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Fast and safe clinical response to sonidegib in a 98-year-old woman affected by locally advanced basal cell carcinoma

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Abstract

A 98-year-old woman presented with histologically confirmed locally advanced basal cell carcinoma of the face. A multidisciplinary approach excluded surgery because of the site near sensitive organs, extension, age, and comorbidities. Patient and caregivers declined radiotherapy considering the necessity of multiple hospital appointments. The patient was then placed on therapy with sonidegib, an oral inhibitor of the Hedgehog signaling pathway. There was a very rapid clinical response after only 28 days of treatment. The basal cell carcinoma improved progressively, with no adverse events reported. This case illustrates the efficacy and safety of this treatment in an advanced age patient. This treatment had a remarkably positive impact on quality of life, including that of the caregivers.

Keywords: advanced carcinoma, basal cell, face, Hedgehog inhibitor, sonidegib

Introduction

Basal cell carcinoma (BCC) is a skin carcinoma derived from either follicular and interfollicular epithelial cells and is the most common malignant tumor in light-skinned populations (75% of all skin cancers). Sporadic BCCs usually result from mutations driving activation of the Hedgehog (Hh) pathway, with 90% inactivating mutations of the protein patched homolog one gene (*PTCH1*) and 10% activating mutations of smoothened gene (*SMO*). Very few BCCs have no mutations in the Hh pathway. A recent classification divides "easy-to-treat" (95%), and "difficult-to-treat" BCC [1]. Easy-to-treat BCCs can be easily managed by standard surgery or by topical/destructive non-surgical methods (curettage, electrocautery, cryotherapy, laser ablation, photodynamic therapy, imiquimod, 5-fluorouracil). Difficult-to-treat BCCs include locally advanced tumors and BCCs with specific management difficulties. Locally advanced BCCs are usually long-term untreated or recurrent tumors that invade and destroy surrounding tissues and are difficult or impossible to manage through standard surgery or radiotherapy [2]. Management of difficult to treat BCCs include surgery (as a palliative option or following a neoadjuvant approach), or radiotherapy in patients who refuse, or have contraindication to surgery. When surgery may be disfiguring or may result in functional impairment, the Hh pathway inhibitors (Hhi), vismodegib and sonidegib, are very important medical treatment options. The anti-PD1 antibody, cemiplimab has been recently approved as a second-line treatment of adult patients who have progressed during Hhi treatment or are intolerant to Hhi therapy [3].

Case Synopsis

Herein, we report a 98-year-old woman with locally advanced BCC of the face. The tumor appeared four years earlier as a nodule of the left nasal ala and gradually grew over time. About 10 years earlier the patient had an ulcerated invasive BCC with baso-squamous features completely removed in the same anatomical site. Comorbidities included arterial hypertension on diuretic therapy, hyperuricemia on allopurinol, and monoclonal gammopathy of

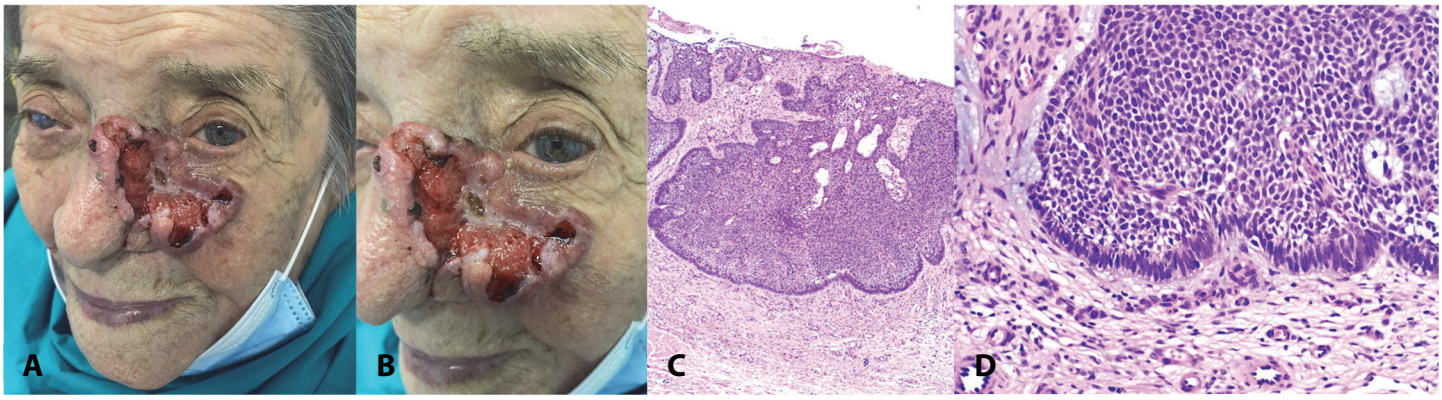

Figure 1. ***A)*** *Large ulcerated plaque on the face, before treatment.* ***B)*** *Closer view of the lesion.* ***C)*** *Histopathology from a punch biopsy showing the typical features of basal cell carcinoma. H&E, 10×.* ***D)*** *Higher magnification of the basal cell carcinoma nodule of BCC. H&E, 20×.*

uncertain significance, IgA type, under hematological follow-up. When the patient presented to our department, the tumor involved the left nasal ala, the ipsilateral malar region and the left lower eyelid. It was ulcerated, had raised and infiltrated margins, and it was bleeding. No associated symptoms were reported. The extension of the lesion was approximately 80mm latero-lateral and 70mm cranio-caudal (**Figure 1A**, **B**). The tumor underwent biopsy, which confirmed the suspicion of BCC, invasive and ulcerated (**Figure 1C**, **D**). A maxillofacial staging magnetic resonance was also performed, showing that the tumor involved the subcutaneous fat and went beyond the muscular plane, without evident involvement of the bones. Ipsilateral eyeball was not involved. Routine laboratory tests confirmed the monoclonal component in the IgA lambda type (14.3g/L normal value), elevated beta2-microglobulin (6.60mg/L; normal range <0.607mg/L), and mild anemia (hemoglobin 10.61g/dL; normal range 12.0-16.0g/dL), normal liver and renal function tests, normal creatine kinase (normal range <140U/L), glycose, and electrolytes.

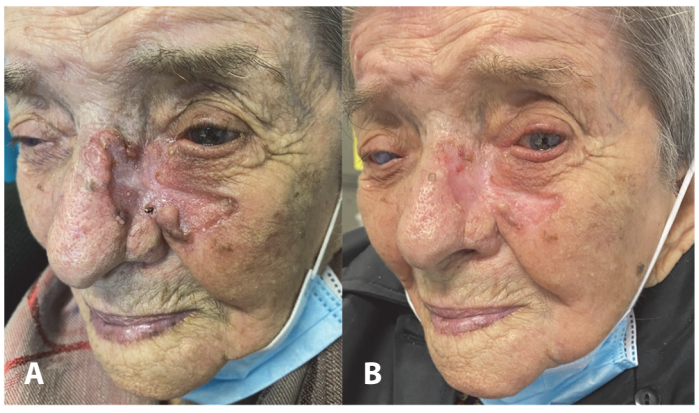

Figure 2. ***A)*** *Clinical evaluation after 28 days of sonidegib treatment.* ***B)*** *Clinical evaluation after three months of treatment.*

A multidisciplinary evaluation excluded surgery because of the site, extension, age, and comorbidities. Patient and caregivers declined radiotherapy considering the necessity of multiple hospital visits. Therefore, medical therapy with sonidegib 200mg/daily was started. After 28 days of treatment, she presented with a remarkable reduction in tumor size (**Figure 2A**). The tumor had flattened and margins were less infiltrated, with resolution of ulceration and almost complete re-epithelialization. The superior edge of the BCC no longer reached the inferior ipsilateral eyelid. No adverse events were reported and creatine kinase values persisted in the normal range. During the monthly follow-up, our patient showed progressive clinical improvement; no adverse events were reported and laboratory findings remained stable. A further reduction in size was observed at the control visit after three months of treatment, with a residual central fibrotic area surrounded by almost completely smoothed margins (**Figure 2B**). After four months, sonidegib was discontinued because the caregivers could no longer accompany the patient to the visits. Patient's clinical condition is currently stable.

Case Discussion

The locally advanced BCC of our patient was not surgically resectable. Radiotherapy is considered a

consensus-based option for BCC on the face, including periorbital regions, in elderly patients and in patients who are not amenable to surgery [4]. However, the experience of each center and patient choice influences the therapeutic decision, as in our case. Hedgehog pathway inhibitors are the first-choice medical therapy in cases of locally advanced BCC unresectable and or untreatable with radiotherapy. Our patient was placed on therapy with sonidegib for several reasons. According to the data from the BOLT pivotal trial, sonidegib has an optimal benefit-risk ratio and no dosage adjustment is required, as supported by safety and efficacy data even in patients older than 65 years [5-6]. Furthermore, sonidegib is well tolerated and is also approved in an every-other-day dose schedule, a valuable option in long-term treatment [7,8]. In our case, no adverse events were reported, supporting an optimal tolerability and safety profile also in elderly patients.

Our patient's advanced tumor had significant impact on her quality of life due to visual limitation and the impossibility of wearing her prescription glasses. Moreover, she required continuous family support for wound dressings. After only 28 days of therapy, life quality of the patient and caregivers improved significantly. No more wound dressings were required and the shrinking of the tumor permitted a wider visual field.

A very rapid response, as in the case here reported, is fundamental for BCC occurring in sensitive and visible areas as the head and neck. Moreover, the rapidity of clinical improvement favors medical and economical management of patients with locally advanced BCCs. Follow up was not very long but the tumor continued to reduce in size. Surgery should be considered if lesion dimensions allow curative surgery. In the case of tumor recurrence, we would consider retreating our patient with sonidegib since it was well-tolerated and Hhi-therapy seems to be the most effective approach, with response rates of 85% in case of relapse after discontinuation [9].

Conclusion

The therapy for difficult-to-treat BCCs may benefit from a multidisciplinary approach. In the case of unresectable and radiotherapy-untreatable BCCs, the first choices for medical therapy currently are Hh pathway inhibitors. Sonidegib is an oral small molecule, which binds to the SMO receptor and suppresses the Hh signaling pathway [10]. In 2015, it gained FDA and EMA approval to treat patients aged >18 years with locally advanced BCC who are not amenable to curative surgery or radiation therapy. Medical therapy with sonidegib is easily manageable unlike other approaches used for difficult to treat BCCs and it is generally safe. Possible adverse events include muscle spasms, dysgeusia, alopecia, fatigue, raised creatine kinase levels, nausea, diarrhea, decreased appetite and weight, myalgia, and headache [11]. These adverse events could cause drug discontinuation. This case underlines the interesting possibility of using Hhi as neoadjuvant therapy to reduce tumor size, allowing access to standard surgery and a better cosmetic result.

Potential conflicts of interest

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