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CASE SERIES

Experience with sonidegib in patients with advanced basal cell carcinoma: case reports

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Abstract

Sonidegib is a Hedgehog signalling pathway inhibitor approved for use in patients with advanced basal cell carcinoma (BCC) not eligible for surgery or radiotherapy. This report describes clinical experience with sonidegib in two patients with locally advanced BCC (one with a tumour adjacent to the right eye and the other with a tumour associated with the left ear) and in one patient with Gorlin syndrome. Two of the patients had recurrent and intractable tumours. Treatment with sonidegib 200 mg/day led to remission in both patients with locally advanced BCC within 7 months and to a reduction in the size and number of lesions after 4 months in the patient with Gorlin syndrome. Adverse effects reported in these patients were cramps, alopecia, ageusia and weight loss, all of which were mild and consistent with the known toxicity profile for sonidegib. Sonidegib has an important role to play in the effective treatment of challenging cases of advanced BCC. In parallel, a need remains to improve management protocols for patients with advanced BCC, particularly through earlier intervention and a multidisciplinary team approach.

Keywords: case reports, Gorlin syndrome, locally advanced basal cell carcinoma, sonidegib, vismodegib.

Citation

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Introduction

Non-melanoma skin cancer is the fifth most commonly occurring cancer in men and women globally.[1] Basal cell carcinoma (BCC) accounts for the majority (~80%) of non-melanoma skin cancer cases,[2,3] and the incidence has been increasing worldwide since the 1970s.[3,4] People with white skin are most susceptible to BCC, with sun-exposed areas, such as the head and neck, being particularly vulnerable.[2,5]

As BCC tumours are generally slow growing, the condition is highly treatable if detected early and managed appropriately.[3] Metastatic BCC (mBCC) is extremely rare (0.003–0.55% of cases)[2] but, when it does occur, the prognosis is poor.[3] Large, aggressive or recurrent BCC tumours, and those which penetrate deeper into the skin or associated tissues, are referred to as locally advanced BCC (laBCC). laBCC poses several therapeutic challenges: the tumours may not be amenable to radiation therapy, surgery may be impractical due to the risk of morbidity, loss of function or disfigurement, and risk of recurrence is high.[3] Until relatively recently, mBCC and laBCC were considered untreatable conditions, with palliative care being the only option.

The Hedgehog (Hh) signalling pathway is involved primarily in embryonic development and control of gene activation. Normally suppressed in adults, aberrant activation of the Hh pathway through gene mutations or excessive expression of Hh signalling molecules can lead to development of certain cancers, including BCC and Gorlin syndrome. 'Smoothened' (SMO), a transmembrane protein and main transducer of the Hh signalling pathway, initiates a signalling cascade that increases the expression of glioma-associated oncogene transcription factors. By binding to SMO, Hh pathway inhibitors (HPIs) prevent downstream activation of Hh pathway signalling.[6,7]

Vismodegib was approved in 2012 for treatment of adults with mBCC or laBCC not eligible for surgery or radiotherapy.[8] Subsequent approval of sonidegib in 2015 provided an alternative option for laBCC patients.[9,10] European consensus guidelines recommend that patients with mBCC or laBCC be offered treatment with vismodegib or sonidegib.[11]

Although the compounds share the same mechanism of action,[12,13] their pharmacokinetic profiles differ. Notably, sonidegib has a large volume of distribution, as indicated by steady-state concentrations sixfold higher in skin than in plasma, whereas vismodegib is confined mainly to the plasma and extracellular spaces.[10,14,15]

The efficacy of sonidegib was established in the phase II, multicentre, randomized, double-blind BOLT (Basal Cell Carcinoma Outcomes with LDE225 [sonidegib] Treatment) study in adults with histologically confirmed laBCC or mBCC not amenable to curative surgery or radiotherapy.[16–19] Cut-off for the final analysis was 42 months.[19] The primary endpoint was the objective response rate (ORR) by central review (ORR-CR), defined as the proportion of patients with complete or partial response assessed by the BCC-modified Response Evaluation Criteria in Solid Tumors (mRECIST). ORR by investigator review (ORR-IR) was a secondary endpoint. In the final analysis, the ORR-CR was 56.1% and the ORR-IR was 71.2% as per mRECIST in patients with laBCC.[20,21] A pre-planned sensitivity analysis compared these efficacy outcomes with those obtained using the composite RECIST criteria (≥30% reduction in externally visible tumour or radiographic dimension, or complete ulceration resolution) applied in the ERIVANCE study of vismodegib.[21,22] Based on these less stringent RECIST criteria, efficacy outcomes with sonidegib were even higher, with an ORR-CR and ORR-IR of 60.6% and 74.2%, respectively.[20] Irrespective of the criteria used to assess response, long-term positive responses to sonidegib 200 mg/day were similar for patients with aggressive or non-aggressive histological subtypes of laBCC.[20,23]

The safety profile of sonidegib was consistent throughout the course of the BOLT study. Median duration of exposure to sonidegib 200 mg/day was 11 months, with 24% of patients having ≥20 months' exposure. Adverse effects (AEs) were mainly grade 1/2 in severity. The most common AEs (≥25% of patients) were muscle spasms, alopecia, dysgeusia, nausea, elevated creatine kinase, weight decrease, fatigue and decreased appetite. Grade 3/4 treatment-related AEs and serious treatment-related AEs were reported in 32% and 5% of patients, respectively. Common AEs requiring treatment interruption or a dosage reduction were elevated creatine kinase, nausea, vomiting, diarrhoea and elevated lipase. Most AEs were manageable and reversible with dose interruptions, with no overall impact on efficacy.[19]

Given that the strict adherence to protocol required in randomized controlled trials can limit generalizing the results to external populations, interventions must also be evaluated under real-world conditions.[24] Herein, we present clinical experience with sonidegib in three patients with advanced BCC.

Patient consent

All data presented in this article have been de-identified to ensure patient confidentiality. Patient consent was not required.

Case reports

Case 1

A 79-year-old woman (height 1.46 m; weight 72 kg) presented to Dermatology Services at the Hospital Universitario Nuestra Señora de Candelaria, Tenerife, Spain, in September 2017 for a pruritic facial lesion of slow evolution over recent years. Examination revealed an erythematous plaque of approximately 13 × 8 mm adjacent to the caruncle of the right eye, with some telangiectasia on the surface. The diagnosis was laBCC. Comorbidities were cholecystectomy, euthyroid goitre and high blood pressure. The patient was sensitized to moxifloxacin.

A biopsy in January 2018 confirmed a diagnosis of BCC with an infiltrative pattern. The patient underwent maxillofacial surgery and was referred for radiation therapy (80 kV X-rays at a daily dose of 300 cGy, reaching a total dose of 4800 cGY) ending on 8 February 2018. She achieved a complete clinical remission.

In October 2019, the tumour recurred and the patient was referred for Mohs micrographic surgery. Due to the COVID pandemic, she declined transfer to mainland Spain, which delayed the consultant oncological dermatology assessment until March 2020. At assessment, an erythematous and crusty plaque of approximately 16 × 8 mm located in the immediate vicinity of the caruncle of the right eye was evident. No adenopathies, masses or megaly were palpated. No significant laboratory abnormalities were identified, and magnetic resonance imaging (MRI) was negative for intraorbital invasion

Figure 1. Case 1: MRI scan of a female patient with a recurrent basal cell carcinoma adjacent to the caruncle of the right eye, showing no intra-orbital invasion.

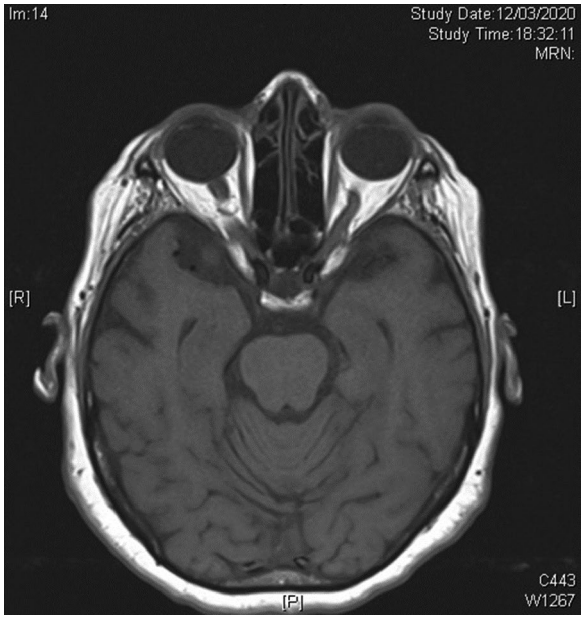
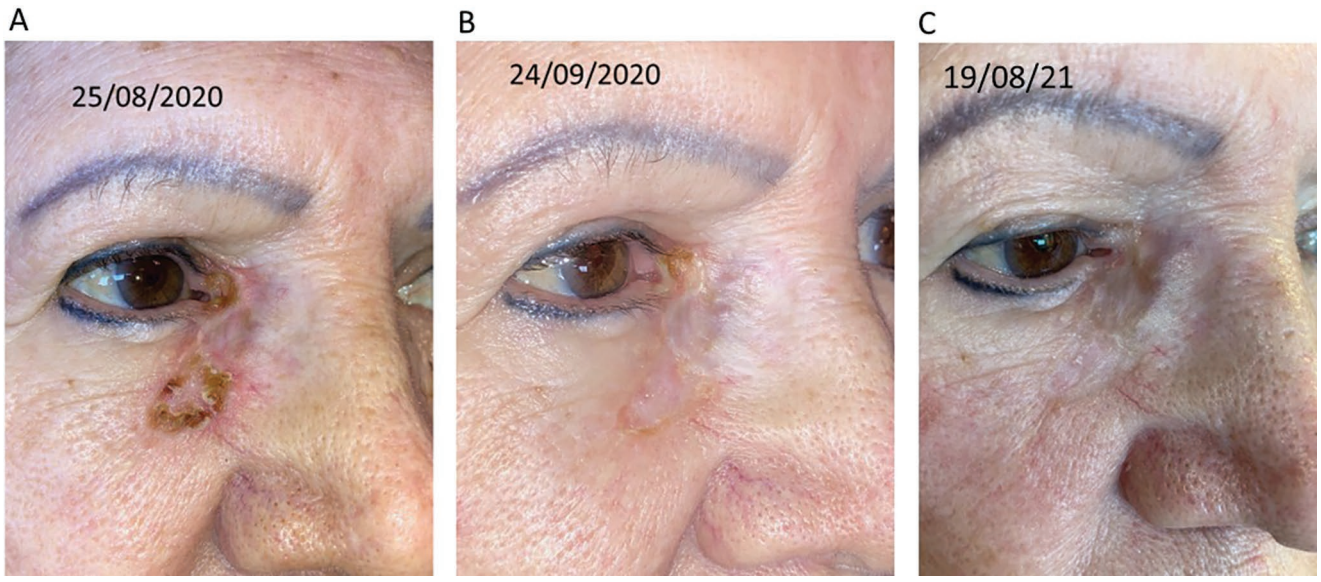


Figure 2. Case 1: Clinical presentation of a basal cell carcinoma in a female patient: (a) pre-treatment, (b) at 1 month (clinical response) and (c) at 1 year (continued remission) after treatment with sonidegib 200 mg/day (for 9 months).



(Figure 1). The patient had an Eastern Cooperative Oncology Group Performance Status of 0.

Sonidegib 200 mg/day was prescribed, beginning 26 August 2020, based on published evidence of its efficacy in laBCC. Tumour evolution is shown in Figure 2. A response was evident within the first month of treatment. By 19 March 2021 (7 months after treatment commencement), the patient had achieved a complete clinical response. After confirming the clinical response by control biopsy, sonidegib was discontinued on 27 May 2021 (after 9 months). In February 2022, 9 months after treatment discontinuation, the patient remained in remission.

Throughout treatment, the patient experienced mild toxicity consisting of grade 1 cramping, ageusia and weight loss. Three months after discontinuing sonidegib, all AEs had resolved.

Case 2

A 69-year-old man was referred for a tumour located in the left ear. The tumour had developed over 6 years, growing slowly until it occupied about two-thirds of the ear, with occasional bleeding. A biopsy indicated metatypical BCC with a mixed pattern (nodular and infiltrative). The patient had no comorbidities and was not receiving any chronic medication.

Examination revealed a plaque of 4 × 3 cm in the helix and antihelix of the left ear, poorly delimited, with retraction of the pinna. The plaque was infiltrated, with clinical evidence of cartilage involvement. The clinical diagnosis was BCC ulcus rodens.

In November 2020, the patient began treatment with sonidegib 200 mg/day. Improvement was evident after 2 months and, by 6 months, a complete clinical response was achieved (Figure 3). A biopsy including cartilage indicated no evidence of tumour.

Sonidegib was well tolerated by this patient, with grade 1 alopecia being the only reported AE. Due to good tolerability, and in the presence of a complete clinical and histological response, sonidegib treatment was continued for 6 months after complete clinical response.

Case 3

A 38-year-old man with a long-term history of Gorlin syndrome (nevoid basal cell carcinoma syndrome) had been in dermatological follow-up since childhood. He had no comorbidities and was not receiving any chronic medication.

From the age of 8 years, the patient had been treated for multiple BCCs by surgery, cryotherapy and electrocoagulation. Most lesions were located on the face and scalp. Mohs surgery was required on some occasions to treat infiltrative pattern lesions. Oral surgery was performed as needed to remove several mandibular keratocysts.

Due to an acceleration of BCCs at the time of consultation, the patient was treated with vismodegib 150 mg/day from November 2019 to October 2020. Treatment response was good, with complete disappearance of lesions. AEs were mild: grade 2 alopecia and grade 1 cramps.

Three months after stopping vismodegib, the lesions began to recur. In May 2021, the patient presented with more than 50 lesions on his face and scalp, mostly pigmented BCCs 4–6 mm

Figure 3. Case 2: Clinical presentation of a metatypical basal cell carcinoma with a mixed nodular and infiltrative pattern in a male patient: (a) pre-treatment and (b) after 6 months of treatment with sonidegib 200 mg/day.

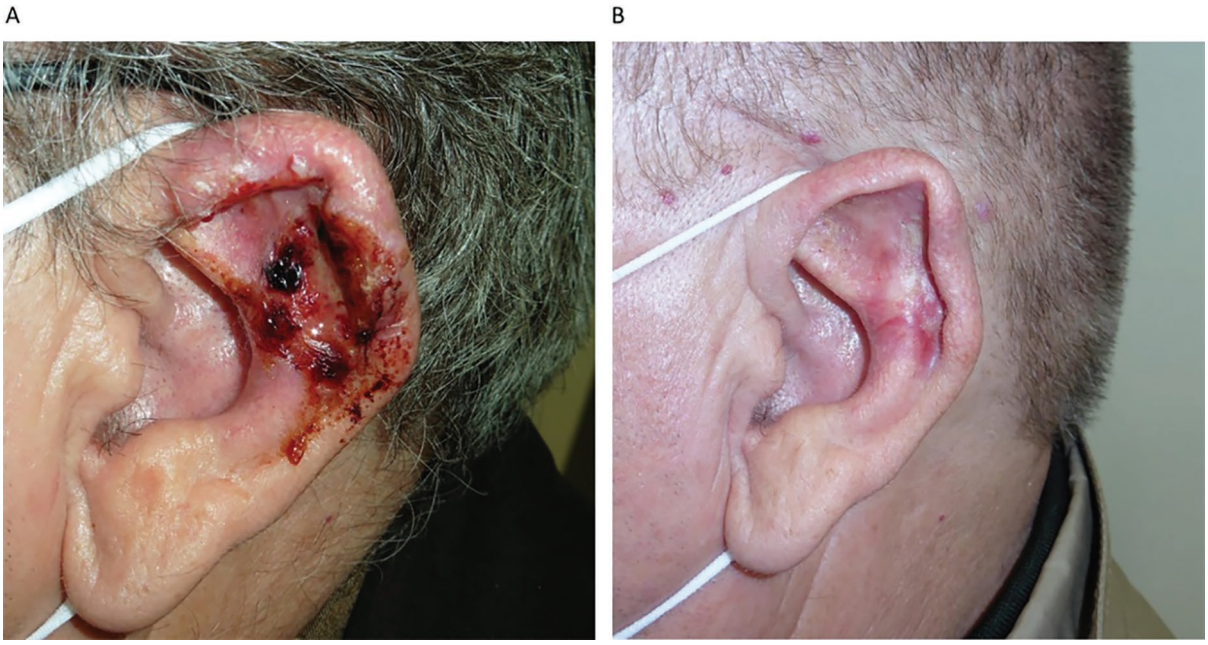
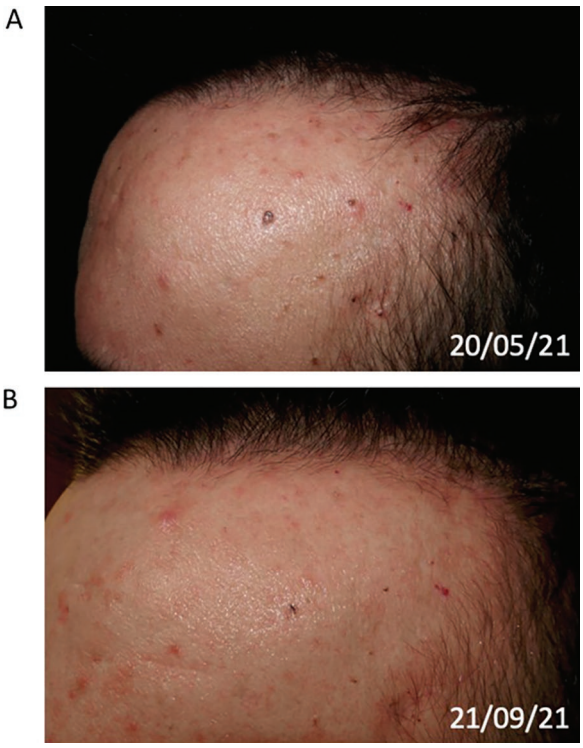


Figure 4. Case 3: Gorlin syndrome lesions on the forehead of the patient: (a) pre-treatment and (b) after 4 months of treatment with sonidegib 200 mg/day.



in diameter and some ulcerated. Due to the patient's concerns about AEs experienced during treatment with vismodegib, sonidegib 200 mg/day was selected.

In September 2021, after 4 months of sonidegib treatment, there was a decrease in the number and size of the lesions (Figure 4). The only side effect the patient experienced was grade 1 alopecia and self-reported changes in hair texture. Laboratory tests performed during follow-up (at 1 month and every 2 months thereafter) showed no abnormalities.

After 6 months of treatment with sonidegib, a complete clinical response in all lesions was observed. With the patient's agreement, treatment was discontinued with a plan to reassess clinically every 3–6 months and reintroduce sonidegib intermittently between rest periods as necessary.

The patient tolerated sonidegib better than vismodegib. He was satisfied with sonidegib treatment with no need to implement every-other-day dosing.

Clinical overview

Periocular localization of BCC (Case 1) with lesion development adjacent to and invasion through the caruncle is appropriately diagnosed as laBCC. The patient's response to sonidegib was notably rapid (within 1 month), consistent with that described in a man with laBCC of the nuchal region who had a 95% reduction in tumour size 3 months after starting treatment with sonidegib 200 mg/day;[25] a 71-year-old man with clinically important tumour regression within 2 months of starting

sonidegib 200 mg/day for multiple laBCC, including on the internal canthus;[26] and a 63-year-old man who had a marked response after 2 weeks of treatment with sonidegib 200 mg/day for multiple laBCC lesions of the face, including a 4-year evolving ulcerated lesion under the right lower eyelid.[27]

The patient with metatypical BCC (mixed nodular and infiltrative pattern) of the left ear (Case 2) also showed an excellent response to sonidegib, achieving a complete clinical response after 6 months of treatment. Numerous other case reports or case series have documented clinical improvement or clearance of laBCC lesions, including complete responses, with sonidegib 200 mg/day most often within a few months of treatment start.[28–34] There are also anecdotal reports of the effectiveness of sonidegib for locally advanced basosquamous carcinomas,[31] locally advanced anal and rectal BCC,[35] and in combination with fractionated radiation for recurrent advanced BCC of the head and neck.[36]

Case 3 shows the promising effectiveness of sonidegib for the treatment of Gorlin syndrome, including in patients with disease recurrence after receiving vismodegib, which is supported by the collective clinical experience of a multidisciplinary expert panel pointing to optimal responses to HPIs in these patients.[37] Italian investigators reported the case of an 89-year-old woman with Gorlin syndrome who had been treated successfully with vismodegib but had to discontinue treatment due to severe asthenia; all lesions relapsed after discontinuation. After 3 months of treatment with sonidegib 200 mg/day, partial re-epithelization and tumour shrinkage were observed in all target lesions, with no AEs. At 6 months, there was further improvement and complete healing of lesions on the face, again without AEs.[38] This outcome, together with Case 3 herein, shows that lesion recurrence after HPI discontinuation following response does not constitute resistance. As such, rechallenge with a drug of the same class should be considered before switching to a completely different treatment such as second-line immunotherapy.

The usefulness of switching between HPIs was also reported in a case involving an 87-year-old man with inoperable laBCC involving the sinuses, nasal cavity and brain. Sonidegib 200 mg/day in combination with itraconazole pulse dosed at 100 mg/day (2 weeks on, 2 weeks off) was effective whereas previous vismodegib had proved inadequate. Vismodegib successfully reduced tumour size by 70% over 3 months when tumour involvement was limited to the nasal cavity and sinuses, but the effects diminished over time. Vismodegib was discontinued and the patient received radiation therapy (total dose of 70 Gy). Two years later, BCC recurred and, despite vismodegib treatment for 6 months, the lesions progressed. Pembrolizumab was tried without success, and the tumour progressed into the brain. Sonidegib/itraconazole combination therapy led to significant improvement after 3 months. After approximately 8 months, the intracranial lesion was no longer visible on MRI and the intranasal and sinus lesions were stable and improved.[39] Treatment resistance in patients receiving HPIs may be due to the development of SMO mutations, which impair effective binding. The efficacy of an alternative HPI in this setting may depend on the specific mutation, the binding location of the drug and whether the mutation produces a conformational change influencing drug binding. Identifying biomarkers of resistance or response would be useful to target HPIs to patients most likely to benefit.[40]

Follow-up of patients with laBCC is of considerable interest to establish whether full lesion clearance can be achieved and whether tolerability is maintained during continued treatment. Our experience suggests that clinical follow-up every 3–6 months during maintenance treatment is appropriate. After discontinuation, consideration can be given to reintroducing sonidegib upon the appearance of multiple new lesions. An alternative approach is to continue sonidegib at reduced dosing (every other day or twice a week) as maintenance therapy. For patients with chronic Gorlin syndrome, a suitable treatment protocol may be sonidegib 200 mg/day until lesion clearance, alternating with no treatment during periods of remission. Irrespective of the condition being treated, any decisions regarding long-term management should be discussed and agreed with the patient. Telemedicine can be a useful adjunct tool for patients who are able to provide digital photos of their lesions of suitable standard for comparison with previous images.[29]

Two of our patients (Cases 2 and 3) reported alopecia as the sole AE to sonidegib, and both opted to continue treatment. The remaining patient (Case 1) experienced mild cramps, ageusia and weight loss, all of which resolved once treatment was discontinued. These AEs are within the established toxicity profile of sonidegib.[9] In the BOLT study, AEs were common but rarely serious in patients receiving sonidegib. At final analysis at 42 months, alopecia (grade ≤2) had been reported in 49% of patients receiving sonidegib 200 mg/day.[19] HPIs may induce alopecia by interfering with the transition of follicles from the telogen phase of hair shedding to the anagen growth phase.[41] The most common grade 3–4 AEs associated with sonidegib 200 mg/day in the BOLT study were elevated creatine and lipase (each in 6% of patients).[19] Elevated creatine levels are also associated with vismodegib,[42] suggesting that this is a class effect. No abnormal laboratory data were recorded in any of the three cases presented.

Most AEs associated with HPI treatment are thought to result from inhibition of the Hh signalling pathway in normal tissue. Although generally not severe, AEs can be persistent, reducing patients' quality of life and necessitating treatment interruption or discontinuation. Indeed, it has been suggested that some patients with laBCC who discontinue HPI therapy due to AEs do so because their intolerance for AEs begins to outweigh the extent of clinical improvement. Healthcare professionals need to be aware of this possibility and manage patients accordingly in order to facilitate continued treatment, if appropriate.[19,41] With respect to sonidegib, a retrospective case series of 20

patients[43] and a post hoc analysis of the BOLT study[44] found that dose adjustments (e.g. dose reductions, alternate day dosing) or treatment delays were practical solutions to reduce the need for treatment discontinuation with no detriment to sonidegib efficacy. Prior to initiating HPI therapy in patients with laBCC receiving statin therapy, it may be prudent to stabilize the patient on a low dose of a hydrophilic statin (e.g. rosuvastatin) not metabolized by CYP 3A4 to reduce the risk of muscle-related AEs.[45] The use of concurrent superficial radiotherapy at the time of maximal therapeutic effect of an HPI led to a high clinical response rate with minimal toxicity in a retrospective review of 12 patients with laBCC treated with vismodegib or sonidegib, and merits further investigation in well-controlled clinical trials.[46]

Conclusions

Collectively, case reports/case series of sonidegib use in clinical practice support its effectiveness in patients with advanced BCC, as demonstrated in the BOLT study.[16–20] Although based on only three cases, and with treatment ongoing in two of these cases at the time of case submission, the clinical experience with sonidegib presented herein demonstrates its ability to induce tumour remission in patients with laBCC or Gorlin syndrome, including recurrent and intractable cases. AEs recorded with sonidegib in these patients were mild and manageable, consistent with its known safety profile. Importantly, strategies such as dose reductions and treatment interruptions to manage patients unable to tolerate dosing schedules or with suspected treatment-related AEs do not appear to undermine sonidegib efficacy and may improve patient outcomes by preventing treatment discontinuations. Overall, sonidegib appears to be a useful addition to the therapeutic armamentarium for patients with advanced BCC, showing efficacy in patients who have previously failed on vismodegib.

Despite the wealth of high-quality evidence regarding therapeutic options for laBCC, delays in disease management are not uncommon in these patients, even in centres with active multidisciplinary teams. As such, continued efforts are required to define and implement optimal care for patients with advanced BCC.

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