Substantial reduction of basal cell carcinoma tumor size with itraconazole following treatment failure with intralesional 5-fluorouracil

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Dear Editor,

Basal cell carcinoma (BCC) is the most common nonmelanoma skin cancer in humans. The pivotal abnormality in all BCCs is associated with malignant activation of the sonic hedgehog (SHH) signaling pathway [1].

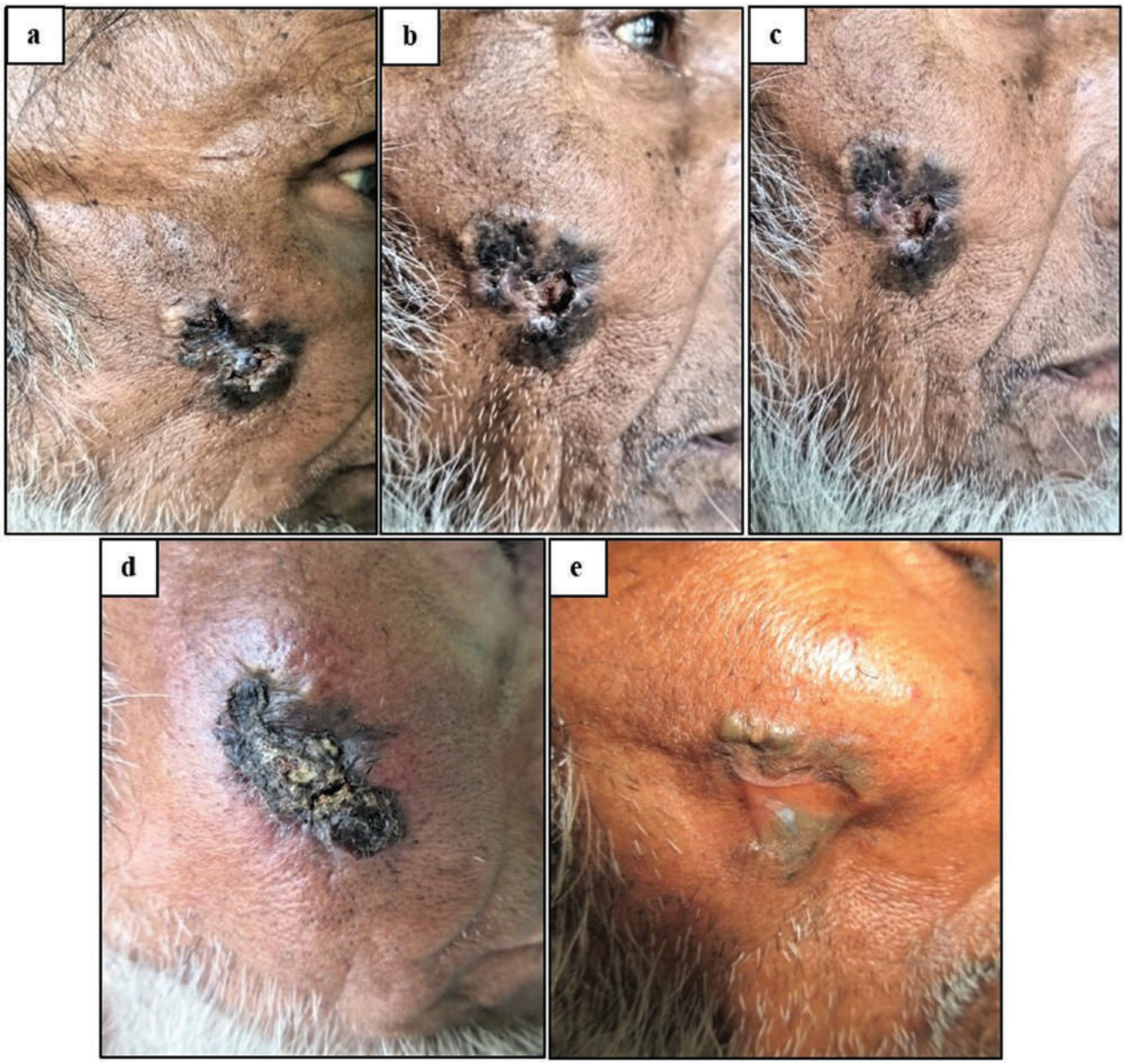
Itraconazole, though primarily an antifungal drug, has been found to be useful in the treatment of BCC. Its role in BCC has been linked to its potent antagonistic activity against the SHH pathway, thereby facilitating reduction in tumor size and proliferation [2]. Furthermore, it has been reported that itraconazole can reduce the SHH pathway by 65% after 1 month of therapy [3].

Our patient was a 75-year-old man who complained of a lesion over the right cheek since the past 2 years. It began as a pea-sized asymptomatic nodule that gradually progressed to attain the current status. There was no history of past treatment/radiation and/or immunosuppression. Examination revealed a 2×2.5-cm pigmented noduloulcerative lesion with well-defined borders over the right cheek (Fig. 1a). Skin biopsy delineated focal ulceration of the epidermis with dermal islands of malignant basaloid cells showing peripheral palisading and a mucoid stroma containing plump spindle cells. No evidence of perineural invasion was observed in the biopsy specimen. A diagnosis of BCC was made and based on tumor size and location (that suggested high risk BCC based upon National Comprehensive Cancer Network guidelines), the patient was advised either Mohs micrographic surgery or standard surgical excision with postoperative margin evaluation and complete margin assessment, with intraoperative frozen section analysis or permanent margin analysis with delayed tissue repair at a higher center, as provisions for these surgeries were not available in our institute. However, the patient desired a nonsurgical alternative and declined any form of surgical intervention.

Owing to unavailability of radiotherapy in our institute, this therapeutic modality could not be employed. Furthermore, because of patient's limitations with regard to family/health issues, he was unable to go to any higher center for this treatment. We, therefore, decided to treat him with the resources that were available at our institute.

As microscopy did not specify an aggressive histological expression of BCC, we initiated therapy with intralesional 5 FU (150 mg/week) for 16 weeks. Following 16 weeks of treatment with intralesional 5 FU, improvement witnessed was negligible (Fig. 1b). We waited for a period of 12 weeks (wherein no drugs were administered to the patient) to assess any residual benefit of 5 FU that had been previously injected into the tumor. Follow-up after the stipulated time did not delineate any reduction in tumor size (Fig. 1c). The patient was then started on itraconazole (100 mg twice daily) for 8 months. At the end of 4 months, surface changes of the growth could be appreciated (Fig. 1d),

Figure 1



(a) Pigmented noduloulcerative basal cell carcinoma (BCC) over the right cheek at initial presentation. (b) Negligible reduction in tumor size after 16 sessions of intralesional 5-fluorouracil. (c) Clinical status of the tumor after 12 weeks of cessation of intralesional 5-fluorouracil. This demonstrates lack of any form of residual activity with respect to the drug. (d) Textural changes seen over the tumor after 4 months of initiation of therapy with systemic itraconazole. (e) Satisfactory reduction of BCC tumor size witnessed after 8 months of systemic itraconazole therapy.

and after 8 months of itraconazole intake, substantial reduction in tumor size was observed (Fig. 1e).

Itraconazole was started on account of treatment failure with 5 FU. This unresponsiveness with 5 FU could perhaps be attributed to regional drug resistance.

It has been documented that like vismodegib and cyclopamine, itraconazole acts on the essential HH pathway component Smoothened (SMO), but at another, yet distinct site [2]. Furthermore, it has also been elucidated by in-vitro signaling studies that the beneficial role of itraconazole in BCC is dose dependent. Besides, both high-dosing (200 mg twice daily) and low-dosing (100 mg twice daily) protocols with itraconazole have been found to be equally effective in reducing the tumor size [4].

Kim *et al.* [4] in their report outlined clinical outcomes following institution of itraconazole monotherapy (dosing: 100 mg OD to 200 mg BD) for BCC for a period of 1–12 months. Of these, 57 primary BCCs in eight patients demonstrated a mean area reduction of 24%.

Another report from Poland elaborated slight clinical improvement following oral itraconazole monotherapy

for locally advanced facial BCC in a 70-year-old man. Skin lesions in this patient stopped seeping, and temporal ulceration had healed partially following 8 months of treatment with itraconazole [5].

Ip and McKerrow [6] though did not demonstrate profitability of itraconazole (200 mg/day) for cutaneous BCC. However, they did elucidate 30% reduction of pulmonary metastasis secondary to BCC, following itraconazole administration.

Yoon [7] reported complete regression of advanced facial BCC in two patients following low-dose vismodegib (150 mg once/twice per week) and itraconazole (100–200 mg/day).

After studying these reports, itraconazole definitely seems to hold promise as a new player for BCC therapy. However, one striking observation was that itraconazole monotherapy was ineffective in bringing about complete regression of the tumor, similar to our finding. Only the report where vismodegib (low dose) and itraconazole were combined, was complete tumor remission obtained. So, whether itraconazole could be utilized as a valuable adjunct along with other treatments (medical and/or surgical) is something worth contemplating upon.

Currently, the exact duration of treatment with itraconazole for BCC has not been determined. Moreover, chronic administration of itraconazole, as well as likely adverse effects following its long-term intake, needs careful study. A report of Aspergillus spondylodiscitis in a patient with acute myeloid leukemia receiving 600–900 mg of itraconazole per day, however, elucidated a manageable toxicity profile [8].

Currently, our patient is being maintained on itraconazole (100 mg Q12H), and even after a year of follow-up, there has neither been any increase or reduction in tumor size as when observed after 8 months of initiation of therapy. Besides, our patient is being maintained well on the drug without any untoward effects.

Based on our findings, we suggest that itraconazole can be considered a second-line agent in certain cases of BCC, especially in those scenarios where access to surgery/radiotherapy (for BCC) is not available or when patients decline surgery or are unsuitable candidates for the same. However, more reports in this regard would help in strengthening our observation further.

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Conflicts of interest

There are no conflicts of interest.

References

1 Epstein EH. Basal cell carcinoma: attack of the hedgehog. Nat Rev Cancer 2008; 8:743–754.

2 Kim J, Tang JY, Gong R, Kim J, Lee JJ, Clemons KV, *et al.* Itraconazole, a commonly used antifungal that inhibits hedgehog pathway activity and cancer growth. Cancer Cell 2010; 17:388–399.

3 Tang JY, Mackay-Wiggan JM, Aszterbaum M, Yauch RL, Lindgren J, Chang K, *et al.* Inhibiting the hedgehog pathway in patients with the basal cell nevus syndrome. N Engl J Med 2012; 366:2180–2188.

4 Kim DJ, Kim J, Spaunhurst K, Montoya J, Khodosh R, Chandra R, *et al.* Open label exploratory phase â¡ trial of oral itraconazole for the treatment of basal cell carcinoma. J Clin Oncol 2014; 32:745–751.

5 Ciazynska M, Narbutt J, Skibinska M, Lesiak A. Itraconazole – a new player in the therapy of basal cell carcinoma: a case report. JCO Oncol Pract 2020; 16:837–838.

6 Ip KH, McKerrow K. Itraconazole in the treatment of basal cell carcinoma: a case based review of literature. Austra J Dermatol 2021; 62:394–397.

7 Yoon J. Vismodegib dose reduction effective when combined with itraconazole for the treatment of advanced basal cell carcinoma. JAAD Case Rep 2021; 7:107–109.

8 Takagi K, Yoshida A, Yamauchi T, Yamashita T, Iwasaki H, Tsutani H, *et al.* Successful treatment of Aspergillus spondylodiscitis with high dose itraconazole in a patient with acute myelogenous leukemia. Leukemia 2001; 15:1670–1671.

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