

## Treatment of Multiple Locally Advanced Basal Cell Carcinomas by Sonidegib Combined with Surgery and Radiation Therapy: A Case Report

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### Abstract

A 63-year-old male had multiple basal cell carcinomas (BCC) developed during about 12 years. Six of 7 BCCs on the trunk and left lower eye lid vanished within about 3 to 7 months by daily use of sonidegib 200 mg capsules been in remission for 2 years. The largest about 16x17 cm BCC reduced markedly in 1 year 2 months in size to about 4 cm, but started to grow in 3 months to 3x5 cm. After confirming the diagnosis as basosquamous carcinoma, the patient was operated surgically followed by negative pressure wound treatment (V.A.C. ®) twice a week with later superficial skin transplant 1.5 months later onto the well granulating wound bottom. Four weeks later radiation therapy was given 33 times as 2 Gy doses, total 66 Gy. A short follow-up for 3 months has not shown a relapse so far, but follow-up continues.

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**Citation:** Harvima RJ, Ilves T, Turunen H, Nuutinen H (2025) Treatment of Multiple Locally Advanced Basal Cell Carcinomas by Sonidegib Combined with Surgery and Radiation Therapy: A Case Report. J Clin Med Re: AJCMR-193.

**Received Date:** 12 February, 2025; **Accepted Date:** 17 February, 2025; **Published Date:** 21 February, 2025

**Keywords:** Basal cell carcinoma, Hedgehog signaling pathway, Sonidegib

### Introduction

Basal cell carcinoma (BCC) is the most common skin cancer with annually about 9,000 cases recorded annually by the Finnish Cancer Registry. However, due to underreporting, it is likely that the real number is around 30,000 to 35,000 cases in Finland with population of about 5.5 million.

BCC is often easily accessible and thus, topical treatments on superficial variants include cryotherapy with liquid nitrogen, photodynamic therapy (PDT), imiquimod or 5-fluorouracil. Nodular forms may be excised by a curette (curettage debulking) followed by cryotherapy or PDT or by surgery. Also, various lasers may be used. Morpheiformic, infiltrative BCC and basosquamous carcinoma are targets for surgery. 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 [1].

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 are extremely teratogenic necessitating extreme cautions in handling of drug capsules.

Vismodegib and sonidegib demonstrate >99% binding to plasma proteins. Binding of vismodegib to proteins is concentration-dependent, whereas that of sonidegib is non-concentration-dependent. Vismodegib has a volume of distribution of 16-27 L, suggesting it is confined to the plasma

and has a limited tissue penetration. In contrast, sonidegib is more lipophilic and has a volume distribution of >9,000 L, indicating extensive distribution in the tissues. Consequently, 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 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 situation after 3-4 months [2].

The efficacy for vismodegib (N=63) was reported in the BOLT and Erivance studies being 22.2% (complete clearance), 25.4% (partial clearance), 34.9% (stable disease), 12.7% (progressive disease), and 4.8% (unknown). These figures for sonidegib (N=66) were 21.2% (CR), 39.4% (PR), 30.3% (SD), 1.5% (PD), and 7.6% (unknown) [2,3].

In Finland, the patients will get reimbursement for costs by a special statement from a multiprofessional meeting, vismodegib came available in 2016, and sonidegib later in 2022. Sonidegib shares about the same efficacy, tolerability and adverse event profile as vismodegib. However, sonidegib has a better skin penetrance than vismodegib (2). Financial monthly costs are at the same level.

Here we describe a case report on our experience of the use of sonidegib combined with surgery, skin transplant and radiation therapy in a patient with multiple BCCs.

**Case Report**

A 63-year-old male had had wounds on different locations in the trunk for about 12 years and was referred for consultation to University Hospital. Biopsies from all lesions showed infiltrative BCC. He had unprotected sun exposure to his skin every summer in the youth. He had worked as lumberjack for decades and carrying a clearing saw caused frictions by harness to the skin areas where the present BCCs were located.

At a multiprofessional meeting with dermatologist, plastic surgeon, and oncologist (Pics. 1,2,3), his situation included 7 partially infected BCCs scattered in different location of the

back and upper front trunk and left lower eye lid, with the following sizes:

- 1) lower back: 15.8 x 17.2 cm being in contact to lumbar L2-L3 processus spinosus
- 2) left medial lower scapula: 15 x 30 mm
- 3) right medial back at lower scapula level superficial: 6x7 mm
- 4) right upper medial scapula area: 48x57 mm
- 5) right shoulder: 50x38 mm
- 6) right upper front: 18x40 mm
- 7) left middle lower eye lid at eyelash: 6x8 mm



**Picture 1:** A general view of back with numerous basal cel carcinomas, December 2022.



**Picture 2:** Basal cell carcinoma on right shoulder, December 2022.



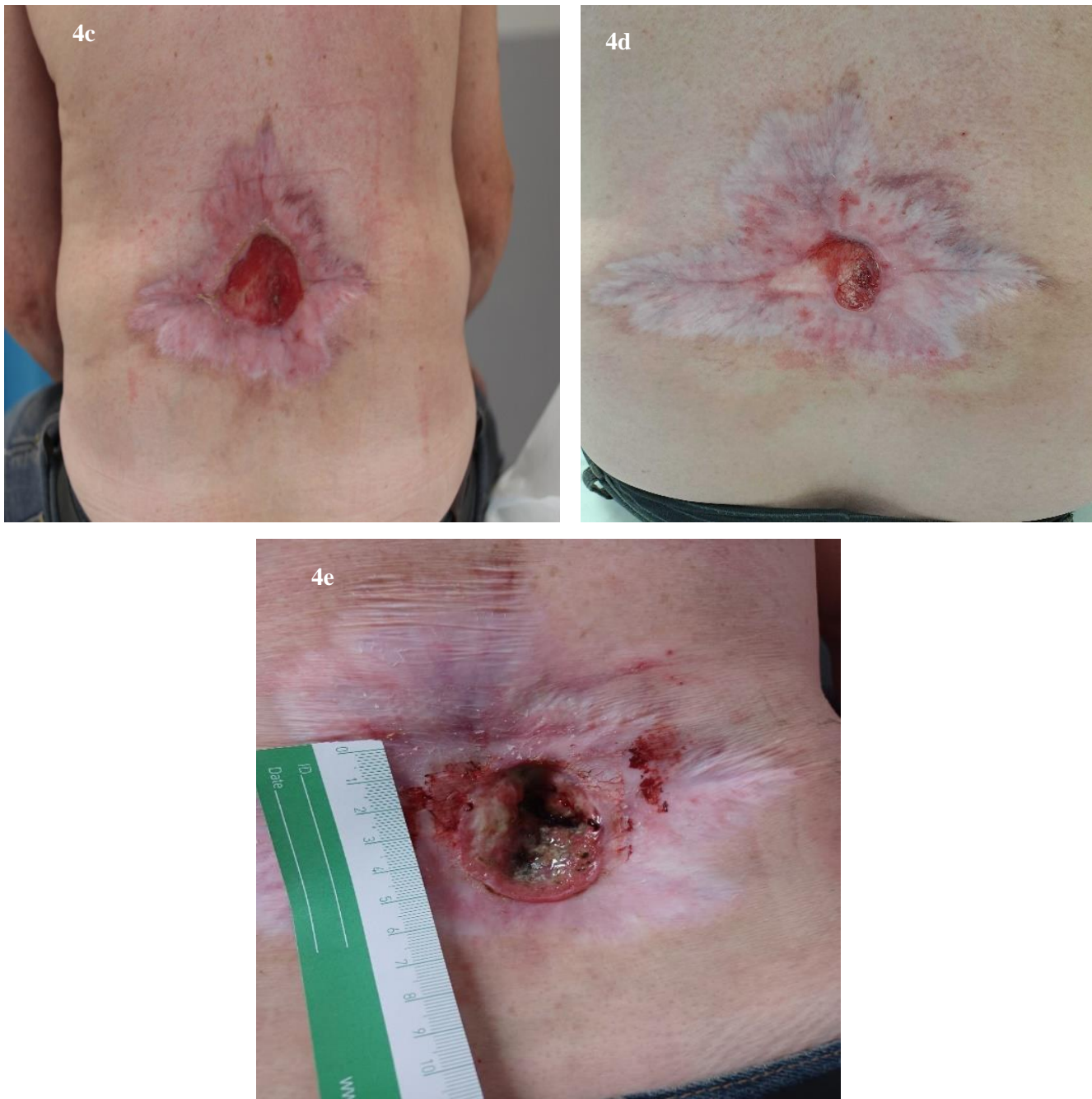
**Picture 3:** Basal cell carcinoma on right upper scapula, December 2022.

His case was considered beyond surgery and radiation therapy for all BCCs, and sonidegib (Odomzo) 200 mg capsules once a day was applied with topical antimicrobial treatments by 0.1% silver nitrate compresses and silver sheets. Bacterial culture revealed plenty of *Staphylococcus aureus*, *Streptococcus anginosus* and *Morganella morganii*. As a very teratogenic property of the drug, careful handling instructions were given. His teeth were partially in a bad condition; thus, he was guided to a Dentist.

All the BCCs started to respond very fast within weeks. The BCCs in left eye lid and right anterior trunk healed within 3 months, those on the upper back and right shoulder healed in about 4 to 7 months.

However, the largest BCC on the lower back lesion (Pic. 4a) started to shrink during the next 4 to 7.5 months (Pic. 4b, Pic.4c) shrink to its minimum size of about 4 cm after 1 year 2 months (Pic. 4d). The patient experienced loss of taste and leg cramps and thus, sonidegib was reduced to every second day, and topically medical honey was applied. The patient had a break in sonidegib use for about 1 month. Biopsies from the lower back lesion showed no basal cell carcinoma in January 2024. Thereafter the lesion started to grow gradually to about 3x5 cm in 3 months (Pic. 4e) with depth to 3.7 cm. MRI study showed ulceration to lumbar L2-L4 processus spinosus and on the left L3 level, a small infiltration to erector spinae muscle on a 9x7 mm area. The biopsy showed basosquamous carcinoma.



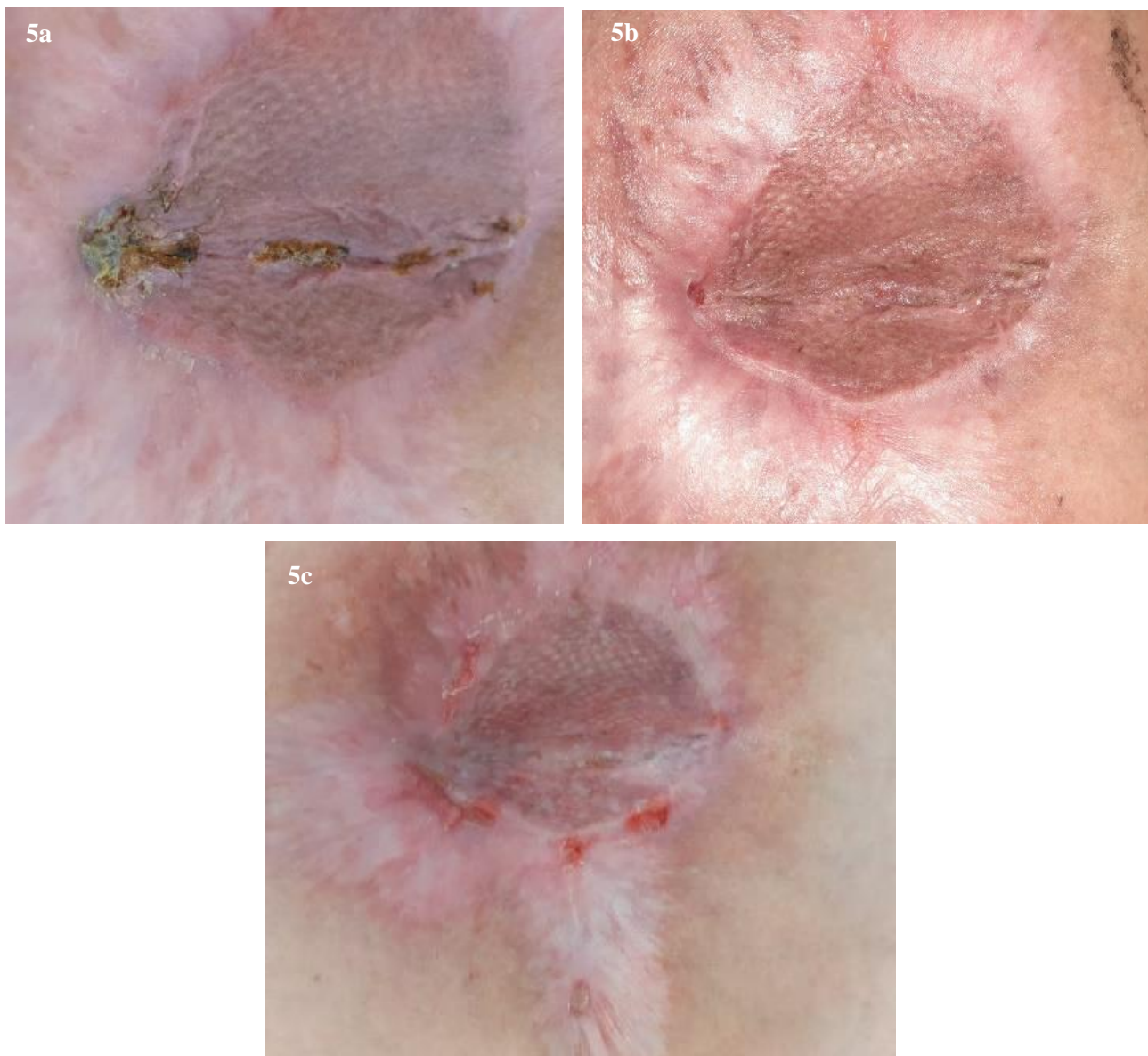


**Picture 4:** Sonidegib treatment for the lower back basal cell carcinoma at start (Pic. 4a), after 4 months (Pic. 4b, May 2023), after 7.5 months (Pic. 4c, August 2023), at 11 months as the smallest in size (Pic. 4d, December 2023), at 1 year 3 months worsening of situation and basosquamous carcinoma was detected in biopsy (Pic.4e, May 2024).

Thus, it was treated by surgery with 1.5 cm margins, L2-L4 processus spinosus was resected, followed by negative pressure wound treatment (V.A.C. ®) twice a week with a superficial skin transplant 1.5 months later onto the well granulating wound bottom. Sonidegib was discontinued at the time of surgery.

The resected processus spinosus removed were with impure margins by histopathology. Thus, a radiation therapy was

performed after 4 weeks of superficial skin transplant (Pic. 5a). The patient was treated during the following 1.5 month by 33 times each 2 Gy, total 66 Gy. At 2 weeks of radiation therapy, the skin was almost epithelized (Pic. 5b). Two weeks prior to the end of radiation therapy, the treated area became superficially irritated and erosive (Pic. 5c), which lasted for about 3 months treated only topically. The follow-up with MRI investigations will be continued.



**Picture 5:** Basal cell carcinoma at lower back after surgery and skin transplant, and radiation therapy (August-October 2024). At start of radiation therapy (Pic. 5a), at 2 weeks of radiation therapy (Pic. 5b), at end of radiation therapy (Pic. 5c).

The healed BCCs in upper back as scars are presented in Pic. 6.



**Picture 6:** A general view of healed basal cell carcinomas in upper back after 4 months of sonidegib use, May 2023.

## Discussion

Hedgehog signaling pathway inhibitors are used only in locally advanced BCC cases when surgery or other treatments are not adequate. Both vismodegib and sonidegib are on the same level in efficacy, and with adverse event profiles. The patient had experienced typical side effects like hair loss, leg cramps, and loss of taste and thus, appetite. Thus, he reduced the use of sonidegib for one month and used thereafter every second day. To ensure optimal wound healing, multivitamin-trace element products were used. For leg cramps, oral magnesium citrate products were used giving some relief. Food taste returned back after 4-5 months.

Hedgehog signaling pathway inhibitors gave an excellent response to 6 of 7 BCCs in 3 to 7 months with correlation with original size, and those have been now in remission for 2 years. The follow-up since the latest treatment by radiation to lower back basosquamous carcinoma as 3 months is too short to make a final estimation of cure. This case also shows that sonidegib reduced the extremely large about 16x17 cm lower back BCC eligible for surgery. The 6 other BCCs vanished by use of sonidegib alone.

The largest BCC/basosquamous carcinoma at lower back stopped to heal. It can be explained by basosquamous carcinoma, since sonidegib does not have an effect for this malignancy. Whether basosquamous carcinoma was already in the beginning of the treatment or developed during the time, remains uncertain. The 1-month break in sonidegib use prior to worsening of the lower back healing is likely not having a marked effect, since sonidegib's elimination half-life is long 28-30 days achieving steady-state situation after 3-4 months [2].

The future follow-up will show whether radiation therapy gave a final cure when the resections of processus spinosus were not obtained with pure margins. The risk of relapse is considerable, since experience with another patient having a similar large lower back BCC some years earlier with pure margins of resected processus spinosus revealed a relapse after close to 2 years.

For the possible future treatments, there are PD-1 drugs, pembrolizumab and semiplimab, useable in addition to BCC,

also for basosquamous carcinoma and squamocellular carcinoma [1,4].

## 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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