Treatment of periocular advanced basal cell carcinoma (laBCC) with Hedgehog pathway inhibitors (HPIs): A single-center study and a new dedicated therapeutic protocol

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Objective

To evaluate the outcomes of HPIs treatment in patients affected by periocular laBCC. We focused on the common adverse events (Aes) and their correlation with the administration schedule, to determine a management protocol specific for the periocular area.

Methods and materials

This observational prospective study included patients who were histologically confirmed to have periocular or orbital laBCC and were treated with HPIs since January 2016 in our Department. Inclusion criteria were: lesions considered inoperable, previously administered radiotherapy unless inappropriate, and at least two cycles of HPI therapy.

Results

Table 1 shows the population sample for the study. Discontinued patients (n=9/15, 60%): 3 patients treated with vismodegib discontinued the drug upon complete response (CR) after an average drug intake of 12 months. 1 patient with a partial response (PR) with vismodegib treatment died after 5 months of treatment from cancer-independent causes. 5 patients who responded well to vismodegib had to stop treatment due to Aes after approximately 5 cycles of treatment. Of these 5 patients, 4 are currently in stable condition, and one patient progressed at about 3 months after the interruption. This latter patient is stable and has successfully undergone surgery. Ongoing patients (n=6/15, 40%): 2 patients were being treated with sonidegib. One of these patients achieved a PR characterized by efficient re-epithelialization *(Fig.1)*. The second patient had previously been treated with multiple surgeries. Ongoing treatment with sonidegib at 200 mg daily led to a significant reduction of the extraorbital invasion after only 4 cycles. 2 patients are currently on an approved schedule treatment with vismodegib. They had a PR after 12 cycles on average. 2 patients treated with vismodegib underwent the first four months of continuous treatment according to the label then, after a PR, they had to be administered an off-label alternative schedule due to intolerable Aes. The most common Aes were: dysgeusia and muscle spasms (80%), followed by weight loss (46.67%); fatigue (40%); anorexia, alopecia, and laboratory alteration (33.33%); nausea and constipation (13.33%); and diarrhea and mood alteration (6.67%).

Conclusion

The possibility of an alternative schedule to the label, the potential as a valid neoadjuvant therapy, the lower incidence and the slower onset of most Aes convinced us to gain more experience with sonidegib. Moreover, our data could lead to a new type of therapeutic scheme *(Fig.2)*. In this approach, periocular BCCs that are not amenable to surgery undergo approximately 4 cycles of neoadjuvant sonidegib at 200 mg daily. If this treatment leads to CR, a pulsed therapy can be applied (sonidegib 200 mg daily one week on and 3 weeks off) until unacceptable toxicity arises. Conversely, if there is a PR after the neoadjuvant approach and the lesion is resectable, the patient may undergo surgery and then pulsed therapy. If there is PR but the BCC cannot be excised, the patient may be put on the approved sonidegib dose of 200 mg every other day for approximately 3 cycles and then reassessed for resectability.

Characteristics	Locally advanced BCC (N=15)
Median age-yr (range)	87 (63-94)
Male sex, n. (%)	7 (46.67)
Patients previously treated with surgery -not eligible for radiotherapy, n. (%)	8 (53,33)
Patients previously treated with radiotherapy after surgery, n. (%)	2 (13.33)
Patients not eligible for surgery and radiotherapy (%)	5 (33,33)
Primary BCC site, n. (%)	
Medial canthus	8 (53.33)
Later canthus	6(40)
Lower eyelid	1 (6.67)
BCC with orbital interest	5 (33.33)
Discontinued patients (%)	9(60)
CR	3(20)
PR	12(80)
Withdrawn for AEs	5 (33.33)
Death for other causes	1 (6.67)
Ongoing patients (%)	6(40)

Table 1 - Patient characteristics and exposure to HPIs

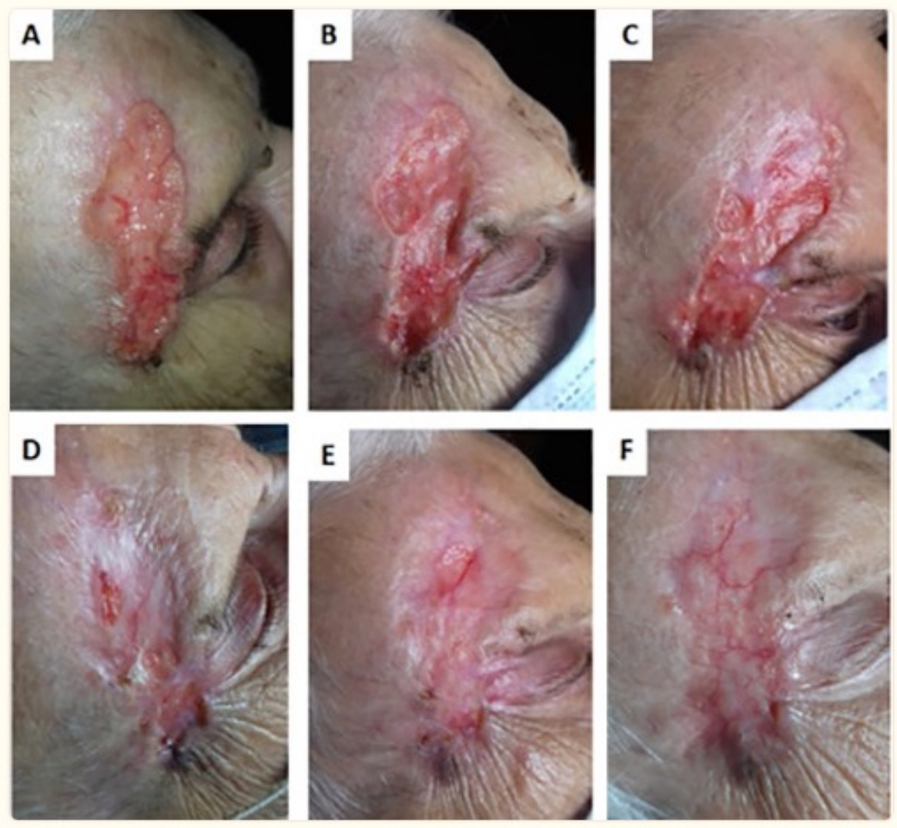

Fig. 1 - 200 mg of daily sonidegib at baseline (A), 1 month (B), 2 months (C), 3 months (D), 4 months (E), and 5 months (F)

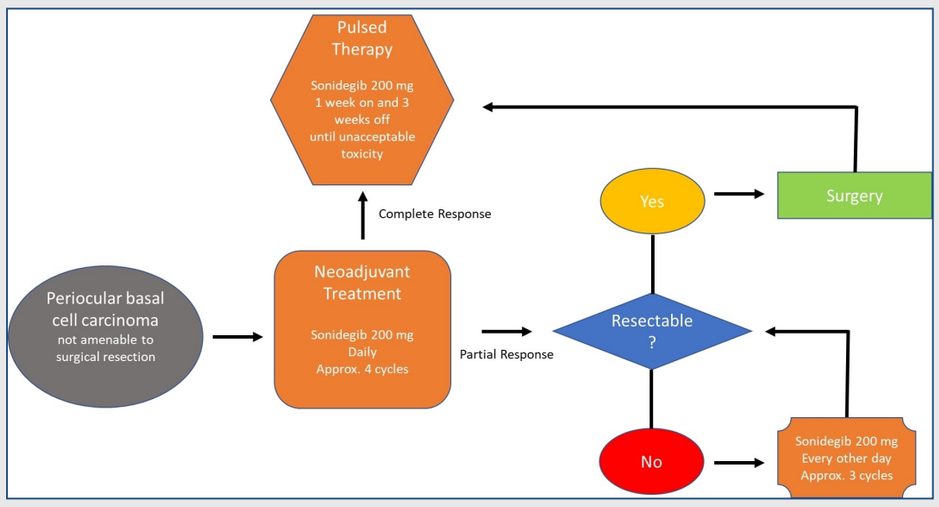

Fig. 2 - Treatment algorithm

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