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SHORT REPORT

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Locally advanced basal cell carcinoma: Real-life data with sonidegib

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Abstract

In recent years, the category of hedgehog pathway inhibitor (HHI) has shown great results in patients with advanced basal cell carcinoma (aBCC), but few real-life data on efficacy and safety profile of sonidegib are available. We report our management of locally advanced BCCs (laBCCs) with sonidegib, also describing the favorable response of locally advanced basosquamous carcinomas (laBSCs) treated with this hedgehog signaling inhibitor. Sonidegib was generally well tolerated and it achieved high response rates, improving quality of life. Our single-center experience could be useful to better delineate long-term efficacy and tolerability profile demonstrated in the trials described in literature. Moreover, our cases provide preliminary evidence that sonidegib might be effective for laBSC.

KEYWORDS
locally advanced basal cell carcinoma, non melanoma skin cancer, sonidegib, treatment

1 | INTRODUCTION

Basal cell carcinoma is the most commonly form of skin cancer worldwide and it accounts for 80% of keratinocyte carcinomas. In a minority of cases, BCCs present aggressive characteristics and progress to an advanced stage that includes both laBCC and metastatic BCC (mBCC).[1] In recent years, the promising category of HHI has shown great results in patients with aBCC.[1] Much experience has been achieved with the first in class agent vismodegib, approved by the FDA in January 2012. Sonidegib was introduced later to the market, in June 2015, for treatment of laBCC, not amenable to curative surgery or radiotherapy.[2] These two alternative treatment options share similar efficacy and tolerability profiles, but they have different pharmacokinetic features, such as half-life and volume of distribution making sonidegib more extensively distributed in the skin compared with vismodegib.[3] However, few real-life data on efficacy and safety profile of sonidegib are available. We report our experience in the management of laBCCs with sonidegib, also describing the favorable response of laBSCs treated with this hedgehog signaling inhibitor.

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2 | SONIDEGIB REAL-LIFE DATA

We collected data from nine patients treated with sonidegib: seven patients with laBCCs and multiple BCCs (78%) and two patients with laBSCs (22%; Table 1). Based on literature data, sonidegib was chosen because it has demonstrated an approximately 10% lower incidences of most adverse effects (AEs) and longer time to AE onset compared with vismodegib.[3] Moreover, as reported in the sonidegib data sheet only, a regimen of 200 mg every other day is allowed to manage side effects.

The group included mainly elderly people, with a mean age of 72 years (range 48–90), a total of nine patients, four men (44%) and five women (56%). The majority of them (67%) showed multiple BCCs, with the prevalent sites being head and trunk. Most of these patients (*n*: 5/9, 55%) had previously experienced surgical excision of their BCCs.

All patients initially received sonidegib 200 mg orally daily. Blood count, creatine phosphokinase (CPK), renal and hepatic function were tested before starting therapy and monthly during treatment.

We observed CPK rise (two folds higher than basal levels) in a patient with nocturnal muscle spasms 2 months after starting

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TABLE 1 Clinical features, tumor responses and adverse events in patients with advanced basal cell carcinomas and basosquamous carcinomas treated with sonidegib

N	Age	G	Comorbidity	Type of BCC	Localization	N & D (larger)	Patch1 mutation	Previous TP	CR	PR	SD	PD	TP duration	Dosage	AE	AE grade	AE onset
1	81	F	Multiple myeloma, hyperthyroidism	Multiple and laBCC	Face, trunk	*N* > 15; *D* = 22 x 10 mm	Neg.	Surgery		After 3 m (after 6 m for BCCs on the back)			21 m	200 mg daily	No		
2	89	M	Stroke, arterial hypertension, hypercholesterolemia, COPD, DM	laBCC	Scalp	*N* = 9; *D* = 30 x 40 mm	No	ECT, PDT		After 2 m			9 m	200 mg daily	No		
3	90	M	Heart disease, arterial hypertension, hypercholesterolemia, DM, chronic gastritis	Multiple and laBCC	Anal-rectum, retroauricular area, abdominal	*N* = 3; *D* = peri anal skin 10 mm + involvement of anal canal+7 mm rectum	No	No	After 4 m				5 m	200 mg daily, then alternate daily dose	Muscle spasms	2	After 3 m
4	48	M	Psoriasis	Multiple and laBCC	Back	*N* > 15; *D* = 24 mm	No	Surgery		After 4 m			7 m	200 mg daily, then alternate daily dose	(a) Alopecia, b) Dysgeusia	(a) 1, (b) 2	After 4 m
5	78	M	Heart disease, mechanical heart valve, stroke, epilepsy, arterial hypertension, hypercholesterolemia	Multiple and laBCC	Right temple, chest, back	*N* > 15; *D* = 35 x 20 mm	No	No		After 3 m (after 6 m for BCCs on the back)			7 m	200 mg daily, then alternate daily dose	Abdominal pain	1	After 6 m
6	52	F	No	Multiple	Trunk, face	*N* > 15, *D* = 17 x 12 mm	Neg.	Surgery		After 3 m			25 m	200 mg daily, then alternate daily dose	Alopecia	1	After 6 m
7	83	F	Hypotiroidism, heart disease, arterial hypertension	laBSC	Left shoulder	*N* = 1, *D* = 9 x 14 cm	No	Surgery		After 3 m			5 m	200 mg daily, then alternate daily dose	Nausea, inappetence, myalgia, bone pain	2	After 3 m
8	59	F	Anemia, thalassemic trait	laBSC	Left upper limb +chest	*N* = 1, *D* = 10 x 15 cm	No	No		After 4 m			4 m	200 mg daily	No		
9	75	F	AF	Multiple	Trunk	*N* > 15, *D* = 15 x 9 mm	Pos.	No		After 4 m (after 5 m for BCCs on the back)			5 m	200 mg daily, then alternate daily dose	Muscle spasms, gastritis, nausea	1	After 3 m

Abbreviations: AE, adverse events; AF, atrial fibrillation; COPD, chronic obstructive pulmonary disease; CR, complete response; D, diameter; DM, diabetes mellitus; ECT, electrochemotherapy; F, female; G, gender; laBCC, locally advanced BCC; laBSC, locally advanced BSC; M, male; m, months; N, number; PD, progressive disease; PDT, photodynamic therapy; PR, partial response; SD, stable disease; TP, therapy.

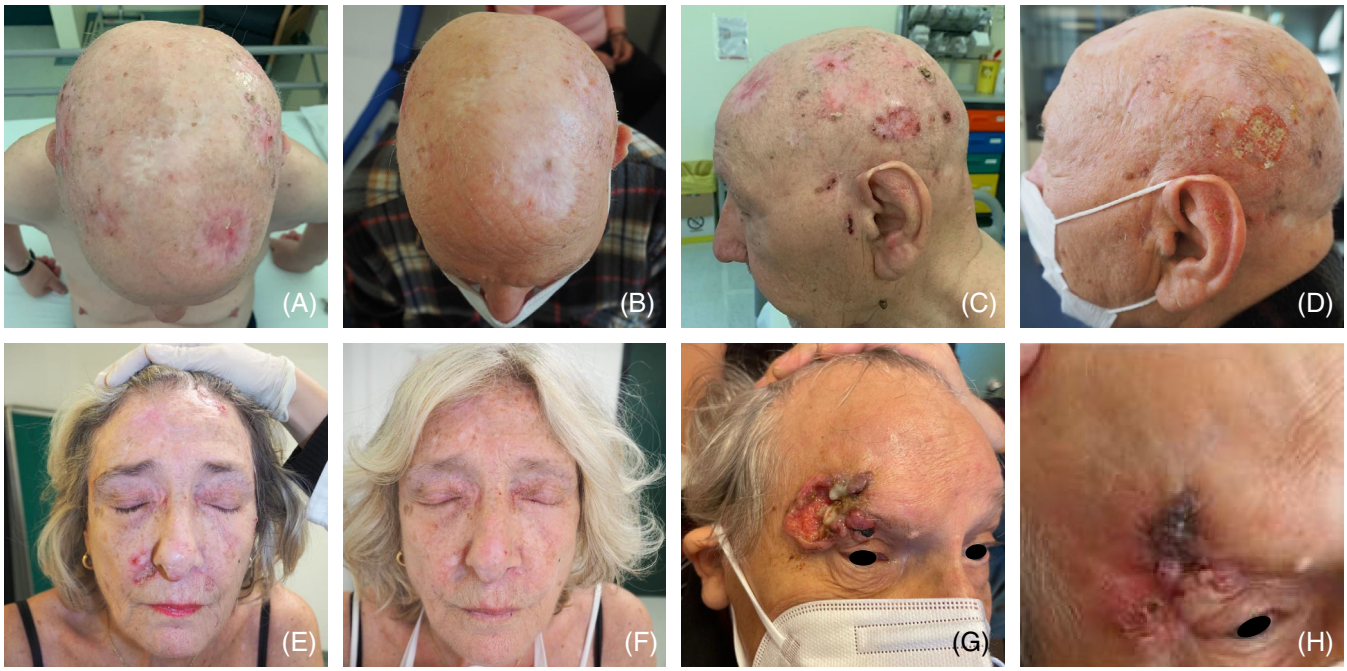

FIGURE 1 (A, C) Locally advanced basal cell carcinomas of the scalp treated with sonidegib. (B, D) Significant improvement of the lesions after 2 months of therapy. (e) Locally advanced basal cell carcinomas of the face treated with sonidegib. (F) Important clinical response of the lesions after 2 months of therapy. (G) Right temporal locally advanced basal cell carcinoma treated with sonidegib. (H) Remarkable improvement of the lesion after 3 months of therapy

sonidegib and remission was achieved 3 weeks after stopping the therapy. Sonidegib was restarted at a dosage of 200 mg every other day, CPK values did not increase and the treatment was better tolerated with rare episodes of nocturnal cramping.

To one patient with temporal laBCC radical surgery was proposed, but he refused invasive treatments including radiotherapy, which could lead to visual loss due to the closeness of the tumor to the eye. The patient preferred to initiate an HH inhibitor. However, he suffered from epilepsy and neurologist advised not to administer sonidegib because of possible interaction with phenytoin. After evaluation by our multidisciplinary team, considering the patient's refusal to other treatments, we decided to start the treatment. After 3 months, the patient showed a good clinical response and a slight reduction in the values of phenytoin. He complained only mild abdominal pain, so he received a dosage of 200 mg every other day, with resolution of the symptom in 10 days.

Overall, AEs were few, mild in severity and reversible after 2 weeks of discontinuation, on overage, or otherwise tolerable with alternate-day dosing. The most common AE were muscle symptoms (*n*: 3/9; 33%), followed by alopecia (*n*: 2/9; 22%), dysgeusia (*n*: 1/9; 11%), nausea (*n*: 1/9; 11%), inappetence (*n*: 1/9; 11%), abdominal pain (*n*: 1/9, 11%), gastritis (*n*: 1/9, 11%) and bone pain (*n*: 1/9, 11%). Three patients (33%) showed no side effects, six patients (67%) switched to alternate-day dosing because of AE 3 months, on overage, after starting therapy.

As previously reported by Villani et al,[4] the clinical response was divided into: complete response (CR) when we obtained the total disappearance of the tumor; partial response (PR) when we achieved more than 50% tumor reduction; stable disease (SD) when we observed less than 50% tumor reduction, or less than 20% increase in tumor area; progressive disease (PD), when we observed a tumor increase of more than 20%. Villani et al first reported one case of laBCC successfully treated with sonidegib with complete response 3 months after starting treatment, without side effects.[5] Moscarella et al also reported a complete clinical resolution in one case after 9 months of therapy, observing fatigue and alopecia 3 months after initiation of the treatment.[6]

In our experience, the following tumor response rates were observed: one patient (11%) achieved a CR; eight patients (89%) achieved a PR (Figure 1); no cases of SD or PD were detected. Therefore, sonidegib showed an overall response rate (100%) higher than previously reported in BOLT trial with modified RECIST criteria.[7]

We observed a CR in one patient, with an anal and rectum laBCC, after 5 months of therapy, confirmed by clinical examination and MRI. A PR was achieved in eights patients 3 months, on average, after starting treatment. In one patient with a subtotal response, a BCC in the popliteal site was reduced in size after treatment, but it showed a dermoscopic pattern suggestive of PR.[8] Therefore, it was surgically excised while receiving 200 mg/day of sonidegib, demonstrating the neo-adjuvant role of the drug.[9]

We observed a significant improvement of BCCs after only 2 month-therapy in one patient who had received prior treatments, in particular electrochemotherapy and photodynamic therapy. These data could underline the fast and effective role of sonidegib in patients with previous treatment history.

In addition, we reported a better response in head and neck BCCs, in fact the tumors located on the back seem to respond less quickly than those in the head and neck area, approximately 5–6 months after starting therapy. Further studies, with a larger number of patients, could investigate the possible different responses to sonidegib based on site-related factors and history of previous treatments.

We managed elderly patients with numerous comorbidities, such as diabetes mellitus, heart disease, arterial hypertension, epilepsy, and the good clinical results obtained demonstrate that sonidegib can be safely used in this quite vulnerable group of patients.

Of note, we treated also two patients with locally advanced basosquamous carcinoma (laBSC), achieving great results. A PR was reported 3 and 4 months after starting sonidegib, respectively. Both lesions were very large in size and the management options were limited. Up to date, in literature, there are only few papers about cases of locally advanced BSCs completely treated with vismodegib and no cases with sonidegib; the PR achieved after only 3 and 4 months of therapy is a good data to consider and investigate further that offers a new treatment option for BSC.

3 | CONCLUSION

The management of patients with laBCC has changed with the HHI. Sonidegib has demonstrated a great efficacy and a safety profile in this type of patients.

Routine laboratory assessments and follow-up visits are required to better evaluate the clinical situation and manage the AEs. The possibility of adjusting the dose of the drug helps clinicians in daily practice to minimize AEs and to reduce the number of treatment discontinuations.

In our clinical setting, treatment with sonidegib was generally well tolerated and it achieved high response rates, improving quality of life. Our single-center experience could be useful to better delineate long-term efficacy and tolerability profile demonstrated in the trials described in literature. Moreover, our cases provide preliminary evidence that sonidegib might be effective for laBSC.

Further studies from the real-life setting are needed.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

All authors have made substantial contributions to the work reported in the manuscript. Iris Zalaudek, Nicola di Meo, Claudio Conforti and Ludovica Toffoli conceived and designed the idea. Ludovica Toffoli and Claudio Conforti wrote the manuscript with the support of Marina Agozzino. Iris Zalaudek, Enrico Zelin, Roberta Vezzoni contributed to the final version of the manuscript.

DATA AVAILABILITY STATEMENT

Data available on request due to privacy/ethical restrictions. The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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