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Clinical determinants of clinical response to Sonidegib in advanced basal cell carcinoma: a monocenter experience

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Abstract. – OBJECTIVE: The purpose of this study is to evaluate the clinical determinants of complete response in locally advanced basal cell carcinoma (laBCC) patients receiving Sonidegib in a real-life, retrospective, observational study. Hedgehog pathway inhibitors (Vismodegib and Sonidegib) are approved for the systemic treatment of locally advanced basal cell carcinoma (laBCC). The objective response rate was the primary endpoint of the trials for both drugs.

PATIENTS AND METHODS: Adult patients with laBCC treated with Sonidegib at the Dermato-Oncology Unit of IFO San Gallicano between June 2020 and September 2022 were included in the study. Patient, tumor, and treatment characteristics were recorded. The complete response rate was the primary outcome. The median time to the best response and complete response were the secondary outcomes. Treatment-related adverse events (TRAEs) and dose adjustments were recorded.

RESULTS: Of the 19 patients included in the study, eight (42.1%) achieved a complete response, seven (36.8%) had a partial response, and four experienced progressive disease (21%). The median time to the best response was 3 months in the group of patients with partial response (range 2.0-4.0, with three patients not evaluable) and 3.5 months in the group of patients with complete response (range 2-5). TRAEs occurred in 14 (73.6%) patients, with 8 (57.1%) reporting ≤2 TRAE categories and 6 (42.8%) >2. A total of 78.9% of patients received a modified treatment schedule; 12.5% of patients who achieved a complete response received full dosage from the beginning to the end of treatment, compared with 27.3% of those with a partial response.

CONCLUSIONS: The associations between the clinical outcome of interest (objective response rate) and the clinicopathological and treatment characteristics were evaluated. No statistically significant association was observed. Our analysis confirms the observation that no statistically significant correlation exists between clinical response and Sonidegib alternate dose regimen.

Key Words:
Sonidegib, Advanced basal cell carcinoma, Objective response.

Introduction

Basal cell carcinoma (BCC) is the most common skin cancer; despite its low mortality rate, BCC is associated with great morbidity and an economic burden on health services. Although most BCCs can be cured by surgery or conservative procedures, in a small proportion of patients, the disease can progress to an advanced stage, including locally advanced (laBCC) and metastatic BCC (mBCC)[1]. The morbidity of advanced disease is due to the disfigurement and loss of function of the tissues involved, resulting in reduced quality of life. Consequently, the aim of therapy is primarily to reduce morbidity. When a surgical approach and/or radiation therapy are not feasible, systemic treatment with hedgehog pathway inhibitors (HPIs) is preferred[2,3]. Since sporadic BCC commonly harbors hedgehog pathway aberrations, therapeutic agents targeting key signaling constituents have been developed and tested against advanced sporadically occurring tumors or syndromic disease[4]. In 2013, the Food and Drug Administration (FDA) approved the first hedgehog pathway-targeted small molecule, Vismodegib[5,6].

The multicenter, randomized, double-blind, phase II BOLT trial[7] evaluated the efficacy and safety of Sonidegib in 2015, obtaining an objective response rate (ORR) of 57.6% for laBCC and 7.7% for mBCC treated with Sonidegib 200 mg; more than 50% of responses lasted over 6 months. Based on these results, Sonidegib was approved as a first-line treatment for laBCC. The long-term analysis at 30 months of the same trial

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showed an ORR of 71.2% with the approved dose of 200 mg in laBCC, with a median duration response of 15.7 months[8].

The primary endpoint of the clinical trials[5-8] for Sonidegib, as well as for Vismodegib, was ORR rather than survival, according to the natural history of BCC and clinical aims. In responding patients, treatment should be continued long-term to prevent recurrences, but dose modifications are routinely used in clinical practice to improve patients' compliance. Therefore, it should be important to understand the prognostic significance of treatment discontinuation and dose changes[2]. In order to assess the relevance of AE development and dose changes in patients with laBCC treated with Sonidegib, we performed a retrospective analysis of cases followed up in our center.

Patients and Methods

This was a retrospective monocenter study conducted at San Gallicano Dermatological Institute, IRCCS, Rome, Italy.

Adult patients with a histologically confirmed diagnosis of laBCC and treated with Sonidegib at the standard (200 mg once daily) or reduced dose (200 mg every 2 days), who had completed at least 5 months of treatment between June 2020 and September 2022, were included.

Clinical evaluation was performed at each treatment cycle (28 days), and radiologic imaging was prescribed according to the clinicians' assessment.

The following clinicopathological characteristics were recorded: i) patient characteristics: sex, age at treatment initiation, solitary *vs.* multiple BCCs; ii) anatomic site of the largest (target) BCC; iii) Sonidegib treatment: duration of treatment in months, clinical response, time to best response in months, dose modifications; iv) occurrence of treatment-related adverse events (TRAEs) assessed by clinicians.

We chose ORR as the clinical outcome of interest. In addition, TRAEs and dose adjustments were evaluated.

Statistical Analysis

The associations between the clinical outcome of interest (ORR) and the clinicopathological and treatment characteristics were evaluated. ORR was the sum of complete responses (CR) and partial responses (PR). We also investigated the associations between the occurrence of toxicities and dose adjustments. We reported the categorical variables through absolute and relative frequencies and continuous variables through means, standard deviations (SD), median values and range. When appropriate, the relationships between categorical variables were analyzed using Fisher's exact *t*-test or Pearson's Chi-square test. A univariate logistic regression model was used to identify variables impacting the response. *p*-values lower than 0.05 were considered significant. All statistical analyses were performed using SPSS statistical software version 21 (IBM Corp., Armonk, NY, USA).

Results

Patient and BCC Characteristics

Our study population included 19 patients who had completed at least 5 months of treatment at the time of examination, including nine (47.3%) males and 10 (52.6%) females, with a median age at the start of treatment of 79 years (range, 57-88 years). Ten patients had a solitary BCC, while nine showed multiple BCCs (three out of nine were affected by Gorlin-Goltz syndrome).

Overall, nine of 10 patients with solitary lesions showed localization on the head/neck region, and 55.5% of these tumors involved the eye. Table I summarizes patient, tumor, and treatment characteristics.

Sonidegib Treatment

Table II shows the characteristics of Sonidegib treatment and outcomes. CR was obtained in

Table I. Demographic characteristics of patients and clinical features of BCCs at the time of treatment initiation.

Patients' characteristics	n=19, n (%)
Sex:	
– M	9 (47.4)
– F	10 (52.6)
Age at the start of the treatment (years):	
– Mean±SD	76.9±9.1
– Median (range)	79 (57-88)
BCC lesions:	
Number of BCCs:	
– Solitary	10 (52.6)
– Multiple	9 (47.4)
Anatomical site:	
– Head/neck	18 (94.7)
– Others	1 (5.3)

Basal cell carcinoma (BCC).

Table II. Treatment duration, dose changes, efficacy outcomes, and tolerability.

Sonidegib treatment	N=19 N (%)
Treatment duration (months):	
– Mean±SD	8.5±5.6
– Median (range)	7 (3-24)
Clinical response:	
– Complete response	8 (42.1)
– Partial Response	7 (36.8)
– Progressive Disease	4 (21)
Time to response in patients with CR (months):	
– Mean±SD	3.2±0.9
– Median (range)	3 (2-5)
Dose adjustment:	
– No	5 (26.3)
– Yes	14 (73.7)
Toxicities	
Occurrence of treatment-related adverse events:	
– No	5 (26.3)
– Yes	14 (73.7)
– Median (range):	1 (0-2)
<2	13 (68.4)
=2	6 (31.6)
Type of toxicity:	
– Ageusia/dysgeusia	4 (20.0)
– Muscle cramps	7 (35.0)
– Alopecia	2 (10.0)
– Fatigue	1 (5.0)
– Weight loss	2 (10.0)
– CPK alterations	2 (10.0)
– Gastric problems	1 (5.0)
– Loss of appetite	1 (5.0)

Creatine phosphokinase (CPK), complete responses (CR).

eight (42.1%) patients and PR in seven (36.8%), while four (21%) patients experienced progressive disease (PD).

In four cases, Sonidegib was prescribed full dosage from the beginning to the end of treatment (200 mg/day), while in one case, an alternate regimen was chosen from the beginning to the end of treatment therapy. Fifteen patients (78.9%) received the alternate treatment schedule (200 mg every 2 days), mainly due to the occurrence of TRAEs.

The median duration of exposure to Sonidegib was 10.4 months (3.0-24.0 months), and in the group of patients with CR, the median time of response was 3 months (range 2-5).

TRAEs occurred in 14 (73.7%) patients. The most frequent TRAEs were muscle cramps (7=35%), followed by ageusia/dysgeusia (4=20%) and, equally, alopecia (2=10%), elevated Creatine phosphokinase (CPK) (2=10%), and weight loss (2=10%) (Table II). Three TRAE permanent treatment discontinuations related to CPK elevation were registered. No BCC-related deaths were observed in our patients.

Table III reports the frequency of demographic characteristics, BCC features, and TRAEs in patients with PD or objective response. No significant difference was observed between the two groups for any factor.

Similarly, no significant association was detected between treatment response and the occurrence of toxicities (Table IV). Treatment response and time to best response were not associated with patient sex and age, target BCC site, and presence of multiple BCCs (Table IV).

Discussion

In patients who are not candidates for surgery or other treatment approaches, systemic therapy with HPIs is recommended[3]. The gold standard for patients affected by laBCC/mBCC should aim at the long-term preservation of healthy skin and reversing/limiting the growth of invasive tumors. However, long-term use of HPIs is limited by medication side effects and subsequent discontinuation rate, particularly in syndromic patients[9].

No association was found between demographic or clinical characteristics and response to Sonidegib treatment in our case series. No factors were identified as possible markers of response. The development of TRAEs, followed by dose modification and intermittent therapy, was not associated with treatment response, suggesting that treatment discontinuation does not impair Sonidegib efficacy. The intermittent schedule of Sonidegib is routinely prescribed to reduce the intensity of AEs and maintain patients on treatment, and in our analysis, the alternate regimen has been shown not to compromise overall efficacy outcomes. We found no statistical correlation between any type of response and dose changes. Furthermore, the published literature[2] did not show a correlation between the efficacy of Sonidegib and the occurrence of AEs. Our study confirmed this result.

Although several reports[2] have highlighted the differences between the two approved HPIs, no head-to-head trials are available. We would like to use our experience to make a comparison with the retrospective study published by Fargnoli et al[10] regarding the clinical determinants of response to Vismodegib. Unlike the analysis by

Table III. Frequency of clinicopathological characteristics and TRAEs in patients with progressive disease or objective response.

Demographic and clinical aspects	PD (n=4), n (%)	ORR (n=15), n (%)	Fisher's exact test, *p*-value
Sex			0.087
– Male	0 (0.0)	9 (60.0)	
– Female	4 (100.0)	6 (40.0)	
Age (years):			0.582
– ≤79	3 (75.0)	7 (46.7)	
– >79	1 (25.0)	8 (53.3)	
Multiple BCCs:			0.999
– No	2 (50.0)	8 (53.3)	
– Yes	2 (50.0)	7 (46.7)	
Anatomical site:			0.999
– Head/neck	0 (0.0)	1 (6.7)	
– Others	4 (100.0)	14 (93.3)	
Sonidegib treatment			
Dose adjustment:			0.530
– No	0 (0.0)	5 (33.3)	
– Yes	4 (100.0)	10 (66.7)	
Toxicities (No. AE categories):			0.234*
– 0	1 (25.0)	4 (26.7)	
– 1	3 (75.0)	5 (33.3)	
– 2	0 (0.0)	6 (40.0)	
Ageusia/dysgeusia:			0.530
– No	4 (100.0)	11 (73.3)	
– Yes	0 (0.0)	4 (26.7)	
Muscle cramps:			0.117
– No	1 (25.0)	11 (73.3)	
– Yes	3 (75.0)	4 (26.7)	
Alopecia:			0.999
– No	4 (100.0)	13 (86.7)	
– Yes	0 (0.0)	2 (13.3)	
Fatigue:			0.999
– No	4 (100.0)	14 (93.3)	
– Yes	0 (0.0)	1 (6.7)	
Weight loss:			0.999
– No	4 (100.0)	13 (86.7)	
– Yes	0 (0.0)	2 (13.3)	
CPK alteration:			0.999
– No	4 (100.0)	13 (86.7)	
– Yes	0 (0.0)	2 (13.3)	
Gastric problems:			0.999
– No	4 (100.0)	14 (93.3)	
– Yes	0 (0.0)	1 (6.7)	
Loss of appetite:			0.999
– No	4 (100.0)	14 (93.3)	
– Yes	0 (0.0)	1 (6.7)	

*Chi-square test. Progressive disease (PD), objective response rate (ORR), Basal cell carcinoma (BCC), adverse events (AE), Creatine phosphokinase (CPK).

Fargnoli et al[10], our study was monocentric and had a smaller sample size (19 *vs.* 45). In the publication by Fargnoli et al[10], Vismodegib dosage changes were correlated with a lower probability of achieving a CR, with 70.8% of patients with dosage changes obtaining NCR. Indeed, intermittent dosing has recently been reported[10-12] as a cause of non-response to Vismodegib.

Although the incidence of TRAEs was slightly lower in our patients than in those described by Fargnoli et al[10] (73.7% *vs.* 82.2%), we did not observe a lower TRAE-related response. This difference may be due to the different pharmacokinetic profiles of the drugs. Vismodegib has limited tissue penetration, while Sonidegib is lipophilic and has a higher concentration in tissues than in

Table IV. Statistical correlation between demographic and treatment data categories (e.g., female *vs.* male) and clinical response.

Demographic and clinical aspects		Odd ratio	95% Ci	*p*-value
Sex	Female *vs.* male		Not estimable	
Age (years)	>79 *vs.* ≤79	3.43	(0.29-40.95)	0.330
Multiple BCCs	Yes *vs.* No	0.87	(0.10-7.95)	0.906
Anatomical site	Head/neck *vs.* Others		Not estimable	
Sonidegib treatment				
Dose adjustment	Yes *vs.* No		Not estimable	
Toxicities (No. of AE categories)	1 *vs.* 0	0.42	(0.03-5.71)	0.513
	2 *vs.* 0		Not estimable	
Ageusia/dysgeusia	Yes *vs.* No		Not estimable	
Muscle cramps	Yes *vs.* No	0.12	(0.01-1.53)	0.103

Basal cell carcinoma (BCC), adverse events (AE).

the blood[2]. It is possible that skin concentrations of Sonidegib may be more stable than those of Vismodegib and less subject to rapid change upon dose changes or treatment discontinuation.

Overall, data from long-term clinical trial analyses[8,6] suggest that Sonidegib may be better tolerated than Vismodegib, as the incidence of grade ≥3 TRAEs was 43% and 55.8%, respectively.

This study has some limitations, including the retrospective design, small sample size, and lack of a centralized review for treatment response.

Conclusions

In conclusion, our real-life analysis of patients treated with Sonidegib confirmed the clinical trial data. This suggests that the necessary dose modifications following TRAE development do not compromise treatment efficacy. Sonidegib has widened the treatment landscape of laBCCs or mBCCs. It is a safe and efficient tool that can be used as first-line treatment or as a rechallenge, especially at a reduced dose when AEs affect patients' medication adherence.

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Conflicts of Interest
The authors declare no conflict of interest.

Informed Consent
Starting in June 2020, all individual participants included in the study gave informed consent to the use of their data.

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Authors' Contributions
Study conception and design: GS, LE; collection and interpretation of data: GS, AC; statistical analysis: FS; manuscript drafting: GS; manuscript editing: LE, PF; approval to submit: PF, LE.

Availability of Data and Materials
The data used and analyzed during this research are available from the corresponding author upon reasonable request.

Ethics Approval
The study has been conducted from 2020 to 2022. Institutional Review Board approval was exempted as the study protocol did not deviate from standard clinical practice. The patient received hedgehog inhibitors as in good clinical practice, in accordance with European Guidelines. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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