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Sonic Hedgehog Pathway Inhibitors: from Clinical Trials to Clinical Practice

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To the Editor:

Basal cell carcinoma (BCC) is the most common malignancy. It can rarely become locally advanced (laBCC) or metastasize (mBCC). For recurrent, inoperable, laBCC and/or mBCC, Sonic Hedgehog (Shh) pathway inhibitors, vismodegib and sonidegib, are treatment options. This case series evaluates limitations surrounding their use in clinical practice.

This was an IRB-approved retrospective case series of BCC treatment with vismodegib and/or sonidegib at our institution between January 2006 and March 2017, with follow-up through August 2018. Patients receiving concurrent Shh inhibitors and radiotherapy were excluded. The examined outcomes included clinical response, progression free survival (PFS), drug holidays (DH), and adverse effects (AE).

Eight patients met inclusion criteria (Table 1). Median follow-up time was 29.9 (3.7 – 53.1) months. Of the 3 patients who experienced complete response (CR), two had laBCC. The third patient has basal cell nevus syndrome, with some lesions initially experiencing continued growth and others achieving CR. Patients with mBCC experienced partial responses (PR). The median duration of PFS was 11.8 (4.1–34.8) months, with two patients lost to follow-up. The median time that patients were on any SHH inhibitor was 16.3 (1.9–28.3) months.

Two patients (25%) discontinued Shh inhibitors indefinitely due to AE (2 patients). The most common AE were myalgias (75%), dysgeusia (75%), and decreased appetite (62.5%). The median time to the first DH and discontinuation of vismodegib was 6.1 (1.4–8.1) and 13.3 (2.3–52.5) months, respectively.

Data establishing the ideal treatment length with Shh inhibitors is limited, as over 25% of patients discontinue due to AE¹. In our cohort, 37.5% (3/8) of patients underwent treatment breaks/discontinuation due to AE. Consistent with findings that DH does not affect efficacy², they ultimately achieved longer durations of response. In our cohort, the time to first DH was comparable to the previously reported 5.5 months³. Further investigations into

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the strategic use of DH are necessary to maximize treatment benefits, while minimizing AEs.

Increasing data suggests that Shh inhibitors are more efficacious for tumor control than as curative agents^{1,3}. Indeed, vismodegib is already commonly used as part of combination therapies³. CR rates have been reported as 3.9% in mBCC and 31.9% in laBCC¹, with histologic clearance varying from 16–44%⁴. In our cohort, CR rates were 0% in mBCC and 100% in laBCC. All three patients had no evidence of disease at last follow-up. However, given recurrences after CR during DH, continued surveillance even after clinical resolution is necessary, as histologic clearance with Shh inhibitors is uncertain.

Our study reports novel clinical use data regarding patients with mBCC treated with Shh inhibitors. Similar to clinical trial findings⁵, our patients with mBCC were less likely to discontinue treatment due to AE (0%) compared to those with laBCC (50%). All 5 mBCC patients achieved PR, compared with 48.5% in the ERIVANCE study⁵. However, CR rates have been reported at 3.9%¹. Our patients experienced a longer PFS compared with 9.3 months in the ERIVANCE study⁵. The increase in PFS in our cohort may be attributed to the limited sample size.

Clinical trial results of Shh inhibitors have been promising for patients with advanced BCC with limited treatment options. However, uncertainties concerning their application in clinical practice remain. In the authors' experience, long-term use of Shh inhibitors was not sustainable due to patient inability to tolerate adverse effects and the necessity for drug holidays. While Shh inhibitors represent an important therapeutic development for this rare, chemo-insensitive disease entity, given that resistance can arise and that tolerability can be an issue, there remains a need to develop novel therapeutic approaches. In addition, it is important to report on real world long-term use, as adverse event considerations and duration of response should be considered before starting therapy. Our study underscores the need for clinical data reporting on usage of Shh inhibitors.

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Table 1.

Clinical overview of patients treated with Sonic Hedgehog pathway inhibitors.

Detailed descriptions of clinical characteristics and treatment course for patients treated with Shh inhibitors. + indicates ongoing length of time after last-follow up. Abbreviations: BCC, basal cell carcinoma; BCCNS, basal cell carcinoma nevus syndrome; CR, complete response; PR, partial response; DOR, duration of response; f/u, follow-up; POD, progression of disease; SHHi, sonic hedgehog inhibitor

Characteristics	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8
Age/Race/Sex	71/White/F	62/Albino White/M	63/White/M	69/White/F	58/White/F	73/Asian/M	62/White/M	94/White/M
Locally advanced / metastatic	Locally advanced	Metastatic	Metastatic	Metastatic	--- (BCCNS)	Metastatic	Metastatic	Locally advanced
Surgical margins status	Negative	Negative	Positive	Positive	---	Positive	Unknown	Unknown
Prior radiation/chemotherapy	Yes/No	No/No	Yes/Yes	Yes/No	No/Yes	Yes/No	Yes/No	No/No
SHHi	Vismodegib	Vismodegib	Vismodegib	Vismodegib followed by sonidegib	Vismodegib	Vismodegib followed by sonidegib	Vismodegib	Vismodegib
Indication for SHHi	Patient preference	Metastasis	Metastasis	Metastasis	BCCNS	Metastasis	Metastasis	Patient preference
DOR (months)	42.7+	17.3	11.8	9.2	--- (variable response)	30.0 (lost to follow-up)	4.1+ (lost to f/u)	6.0+
Time until discontinuation of vismodegib (months)	39.1	13.8	12.8	9.2	52.5+	29.3	2.8	2.3
Total Time on any SHHi excluding drug holidays (months)	26.0	19.8	12.8	9.5	27.1+	28.3	1.9	1.9
Best overall response	CR	PR	PR	PR	CR	PR	PR	CR
Drug holidays (and cause)	1 (co-morbid psychiatric issues)	---	---	---	2 (weight loss; appetite loss)	3 (dental procedure; fatigue; failure to thrive)	---	1 (dental procedure)
Duration to 1 st drug holiday (months)	4.8	---	---	---	7.3	8.1	---	1.4
Drug status (and cause if discontinued)	Off drug (CR)	Off drug (POD)	Off drug (POD)	Off drug (POD)	On pulsed dosing: 1 week on, 1 week off	Off drug (adverse effects and hospitalization)	Off drug (hospitalization)	Off drug (adverse effects)