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Case Report
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Overcoming Resistance to Hedgehog Inhibitors with Radiotherapy: The First Clinical Case of Concurrent Sonidegib and Radiotherapy for Advanced Basal Cell Carcinoma Progressing on Hedgehog Inhibitors

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Abstract

Introduction: Basal cell carcinoma is the most common human skin cancer. Systemic therapy with a hedgehog inhibitor should be considered as first-line treatment of unresectable advanced BCC. Some case reports were published on concurrent use of radiation therapy with hedgehog inhibitors and have especially been focused on vismodegib.

Case Report: We present a case report of a patient with locally advanced basal cell carcinoma involving a large and high-risk area of the face who, after an initial response to the hedgehog inhibitor sonidegib, progressed during treatment. The patient then received combined treatment of fractionated radiation with concurrent sonidegib and had complete clinical response with no significant toxicities.

Conclusion: This is the first reported case on the use of concurrent radiotherapy and sonidegib for management of locally advance basal cell carcinoma of the head and neck progressing during hedgehog inhibitors treatment. It suggests that radiotherapy may be useful to overcome the resistance to the hedgehog inhibitor, retain the patient on the most efficacious first-line hedgehog inhibitor and avoid or postpone the switch to the second-line immunotherapy.

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Introduction

Basal Cell Carcinoma (BCC) is the most common human skin cancer, with an incidence rate of over 4 million cases annually worldwide. Standard surgical excision or Mohs surgery is the primary modality and most effective and efficient treatment [1]. Radiotherapy (RT) is an option for patients with high-risk BCC who are not candidate to surgery and is an important option for cosmetic and functional preservation.

In advanced BCC, which is defined as locally advanced (laBCC) and metastatic BCC (mBCC, a rare scenario for BCC that refers to distant metastases or nonregional lymph node or skin involvement) that are not amenable to curative surgery or RT [2], systemic therapy with a Hedgehog pathway Inhibitor (HHI) should be considered as first-line treatment per current guidelines. The two HHI approved for laBCC are vismodegib and sonidegib. They work as cell surface receptor Smoothened Homolog (SMO) inhibitors, blocking activation of the hedgehog pathway [3]. Per current guidelines, treatment with cemiplimab, an anti PD-1 immunotherapy, is recommended as second line therapy for those patients that progress during therapy with HH inhibitors [4].

Literature reports on concurrent use of RT with SMO inhibitors have been few and far between, and were mostly focused on vismodegib. Current ASTRO guidelines suggest avoiding concurrent use of radiation [5] and SMO inhibitors due to the lack of clinical data demonstrating tolerability. Here, we report the first case of concurrent RT and sonidegib in a patient with laBCC of the head

and neck progressing during treatment with sonidegib.

Case Presentation

The patient, born in 1933, is a 90-year-old female with past medical history of arterial hypertension. Her cancer history began with a nasal tip skin lesion, for which she was followed by a dermatologist with local treatments. After two years the lesion started to grow rapidly with swelling underlying the right nasogenian sulcus with deformation of the bone and large ulceration of the nasal pyramid. A core biopsy was performed on September 2021 and showed basal cell carcinoma, nodular type. The patient went to another hospital and was visited by a new dermatologist that reported the presence of a 3 cm lesion involving the right alar rim, nasal tip, and right nasal sidewall. Given the extensive disease prohibitive of surgical resection without cosmetic deformity, she was deemed unsuitable for surgery and referred to medical oncology. On September 07th, 2021, she was seen by medical oncologist and was started on sonidegib (200 mg daily) (Figure 1 and 2; September 2021). She had an initial partial response with a clinical reduction in size of the BCC (Figure 3; August 2022) and minimal side effects except for grade 1 fatigue and grade 1 dysgeusia. Partial remission continued until December 2022, without significant toxicity then progressed clinically since January 2023.

On February 28th, 2023, an MRI with contrast showed an infiltrating lesion in the right nasogenian sulcus and the right nasal surface with dimensions of 58 mm × 52 mm × 52 mm. On March 2023, the patient arrived at our hospital. Looking at the progressing lesion, according to the regulatory guidelines, we should have stopped the treatment with sonidegib and start immunotherapy with the anti PD-1 monoclonal antibody, cemiplimab. Instead, we decided to continue sonidegib 200 mg/day and to treat the patient with concomitant RT. The patient received VMAT (Volumetric modulated Arc Therapy) intensity-modulated radiation therapy with 60 Gy in 30 fractions with concurrent sonidegib 200 mg/day from March 30th to May 15th, 2023. A 0.7 cm CTV margin and a 0.5 mm PTV margin were used. A thermoplastic mask was used for immobilization. Images before and after the radiation treatment are displayed in Figures 4 and 5, respectively. The MRI with contrast performed on July 04th, 2023, after the radiotherapy, showed stable disease. She tolerated the treatment well and side effects were limited to fatigue, crusting inside his nasal passage, and erythema of his nasal skin managed with symptomatic treatment. After one month, patient reported the resolution of the acute symptoms. On September 2023, the patient achieved clinical complete remission (Figure 6). On November 30th, 2023, a new MRI with contrast showed a major

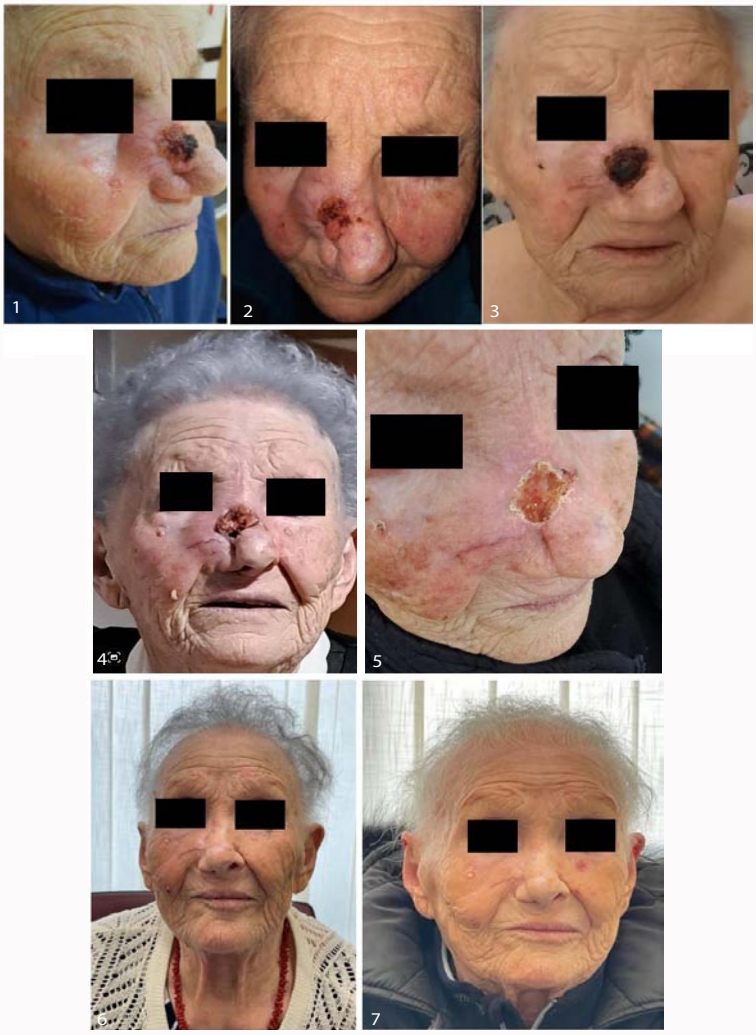

Figure 1 and 2: Diagnosis of locally advanced unresectable BCC [September 2021]; **Figure 3**: Response to sonidegib [December 2022]; **Figure 4**: Progression of disease [February 2023]; **Figure 5:** End of radiotherapy [May 2023]; **Figure 6:** Complete remission [September 2023]; **Figure 7:** Complete remission [December 2023].

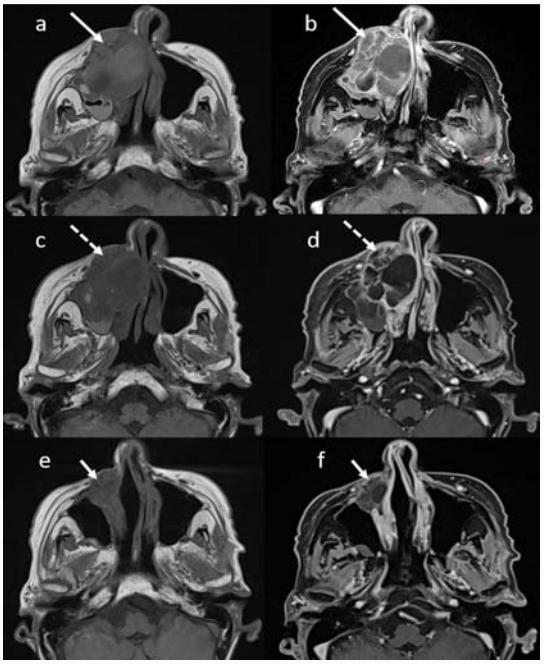

Figure 8: a) and b): Baseline MRI of 28 FEB 2023 that documented the progression of disease; c) and d) MRI of 04 Jul 2023, performed after Radiotherapy, that showed stable disease; e) and f) MRI of 30 Nov 2023 demonstrating major partial response (near complete remission).

partial response (near complete remission) for a significant reduction in volume of the lesion in the right nasogenian sulcus and the right nasal surface with minimal residual tissue. The patient continues the treatment with sonidegib at the same dosage and schedule (Figure 7, 8).

Discussion

Sonidegib has only been used as a single agent in laBCC. This inhibitor was approved by international guidelines for patients with laBCC based on the phase II, multicenter, randomized and double-blinded BOLT clinical trial [6]. This trial evaluated two doses of sonidegib (800 mg or 200 mg daily) in patients with laBCC or mBCC until disease progression or unacceptable toxicity. The study demonstrated a clear role of SMO inhibitors in the treatment of advanced BCC, with high objective response (74% by investigator review), long-term efficacy and a manageable safety profile in patients with laBCC [6].

This is the first reported case of the use of sonidegib concurrently with RT in a patient progressing on HH inhibitor treatment. The patient had excellent clinical response (Figure 6) and minimal acute side effects.

We decided to treat this patient progressing on sonidegib with RT, continuing the treatment with the HHI due to several considerations. The combination of HHI and RT was described in some case reports with good safety data and high response rates. Vismodegib has been previously used concurrently with RT, albeit in small clinical series. Pollom et al. [7] reported 2 cases of recurrent advanced BCC treated with concurrent RT and vismodegib with good efficacy and tolerance, and no evidence of progressive disease at follow-up. Another case reported by Raleigh et al. [8] on an auricular laBCC treated with induction vismodegib and radiation showed durable local control and acceptable level of acute toxicity. Schulze et al. [9] reported 4 cases (3 recurrent BCC, 1 with locoregional lymph node involvement) treated with concurrent vismodegib and RT. Three of the 4 patients experienced a persistent complete response, whereas one case remained stable for 6 months before further tumor progression. There are no trials directly comparing sonidegib with vismodegib. Existing studies attempted to indirectly compare the BOLT (sonidegib) and ERIVANCE (vismodegib) trials using statistical adjustments. Odom et al. [10] found that in laBCC, sonidegib has a higher Objective Response Rate (ORR), longer median progression-free survival, and longer median duration of response. Similarly, Dummer et al. [11] found higher ORR, slightly less frequent and less severe AEs and later onset of most AEs for sonidegib compared with vismodegib. The expert also concluded that differences in efficacy and tolerability between the two HHI may be explained by a different pharmacokinetics, with sonidegib being extensively distributed in the skin [11]. In mBCC however, sonidegib has a lower ORR compared to vismodegib [12].

The patient, a 90 years old woman, needed a fast response on the progressing lesion that already closed her right nasal cavity and infiltrated the bone of her face. The radiotherapy could have had a synergistic effect with sonidegib giving the fast response that the patient experienced according with the preclinical data published so far. There are several hypotheses on possible mechanisms of action for combination therapy with radiation and HHI. Ionizing radiation are able to cause direct and indirect damage to cellular DNA while the hedgehog pathway has been found to be responsible for resistance to radiotherapy and chemotherapy and recurrence in multiple types of cancers [3]. Therefore, the combination of radiotherapy and a hedgehog inhibitor makes sense theoretically. Molecular and animal studies demonstrated that radiotherapy induce expression of selected HH target genes, and that HH signaling is involved in the maintenance of cancer stem cells, which are intrinsically resistant to radiation and some chemotherapies [13,14]. Gu et al. [14] also demonstrated that the combination of focal radiation with HH inhibitor has 'more than additive' inhibition of tumor metastasis as shown in an orthotopic mouse model for pancreatic cancer. There was also increased sensitivity to radiation in both the aforementioned mouse model and in basal cell carcinoma and head and neck squamous cell carcinoma cell lines [15].

In case of further progression of disease, the radiotherapy should not to be considered a useless treatment because of the possibility of the ionizing radiations to "inflame" the basal cell carcinoma with the recruiting of inflammatory cells, and consequent changing of the tumor microenvironment, much more prepared to anti PD-1 based immunotherapy [16].

Anyway, adding the radiotherapy, the patient who was progressing on sonidegib, achieved a clinical complete response in only 4 months, with minimal side effects and long-term durability. The treatment with sonidegib at 200 mg/day was never interrupted before, during and after radiotherapy, clearly demonstrating that the radiations overcame the resistance to sonidegib without limiting toxicities. The effect of the combination resulted long lasting because the complete remission is still ongoing 7 months after the end of the radiotherapy. The combination of HHI and radiations allowed to prolong the first-line sonidegib treatment, to achieve a significant and long-lasting response beyond resistance and avoid or postpone the less efficacious second-line treatment with immunotherapy by several months or maybe years later, therefore improving OS. Recently, a panel of

experts recommended keeping patients on HHI as long as possible and limiting immunotherapy to those who developed resistance during HHI therapy or in case of persisting toxicity despite long-term management of adverse events (*e.g.* dose reduction, interruptions, active pharmacologic treatment of AE) [17].

Conclusion

Our case report, to our knowledge, is the first reported case of concurrent use of RT and sonidegib in laBCC progressing on sonidegib. The patient had excellent clinical response with minimal acute side effects. Combination therapy of HHI so far has only been limited to case reports in not-progressing patients, with no phase II trials reported. We have explored possible mechanisms regarding the synergistic efficacy of RT and HHI as well as HHI potential for radio sensitization. Future directions include potential synergistic toxic effects and impaired wound healing due to SHH inhibitors [18]. Our report demonstrates that the combination of sonidegib and RT is feasible and can overcome the resistance to HHI, therefore retaining the patient on the most efficacious first-line HHI before considering moving to the second-line immunotherapy. Additional prospective clinical trials are needed to determine if the combination with radiotherapy can be the right strategy of treatment in progressing patients with laBCC.

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