Dose reduction during routine treatment of locally advanced basal cell carcinoma with the hedgehog inhibitor sonidegib to manage adverse effects: A retrospective case series

To the Editor: Sonidegib is a novel molecule that acts by inhibiting smoothened (SMO) protein, thus blocking the hedgehog pathway and tumor cell transcription. It was approved in July 2015 by the US Food and Drug Administration and is available in 200-mg capsules for patients aged 18 years and older with locally advanced basal cell carcinoma (laBCC) who present with recurrence after other treatments or who are not candidates for surgery or radiotherapy.[1] Muscle spasms (71.2%), alopecia (66.3%), dysgeusia (55.8%) and weight loss (50%) are the adverse effects (AEs) most frequently experienced and can be so severe as to cause treatment discontinuation.[2] The adoption of an alternate dosing regimen consisting of 200 mg sonidegib every other day should be considered to reduce the degree and frequency of emerging AEs, thus increasing patients' compliance and adherence to treatment. However, although the use of an alternate dosing regimen is already reported in the drug data sheet,[3] to date, the effect of dose reduction during sonidegib treatment in real-life experience has not been reported.

Here, we report the data of a single center's experience in dose adjustment in 9 patients with laBCC treated with sonidegib. This retrospective analysis included patients with laBCC treated with sonidegib at the nonmelanoma skin cancer unit at the University of Naples from January 2020 to October 2020. Therapeutic response was divided into complete remission (CR), partial remission (PR) for patients showing greater than 50% tumor regression, stable disease for patients showing up to 50% tumor regression, and progressive disease for patients who presented with greater than 20% tumor increase. Twenty patients received treatment with sonidegib. The medium age at diagnosis was 77.8 years (range, 52-96 years), and 2 (10%) were female. Sixteen (80%) patients had solitary BCC, and 4 (20%) patients presented with multiple primary BCCs. The median duration of sonidegib treatment was 6.5 months (range, 6-9 months).

At treatment end, 12 (60%) patients were considered to have CR, 6 (30%) had PR, and 2 (10%) had stable disease. None presented with progressive disease. Overall, 16 (80%) patients experienced more than 1 AE during sonidegib treatment. For the remaining patients, 1 reported no AEs, 2 (10%) developed dysgeusia, and 1 reported muscle pain. Overall, 9 (45%) of these 20 patients received a modified treatment scheme based on dose adjustment to avoid severe AEs and treatment discontinuation (Table I). Patients who received dose adjustment during treatment showed comparable clinical responses with a milder adverse effect profile compared with patients receiving the daily dosing regimen. In the dose adjustment group, 66.7% (6/9) patients and 33.3% (3/9) presented with CR and PR of the BCC, respectively. Moreover, all of these 9 patients experienced mild (grade 1-2) adverse events. No severe AEs were described. In line with the literature,[4,5] our retrospective study suggests that a dose adjustment regimen

Table I. Characteristics of the 9 patients treated with dose adjustment

Patient/sex (age, y)	Location	Dose reduction scheme*	Response at treatment end	Adverse effects	Degree of adverse effects	Observation period, mo
1/M (80)	Left leg	16 weeks 1/1; 16 weeks 1/2	CR	Dysgeusia, muscle spasms	1-2	8
2/M (67)	Periauricular region	12 weeks 1/1; 16 weeks 1/2	CR	Muscle spasms	1-2	7
3/M (68)	Central face	16 weeks 1/1; 12 weeks 1/2	PR	Fatigue, muscle spasms, dysgeusia	1-2	7
4/M (96)	Central face	20 weeks 1/1; 8 weeks 1/2	CR	Muscle spasms, fatigue, alopecia	1-2	7
5/M (84)	Ocular region	24 weeks 1/1; 8 weeks 1/2	PR	Diarrhea, dysgeusia, muscle spasms	1-2	8
6/M (96)	Multiple BCCs Central face	12 weeks 1/1; 12 weeks 1/2	CR	Dysgeusia	1	6
7/F (82)	Nose	16 weeks 1/1; 16 weeks 1/2	CR	Muscle spasms, dysgeusia	1-2	8
8/M (82)	Multiple BCCs Central face	12 weeks 1/1; 16 weeks 1/2	PR	Muscle spasms, fatigue, alopecia	1-2	7
9/M (85)	Forehead	16 weeks 1/1; 12 weeks 1/2	CR	Muscle spasms, dysgeusia	1-2	7

BCC, Basal cell carcinoma; *CR*, complete remission; *F*, female; *M*, male; *PR*, partial remission.
*Weeks indicates weeks of treatment, 1/1 indicates 1 dose daily, and 1/2 indicates 1 dose every second day.

could be an effective method to reduce the severity of AEs and avoid treatment discontinuation in patients with laBCC treated with hedgehog inhibitors. However, our study is limited by the retrospective design and lack of randomization. Further study is required to better assess the correct treatment scheme.

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Conflicts of interest

None disclosed.

REFERENCES

1. Villani A, Fabbrocini G, Costa C, Scalvenzi M. Sonidegib: safety and efficacy in treatment of advanced basal cell carcinoma. *Dermatol Ther (Heidelb)*. 2020;10(3):401-412.
2. Dummer R, Ascierto PA, Basset-Seguin N, et al. Sonidegib and vismodegib in the treatment of patients with locally advanced basal cell carcinoma: a joint expert opinion. *J Eur Acad Dermatol Venereol*. 2020;34:1944-1956.
3. Odomzo (sonidegib) [package insert]. Sun Pharma Global. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/205266s004lbl.pdf.
4. Wong C, Poblete-Lopez C, Vidimos A. Comparison of daily dosing versus Monday through Friday dosing of vismodegib for locally advanced basal cell carcinoma and basal cell nevus syndrome: a retrospective case series. *J Am Acad Dermatol*. 2020;82(6):1539-1542.
5. Scalvenzi M, Costa C, Cappello M, Villani A. Reply to Woltsche N. et al. Managing adverse effects by dose reduction during routine treatment of locally advanced basal cell carcinoma with the hedgehog inhibitor vismodegib: a single-centre experience. *J Eur Acad Dermatol Venereol*. 2019;33(4):e145-e147.

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