clinical trial still ongoing (11). A retrospective analysis of laBCC patients treated with sonidegib reported encouraging outcomes, as 43% achieved sufficient tumour shrinkage to allow surgery, with no observed relapse (5).

Our case 2 developed grade 2 cramps and dysgeusia, the most common adverse events during HHI therapy (12), which were managed by reducing the dose from the initial daily regimen to 1 tablet every other day. This adjustment is permitted only in the sonidegib label (12).

Radiotherapy combined with HHI and/or surgery provides an additional therapeutic option. In a case series of 12 laBCC patients, induction therapy with HHI followed by radiotherapy achieved an exceptionally high clinical response rate with minor and reversible toxicity (13). In a recent phase II trial, 24 patients with laBCC received 12 weeks of induction vismodegib followed by 7 weeks of concurrent vismodegib and radiotherapy; with a median follow-up of 5.7 years, progression-free survival was 100% at 1 year and 78% at 5 years (14). Radiotherapy has also proven effective in consolidating complete responses obtained with HHI (15). Notably, our case 2 underwent VMAT radiotherapy to treat a local recurrence of laBCC after complete remission achieved with sonidegib and surgery.

In conclusion, although the efficacy of HHI in laBCC treatment is well established, the scientific evidence supporting their neoadjuvant use remains insufficient to justify routine application in clinical practice. A multidisciplinary approach and individualized treatment therefore remain essential. We have presented 2 real-life cases of

successful neoadjuvant therapy with HHI. The potential of the cytoreductive activity of HHI should be further investigated in future clinical studies.

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