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Case Report

Treatment of Locally Advanced Morphea formic Basal Cell Carcinoma with Sonidegib Combined with Pembrolizumab

Rauno J Harvima[1,2]*, Antti P Kaukinen[1] and Ilkka T Harvima[1,2]

[1]Department of Dermatology, Kuopio University Hospital, Kuopio, Finland

[2]Department of Dermatology, University of Eastern Finland, Kuopio, Finland

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***Corresponding author:** Dr. Rauno J. Harvima, MD, PhD, DSc, Department of Dermatology Kuopio University Hospital, FIN-70210 Kuopio, Finland, Tel: +358-40-9309150, Fax: +358-17-174420, Email: rauno.harvima@kuh.fi

ABSTRACT

Basal cell carcinoma (BCC) is the most common skin cancer. At early stages, various topical treatments or light surgical procedures will give effective results. However, when the commonly used treatments are not appropriate, the hedgehog signaling inhibitor may be considered. After morphea formic BCC did not respond anymore to vismodegib, we describe a case with locally advanced BCC treated with sonidegib combined with pembrolizumab.

Keywords: Basal cell carcinoma; Hedgehog signaling pathway inhibitor; Sonidegib; Pembrolizumab

Introduction

Basal cell carcinoma (BCC) is the most common skin cancer. Superficial BCC is often treated by topical treatments with cryotherapy by liquid nitrogen, photodynamic therapy (PDT), imiquimod cream or 5-fluorouracil cream l. Nodular forms may be excised by a curette followed by cryotherapy or PDT or by surgery. Various lasers may also be used.

Morpheaformic, infiltrative BCC and basosquamous carcinoma are targets for surgery[1]. In some cases, oncologic treatments by radiation therapy or cytostatic drugs may be used. In addition, various combination of the treatments may be applied. The newest treatment option is immunotherapies by anti-PD1- drugs[2].

When surgery or other treatments are not applicable, Hedgehog signaling pathway inhibitors may be considered. Presently, there are two drugs in this group: vismodegib (Erivedge) 150 mg capsules and sonidegib (Odomzo) 200 mg capsules[2]. Both are very effective drugs, but both are extremely teratogenic necessitating extreme cautions in handling of drug capsules.

Vismodegib and sonidegib demonstrate >99% binding to plasma proteins. Vismodegib has a limited tissue penetration. In contrast, sonidegib is more lipophilic with an extensive distribution in tissues. Consequently, the concentration of sonidegib is 6 times higher in skin than in plasma. This might explain potential differences in efficacy and toxicity between these drugs. Vismodegib has an elimination half-life of 4-12 days achieving steady-state situation after 7-21 days. In contrast, sonidegib‘s elimination half-life is longer 28-30 days achieving steady-state after 3-4 months[3].

Sonidegib shares about the same efficacy, tolerability and adverse event profile as vismodegib[3,4]. However, sonidegib has

a better skin penetrance than vismodegib[3]. Vismodegib came available in Finland for patients in 2016 and sonidegib later in 2022.

Here we describe a case on the treatments of locally advanced BCC with sonidegib combined with pembrolizumab that is officially indicated for melanoma.

Case Report

A male born in 1947 showed at the age of 46 in his left ear-cheek area a morphea formic BCC that was operated numerous times with pure margins, but relapses were encountered. Also, radiation therapy was given in 2003. In 2007, petrosectomy and microvascular flap were performed and in preoperational pulmonary X-ray, a squamous cell carcinoma was detected and treated with cytostatic drugs. In 2013, a relapse of BCC was detected infiltrating along the skull base being beyond surgery. It affected his jawbone and jaw joint movement causing difficulties in eating. Thus, vismodegib was initiated in March 2015 and the lesion shrank gradually over the following months and at 7 months it was clinically clear with the histopathology of scar. In addition, his yaw movement restored back. Vismodegib was continued for a total of 1 year and 3 months. At a follow-up 6 months later in November 2016, a clinical remission was still noticed **(Figure 1)**. This case has been presented recently[5].

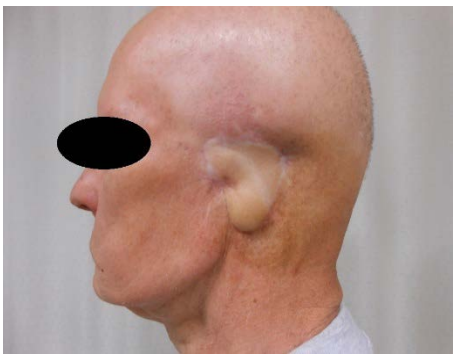

Figure 1: Treatment of morpheaformic basal cell carcinoma with vismodegib for 1 year 9 months in a 68-year-old male with successful response in 7 months being clinically and histopathologically clear. At follow-up at 1 year later from start a clinical remission was noticed in November 2016[5].

After a remission stage, the BCC lesion started to relapse one year later. Thus, vismodegib was readministered in November 2017 with weak response and biopsies showed also infiltrative BCC. Due to marked adverse events vismodegib was discontinued in September 2018 despite oral magnesium citrate supplements and topical creams. A radiation therapy given 10 times at 3.4 Gy was performed in October 2018 **(Figure 2)**. Two months later, 0.1% vismodegib in Novalan base cream was applied daily followed by intralesional 0.1% vismodegib in saline solution at 1–2-week intervals (both made from vismodegib capsules in the Pharmacy of Kuopio University Hospital). However, progress was seen in 3 months with deep pockets and invasion to skull bone areas **(Figure 3)**. Therefore, vismodegib was readministered in March 2019, but soon after a month the daily dose was tapered to one capsule every second day and severe leg cramps subsided.

When oral vismodegib combined with topical 0.1% vismodegib daily and intralesional 0.1% vismodegib at 1–2-week intervals as an off-label treatment, some beneficial response was detected. The bacterial cultures from ulcer revealed colonizations of Staphylococcus aureus and Citrobacter koseri which were treated with topical and oral antimicrobics.

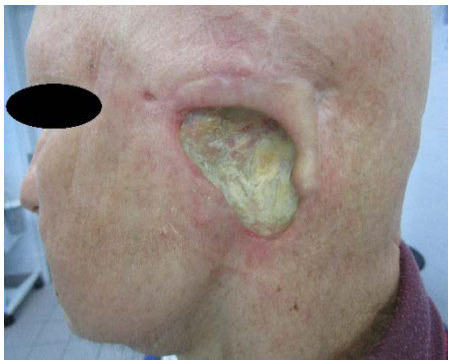

Figure 2: A relapse in BCC started in November 2017 gradually making a wider cancer lesion, Follow-up in December 2018 after radiation therapy (10x at 3.4 Gy).

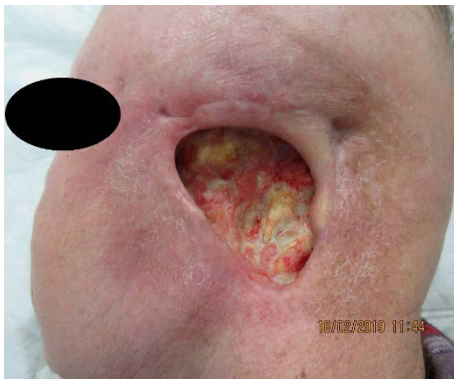

Figure 3: A relapse in BCC gradually making a wide about 75 x 48 mm cancer lesion despite oral 150 mg/every 2nd day, 0.1% topical cream and 1-2-week intervals of 0.1% intralesional vismodegib (February 2019), when pembrolizumab was initiated.

This triple-vismodegib medication lost its response and skull bone became more visible. Thus, intravenous pembrolizumab as an off-label medication, reported to be effective for BCCs by literature[6], was initiated in July 2019 at a dose of 2 mg/kg at every 3 weeks together with oral vismodegib taken every 2nd day due to leg cramps. After 3 infusions, pembrolizumab dose was increased to 3 mg/kg. After a few months, no marked response was noticed in October 2019 **(Figure 4)**. However, clear slow progress was noticed after about 5 to 6 months continuing slowly during the next one year in July 2021 **(Figure 5)**. For practical reasons, after 32 infusions pembrolizumab dose was changed to 6 mg/kg at every 6 weeks starting in June 2021. The slow response continued over the next year in August 2022. In addition, two suspected SCC lesions with a size of few centimeters disappeared according to X-Ray.

Vismodegib was replaced by sonidegib (200 mg/day) when this became available in July 2022. Slowly, the deep pockets at anterior, inferior and superior edges and later the dorsal deep pocket were filled by granulation tissue and epithelized as well as mostly the central part of the lesion **(Figure 6)**.

However, a small area at anterior lower edge and upper-dorsal part of the lesion progressed and showed no response at size of about 2-2.5 cm lesion. In Magnetic Resonance Image, the tumor had invaded through the skull bone into the brain causing neurological symptoms. Thus oral sonidegib and intravenous 46th pembrolizumab dose was discontinued in January 2023, a follow-up in July 2023 **(Figure 7)**. The patient was transferred to good terminal care and the patient passed-away in September 2023.

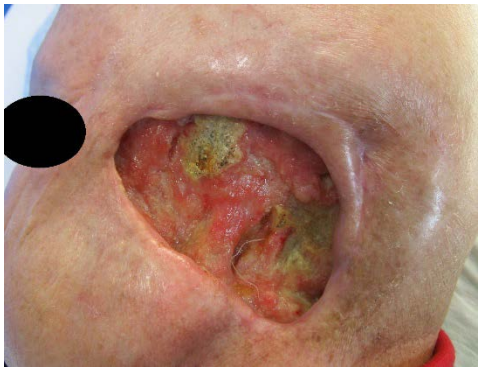

Figure 4: The response of pembrolizumab after 3 months in October 2019 with 2 mg/kg, but after 3rd infusion increased to 3 mg/kg with appropriate laboratory value motoring. After 32 infusions, infusions were performed at 6 mg/kg every 6 weeks.

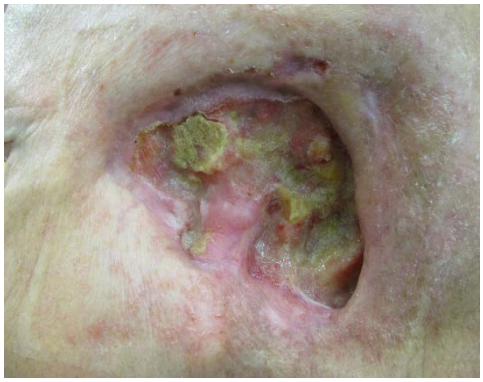

Figure 5: Marked response of pembrolizumab in July 2021. The deep pockets grow and epithelized in other edges except at dorsal side, which occurred after changing vismodegib to sonidegib.

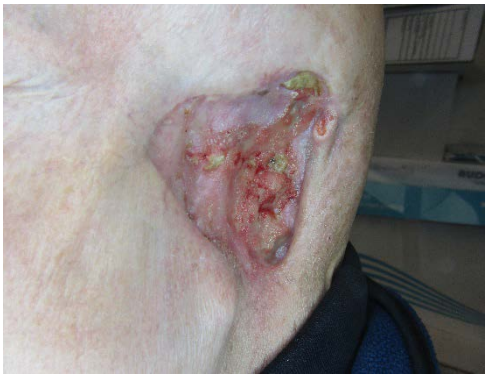

Figure 6: Basal cell carcinoma with combination of sonidegib and pembrolizumab in September 2022. The dorsal deep pocket grown and epithelized. Scull bone visible in 3 small areas.

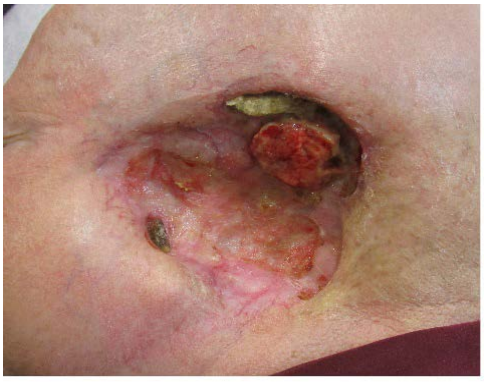

Figure 7: The final response of 46 infusions of pembrolizumab in 3- or 6-week-intervals with oral 150 mg/every 2nd day vismodegib or 200 mg daily sonidegib in July 2023.

Discussion

Hedgehog signaling pathway inhibitors are used only in locally advanced and metastatic BCC lesions when operational or other treatments are not sufficient. Both vismodegib and sonidegib are on the same level in efficacy, showing similar adverse event profiles according to literature[3,4]. Most patients have experienced typical adverse effects, like hair loss, leg cramps and loss of taste and thus, appetite. The patients with Gorlin syndrome felt it beneficial to use oral magnesium citrate and magnesium containing topical cream products[5].

The present case with morpheaformic BCC responded first well to vismodegib treatment, despite multiple wide mutilating surgeries previously. However, after a 1-year-break in vismodegib use, a relapse occurred. It Is possible that skin blood microcirculation was not sufficient for vismodegib to penetrate sufficiently to the BCC tumor. This may explain, why BCC lesion responded weakly during vismodegib treatment, even though he used the drug continuously.

Oral vismodegid combined with topical 0.1% vismodegib in Novalan emollient and intralesional 0.1% vismodegib in saline solution showed a slight response as a combination. When sonidegib with a better skin penetrance became available, vismodegib was changed to sonidegib. By this combination a response was detected, especially in the healing of lower dorsal pocket. However, the response was slow as compared to another case of BCC treated with sonidegib gaining a full response in 4-7 months without any previous surgery for 6 of 7 BCC lesions and the biggest lesion in the lower back originally with the size of about 16x17 cm shrank to about 4 centimeters and started to grow due to presence of basosquamous carcinoma[7].

Vismodegib or sonidegib is usually not the 1st line treatment due to extreme teratogenicity, high costs (about 5,000 EUR/month) and to some extent the adverse events. It is an interesting question whether vismodegib or sonidegib should be used as the 1st line treatment.

It could be questioned what the efficacy would be without numerous previous surgical excisions and operations, when the skin blood vessel network is in a good condition delivering vismodegib to the BCC lesion. The results from the other cases (without earlier operations)[5] might support the conclusion that vismodegib or sonidegib should be used earlier than recommended at this moment. Some beneficial response was noticed when also topical and intralesional vismodegib was used. However, due to better skin penetrance of sonidegib as compared to vismodegib, it might be expected a better response with sonidegib. Here we did not find a marked difference between these drugs in this morpheaformic case when also an infiltrative BCC appeared, possibly due to numerous earlier large surgical operations. Also, it might be possible that there was a selection or transformation of tumor variants to a less responsible strain. This is supported by the partial response of pembrolizumab.

Some question will arise based on our case: 1) whether pembrolizumab alone without sonidegib would give the same final result. 2) whether pembrolizumab would be more effective than Hedgehog signaling pathway inhibitors, when no marked earlier surgical treatment(s).

In mice studies, the inhibition of BCC carcinogenesis was noted with topical hedgehog antagonist[8]. Interesting findings

in mice studies are the inhibition of BCC carcinogenesis with tazarotene[9] and with D-vitamin that mediated at least in part its effect on the Hedgehog signaling pathway[10]. Whether these might have any synergistic effect with hedgehog signaling pathway inhibitors remains to be elucidated. UV-radiation is a known risk factor for development of skin cancer. However, in an animal study, Vitamin D3 produced by skin exposure to UV radiation inhibits BCC carcinogenesis[11] whereas dietary Vitamin D does not do so[12].

Another interesting question is, how long vismodegib or sonidegib treatment for each patient should go on without interruptions or if a break occurs, the length of such. It is assumed that it is necessary to make an individual decision for each patient. Also, the effect of pembrolizumab on BCC an SCC was detected as reported in the literature[6] and it is assumed that these cancers will be indicated in the future also for use of pembrolizumab.

Ethical Approval

The patient has given his consent for this case report.

Conflict of Interests

Author (RJH) has participated in producing a patient information booklet on sonidegib in Finnish and Swedish languages. Other authors declare no conflicts of interest.

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