Smoothed receptor inhibitor vismodegib for the treatment of basal cell carcinoma: a retrospective analysis of efficacy and side effects

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ABSTRACT

Background: Smoothened receptor inhibitor vismodegib is indicated to treat locally advanced basal cell carcinoma (laBCC) and lesions in nevoid basal cell carcinoma syndrome (NBCCS).

Methods: We treated 11 patients – including four NBCCS and seven laBCC patients – with vismodegib at our department.

Results: Complete remission was achieved in three cases, without relapse after discontinuation. Two of the aforementioned patients had NBCCS, in their cases further treatment might be needed. Two patients showed improvement, but later passed away due to unrelated conditions. Two patients with laBCC initially showed remission, then the treatment was suspended due to side effects. After re-administration of the drug, loss of efficacy was observed. We did not observe therapy resistance in our NBCCS group. The rest of the patients showed good response to therapy, but have not reached full remission yet. The main side effects of vismodegib were muscle cramps, dysgeusia, nausea and alopecia. The frequency of adverse events did not show significant differences between the patient groups.

Conclusions: Our results show that vismodegib therapy is effective in the treatment of BCC; however, side effects are often severe. Since the suspension of treatment can lead to therapy resistance, the management of side effects is of great importance.

Introduction

Basal cell carcinoma (BCC) is the most common malignancy in fair-skinned humans with an increasing incidence. Although the chance to develop BCC is greater with older age, a shift toward younger patients and more aggressive forms can be observed. It may be safely presumed that BCCs are often not reported to chance to develop BCC is greater with older age, a shift toward younger patients and more aggressive forms can be observed. It may be safely presumed that BCCs are often not reported to

Smoothened (Smo) protein, a 7-pass transmembrane receptor, which may act as an oncogene in the pathogenesis of medulloblastoma, basal-cell carcinoma and prostate cancer (7,8). In the presence of hedgehog ligands, the suppression of Ptc on Smo is released which activates signal transduction.

In NBCCS, the mutation in PTCH1 usually results in the production of a truncated protein which cannot inhibit Smo, which leads to a constant activation of the pathway and unregulated transcription of target genes (9) (Figure 1).

The misactivation of this pathway is most frequently the result of loss-of-function mutations in PTCH1 or, as reported in sporadic cases of BCC, gain of function mutations in SMO genes (2,5,10–12).

Surgical excision remains the gold standard method to treat BCCs with a success rate of approximately 95% and favorable cosmetic outcome in most patients (13). However, other treatments modalities need to be applied in a number of cases. Mohs micrographic surgery (MMS) combines staged resection with intraoperative examination of the tumor margins using frozen sections. Although MMS is expensive and resource-demanding, lower recurrence rates are seen with its use. It is highly indicated in tumors which are large in size or show aggressive histological features (13). Physical destruction with curettage, cautery, cryosurgery, or ablative laser therapy is also applicable in low-risk lesions. The outcome greatly depends on two factors: careful patient selection and the surgical skills of the dermatologist. Another therapeutic
possibility is photodynamic therapy, which is appropriate particularly for superficial tumors resulting in an excellent esthetic outcome at the cost of higher recurrence rates if not applied carefully (14). Radiotherapy is now being used less commonly, yet it is a feasible alternative for patients when surgery is contraindicated (13). Conversely, radiotherapy is not recommended in NBCCS since it promotes tumor formation (15).

Several pharmacological agents are available in the treatment of BCC, including topical imiquimod, or 5-fluorouracil for superficial tumors (16). Alternatively, intralesional interferon and topical retinoids have been used with some success. A novel treatment option, Smo inhibitor vismodegib (Erideve Genentech) was approved by the US Food and Drug Administration (FDA) in 2012 and by the European Medicines Agency (EMA) in 2013. A second Smo inhibitor, sonidegib (Odomzo, Novartis) was approved by the FDA and EMA in 2015. Smo inhibitor drugs can be used in incurable cases with surgery or radiotherapy. A tumor is considered inappropriate for surgery either because it is unresectable, or because the removal would result in severe deformity and loss of function. It can also be a therapeutic option in NBCCS where the continuously growing number of lesions would require repeated surgical excisions. According to the final results of the ERIVANCE study in the cases of locally advanced (la)BCC, vismodegib showed impressive response rates. The ORR (objective response rate) for vismodegib was 60.3%, which consists of 31.5% all response and 28.4% partial response (17). However, drug-related adverse events (AEs) related to vismodegib are quite frequent. The most common side effects of vismodegib include muscle spasms, dysgeusia, alopecia, weight loss and fatigue, which could lead to decreased quality of life and the discontinuation of the treatment (17,18). In adults, the hedgehog-pathway is quiescent with some exceptions. The adverse effects of vismodegib are consistent with the role of the Hedgehog pathway in these particular organs (19). The Hedgehog pathway has a key role in regulating follicular growth and the telogen to anagen transition of hair follicles in adults; therefore, its inactivation can lead to alopecia. It has also been postulated that a hedgehog-pathway agonist can stimulate follicular cycling and induces hair growth in mice (20). The pathomechanism that causes muscle cramps is not fully understood. It has been reported that the Hh pathway also affects adult skeletal muscle cell differentiation, survival, hypertrophy and proliferation; interfering with these may result in muscle cramps.
(21). However, other reports suggest that vismodegib agonizes noncanonical Hh signaling, causing cell membrane calcium channel activation, which induces muscle cramps (22). As for the dysgeusia, to maintain adequate tasting function, taste papilla and taste bud cells need to be continuously replaced, the process is principally regulated by the Hedgehog pathway. The disruption of the hedgehog signaling by the inhibition of glioma-associated oncogene (GLI) transcriptional activity leads to taste disturbances. However, the innervation remains intact even after prolonged GLI blockade. Therefore, after the restitution of the pathway, the taste organ returns to its original function (15). As the Hedgehog pathway has a crucial role in embryonic cell development and patterning, its inhibition results in embryotoxic, fetotoxic or teratogenic effects (19,23); therefore, the use of vismodegib is strictly forbidden during pregnancy.

We aimed to evaluate our experience with the use of vismodegib, mostly focusing on the management of side effects and compare our findings with the literature.

**Patients and methods**

We performed a retrospective analysis of the clinical data of 11 Hungarian patients treated with vismodegib at our department between March 2013 and September 2017. Nine female and two male patients were included with the mean age of 73 ± 15 years (81.14 ± 6.79 vs. 58.75 ± 16.09; laBCC vs. NBCCS respectively; $p = 0.009$). Four patients fulfilled the criteria of NBCCS and seven patients had locally advanced basal cell carcinoma (laBCC) without NBCCS. The therapeutic effect was monitored by applying the following parameters: the total diameter of the tumors, the diameter of the biggest lesion and the number of lesions according to medical documentation and regularly taken clinical photographs.

**Patients with laBCC and without NBCCS**

**Patient 1**

A 74-year-old male patient presented at our department with numerous BCCs that had been seen since the age of 30. In the past, multiple BCCs were treated with cryotherapy or electrocautery, and the patient underwent a great number of surgical procedures. The diagnostic criteria of NBCCS were not met, as no attribute was seen other than multiple BCCs. Clinical examination revealed a 20 cm large exulcerated tumor on his chest, which was unequivocally inoperable, and, additionally, he had several other exulcerated, bleeding BCCs on his back (Figure 2). His medical history included polycythemia vera, which had been treated with hydroxycarboxamide for over ten years. We started vismodegib therapy, and after six weeks of treatment, the lesions started to show regression and scarring. The skin status of the patient improved considerably after 15 months, also, vismodegib treatment did not affect the status of the patient’s polycythemia vera.

![Clinical photos of Patient 1](image-url)
The first side effects appeared after six weeks of treatment, and after 6 months, they worsened significantly. The patient showed rapid weight loss, so nutritional supplementation had to be introduced. Initially, the weight loss was manageable, but after another 5 months of treatment, the side effects persisted despite the nutritional supplementation, and the therapy had to be discontinued for this reason. After the cessation of therapy, his weight started to increase with no further development of BCCs.

**Patient 2**

A 75-year-old male patient presented with a BCC of the right periocular region which progressed to infiltrate the orbital muscles despite multiple surgeries and radiation treatment. The patient also suffered from locally-advanced prostate cancer, for which he received GnRH agonist leuprolide treatment. We initiated vismodegib therapy to avoid enucleation. After 8 months of therapy, the regression of the patient’s BCC was seen, and, at follow-up, the CT scan showed the regression of his prostate cancer, and his urination difficulty ceased as well. Besides moderate hair loss, taste disturbance, loss of appetite, and severe, but tolerable muscle cramps presented during the treatment. However, after the initial phase of regression, drug resistance developed, and the patient’s BCC progressed, infiltrating the orbit, bulbar muscles and fat. After the loss of therapeutic effect, the exenteration of the orbital contents was performed, no recurrence was observed after enucleation.

![Figure 3. Clinical photos of Patient 3. Patient 3 before Vismodegib treatment (A), after 3 months of treatment with partial response (B), after 5 months of treatment (C), and after 8 months of treatment with considerable deterioration of the lesion (D).](image-url)
**Patient 3**

A 82-year-old female patient came to our view with a large, ulcerated BCC on the right cheek (Figure 3). According to medical documentation, the lesion appeared approximately 40 years before. It was treated surgically once, and after it recurred, no further treatment was carried out due to lack of compliance. Given the age of the patient and the extent of the lesion, curative outcome would not have been achievable with surgical or radiological interventions. Therefore, vismodegib therapy was introduced after the diagnosis was confirmed by biopsy. A diagnostic CT scan proved bone involvement beneath the tumor and also described an intracranial lesion above the cerebellar tentorium, considered as a meningioma, but no invasive sampling was performed because of the potential side effects of the procedure. No other NBCCS criterion was observed. Significant regression of the BCC occurred after 3 months of treatment. The size of the patient’s intracranial lesion did not change considerably, which also supports the fact that it was not a BCC metastasis. Due to personal circumstances, the patient missed one month of treatment, which resulted in tumor progression. After the re-administration of vismodegib, resistance developed, and the therapeutic effect of the drug decreased considerably. This led to disease progression, the tumor infiltrated her orbital structures and nose cartilages. For this reason, radical surgery was planned, but the patient deceased due to a severe gastrointestinal infection, which was unrelated to the vismodegib treatment.

**Patient 4**

A 76-year-old female patient, with a medical history of multiple BCCs, who previously underwent surgery numerous times and also received cryotherapy. She came to our department with no obvious visible signs of a BCC, since it was formerly operated several times in another institution. After each operation, all the histological margins of the excised samples were positive for tumor cells. The curative surgical solution would include the resection of the nose, and for this reason, vismodegib therapy was introduced. The tumor was followed with ultrasound, and the recurrent BCC showed remarkable regression after 2 months, with only mild side effects. Although vismodegib therapy was suspended after 3 months, the possibility of recurrent or new lesions was excluded by ultrasound scans after 10 months of the discontinuation of the treatment, and the patient remained tumor-free up till now.

**Patient 5**

A 55-year-old female patient presented with laBCC of the nose. Despite attempted various treatment modalities including radiotherapy, surgical interventions and laser ablation, the tumor recurred 4 years ago. The patient refused the radical surgical procedure, a major resection of the nose; therefore, vismodegib was initiated. In the last 4 years, the therapy was suspended several times for various reasons. After 2 weeks of administering vismodegib, severe muscle spasms occurred, muscle relaxant tolperison, later tizanidine was administered with partial effect. Later, amlopidine was introduced for high blood pressure without significant improvement in regard to muscle cramps. After 3 months, the therapy was suspended due to side effects, most of which disappeared except for alopecia after 4 months of suspension. After the re-administration of the drug for 9 months, we achieved partial response again. Then, due to unrelated hypertensive episodes, the therapy was suspended again and then reinitiated. Due to a suspected diagnosis of lung cancer, the treatment was terminated after 3 years when the patient was in partial remission. However, when lung cancer was excluded, we reinitiated the therapy because of BCC progression and noticed a partial response.

**Patient 6**

A 83-year-old female patient presented with a recurrent BCC of the temporal and nasal region, which was considered inoperable and inadequate for radiotherapy due to the extent and localization of the tumor. The disease showed improvement after 1 month of vismodegib with the appearance of severe adverse effects, such as alopecia, dysgeusia, weight loss, loss of appetite, reflux, fatigue, nausea and muscle spasms. The drug administration was suspended after nearly 5 months of treatment due to the severe side effects and the poor general condition of the patient. Shortly thereafter, the patient died of pneumonia, unrelated to vismodegib.

**Patients with NBCCS**

**Patient 8**

A 40-year-old female patient presented with the medical history of multiple BCCs, positive family history of BCCs, calcification of falx cerebri and bone abnormalities, thus, the diagnosis of NBCCS could be made. She had undergone several surgeries, and due to an inoperable tumor of the right orbit, the patient had to undergo ophthalmic enucleation and evisceration. The patient developed chronic anemia due to bleeding from the inoperable BCC lesions of the head and right orbit, which later also invaded the left orbit. After 2 months of vismodegib treatment, the dermatological status of the patient improved significantly. Unfortunately, due to sepsis from a urinary tract infection, the patient deceased only after 2 months of treatment. The fatal outcome was considered unrelated to the drug.

**Patient 9**

A 51-year-old female patient was referred to our department, who fulfilled the clinical criteria for NBCCS. BCC had been appearing from the age of 17, and the patient also presented palmar pitting, bone abnormalities and calcification of the flax cerebri. Previously, the patient received surgical treatment, radiotherapy and cryotherapy. Due to the extent of the disease, surgical and radiological treatment would not have been a definitive treatment option. Vismodegib therapy resulted in complete remission after 1 year; however, the patient developed severe muscle spasms and generalized alopecia throughout the treatment. The combination of tizanidine and amlopidine achieved slight reduction of muscle spasms. The treatment was administered for 4 years, then it was suspended due to intolerable muscle spasms, muscle weakness and dysgeusia. Three months after the therapy was stopped, BCCs reappeared (Figure 4), and the patient is now going to be operated.
Patient 10

A 35-year-old female patient presented with multiple BCCs first appearing at the age of 17, palmar and plantar pitting, bifid rib and mandibular cysts. Based on clinical criteria, the diagnosis of NBCCS could be made. The patient had about 30 surgical interventions and also received 6 months of acitretin treatment without considerable effect. Vismodegib remained the only possible therapeutic choice, as due to her young age and NBCCS, radiotherapy was considered inadequate. The patient showed a good therapeutic response after 1 month of the administration of vismodegib (Figure 5). Adverse effects, such as dysgeusia, muscle spasms, mild nausea and hair loss appeared. Muscle spasms ceased after the administration of magnesium, in addition, nutritional supplementation was also introduced. The patient achieved partial remission, then treatment was suspended after 13 months on the request of the patient mainly due to her alopecia. Recently, however, the treatment was re-initiated.

Patient 11

A 79-year-old female patient presented with multiple BCCs on the face. The nasal area was severely infiltrated, and palmar pitting was also observed. She did not receive any treatment before, and the disease was considered incurable elsewhere as no surgical or radiological interventions were doable at the time of her admission. Therefore, Smo inhibitor therapy remained the only effective treatment option. After 10 months of vismodegib treatment, due to the complete remission of the disease and the severe adverse events, the therapy was terminated to accommodate the request of the patient (Figure 6), and since that time, no recurrence has been observed.

Statistical analysis

All statistical analyses were performed using Graphpad Prism version 7.00 (Graphpad Software Inc, CA, USA). Data were tested using the Kaplan–Meier analysis and Student’s t-test as applicable. Graphs display arithmetic means and error bars represent standard deviations (SD). A value of $p < 0.05$ was considered statistically significant.

Results

Efficacy

The 11 patients reviewed received vismodegib treatment for a mean of $16 \pm 15.69$ months. Patients with LaBCC have been taking...
the drug for 14 ± 10.89, while patients with NBCCS for 20 ± 23.17 months.

All the patients who were suffering from NBCCS had more than 8 BCCs, and only one patient without NBCCS had more than 2 lesions. Loss of function mutation in PTCH1 was identified in 3 out of 4 NBCCS patients. More than two-thirds of the lesions (67.7%) were localized on body parts exposed to UV radiation (Table 1). Only one patient with laBCC presented BCCs on both sun exposed and nonexposed parts of the skin, while the other patients in this group had mainly BCCs on sun-exposed areas. In patients of the NBCCS group, BCCS occurred both on sun-exposed and non-sun exposed skin. The average time which elapsed after improvement was 2 ± 0.7 months, which was similar in both patient groups (2 ± 0.69 vs. 2 ± 0.82 months; laBCC vs. NBCCS respectively; \( p = 0.76 \)). The average number of tumors was 20 ± 25.47 before vismodegib treatment (7 ± 15.81 vs. 43 ± 24.5; laBCC vs. NBCCS respectively; \( p = 0.016 \)), which decreased to 5.5 ± 16.52 by the end of our follow-up period (Figure 7). We presumed that the total tumor burden was proportional to the diameter of the lesions, so we calculated tumor shrinkage based on this parameter. The average diameter of the biggest lesion was 5.18 ± 4.25 cm (5.3 ± 4.7 cm vs. 4.9 ± 3.9 cm; laBCC vs. NBCCS respectively; \( p = 0.89 \)) and the average of total diameter was 17.16 ± 27.03 cm (17.43 ± 32.62 cm vs. 16.53 ± 9.82 cm; laBCC vs. NBCCS respectively; \( p = 0.97 \)) before treatment (Figure 7). The size of the biggest tumor significantly decreased after treatment.
(2.7 ± 2.7 cm; 3.1 ± 2.2 cm vs 6.1 ± 10.5 cm; laBCC vs NBCCS respectively; \( p = 0.47 \)). However, the sum of the diameter of the lesions showed regression, yet it did not reach the level of significance (Figure 8). The most common treatment modality prior to vismodegib therapy was surgical excision of the tumor, followed by radiotherapy and cryotherapy. Only one patient did not receive any other treatment before vismodegib therapy was begun (Table 1). Complete remission was achieved in 3 patients, and no

| Sex  | Age | Clinical findings | Number of lesions before treatment | Other tumors | Treatment before vismodegib |
|------|-----|------------------|------------------------------------|--------------|-----------------------------|
|      |     |                  | Sun exposed areas | Not exposed |                             |
| Patient 1: Male | 84 | laBCC | 14 (32.55%) | 29 (67.45%) | Polycytemia vera | Surgical excision, electrocauterization, cryotherapy |
| Patient 2: Male | 78 | laBCC | 1 (100%) | 0 (0%) | Prostate cancer | Surgical excision, radiotherapy |
| Patient 3: Female | 85 | laBCC | 1 (100%) | 0 (0%) | Meningeoma | Surgical excision |
| Patient 4: Female | 80 | laBCC | 1 (100%) | 0 (0%) | Morbus bowen | Surgical excision, cryotherapy |
| Patient 5: Female | 68 | laBCC | 1 (100%) | 0 (0%) | – | Radiotherapy, plastic surgery, CO2 laser ablation |
| Patient 6: Female | 89 | laBCC | 2 (100%) | 0 (0%) | Colon carcinoma, Myoma uteri, meningioma | Surgical excision, cryotherapy |
| Patient 7: Female | 84 | laBCC | 1 (100%) | 0 (0%) | – | Radiotherapy, surgical excision |
| Patient 8: Female | 53 | NBCCS | 38 (71.7%) | 15 (28.3%) | Angiomyolipoma renis | Surgical excision, radiotherapy, cryotherapy, pharmacological: acitretin, imiquimod, CO2 laser ablation |
| Patient 9: Female | 58 | NBCCS | 36 (81.82%) | 8 (18.18%) | Meningeoma | Surgical excision, radiotherapy, cryotherapy |
| Patient 10: Female | 43 | NBCCS | 48 (73.85%) | 17 (26.15%) | – | Surgical excision, pharmacological: acitretin |
| Patient 11: Female | 81 | NBCCS | 6 (75%) | 2 (25%) | Bladder carcinoma | – |

BCC: basal cell carcinoma; NBCCS: nevoid basal cell carcinoma syndrome.

Figure 7. Comparison of the number of tumors and the diameter of the biggest lesion in laBCC and NBCC patients before vismodegib treatment. The number of tumors in NBCCS patients was significantly higher compared to that of laBCC patients (A). However, the diameter of the biggest lesion did not differ significantly between the two patient groups (B). (\( \ast \): \( p < 0.05 \) laBCC vs. NBCCS).

Figure 8. The therapeutic effect of smoothened-inhibitor vismodegib in 11 patients. The average diameter of the biggest tumor showed significant regression after treatment (A). The number of lesions significantly decreased after vismodegib treatment. (\( \ast \): \( p < 0.05 \) before vs. after; \( ** \): \( p < 0.01 \) before vs. after).
The management of alopecia for female patients was mainly a prescription for topical estradiol and prednisolone lotion without considerable effect. After the discontinuation of vismodegib therapy, we observed hair regrowth in all cases. In case of grade 2 and 3 muscle cramps, the combination of tizanidine and amlodipine, found mostly in the literature, did not result in marked improvement, tizanidine and tolperisone together only moderately relieved muscle cramps. Grade 1 muscle cramps were alleviated with magnesium and calcium supplementation. For the management of decreased appetite and weight loss, oral nutrition supplementation was introduced. Although weight loss initially slowed down, the treatment had to be discontinued in two patients due to further weight loss. For dysgeusia, specific treatment could not be applied; however, dietary guidelines were followed to alleviate food intake.

Discussion

Smo inhibitor vismodegib is the first target therapy in the treatment of BCC approved by the FDA and EMA. It is indicated for metastatic or locally advanced BCC in patients who are not candidates for surgery or radiotherapy (18). We present our single-center retrospective study of vismodegib for the treatment of locally advanced BCC and NBCCS in 11 Hungarian patients. Considering that vismodegib is a relatively new treatment option in BCC, most of the existing data are from clinical trials. Locally advanced BCC, besides the rare cases of NBCCS, mainly affect the elderly population, which cannot be often included in clinical trials, due to the high occurrence rate of comorbidities or other malignancies. Therefore, the experience with the drug in such patients is limited (24). Our patients received vismodegib therapy despite comorbidities and other malignancies, giving us a chance to investigate the effect of vismodegib in a real-life setting. Patients with other malignancies received vismodegib treatment in our department, including a patient with a history of polycythemia vera treated with hydroxyurea for over 10 years, which remained under control during vismodegib treatment. Although cytoreductive agents increase the risk of non-melanoma skin cancer, the patient developed BCCs long before hydroxyurea administration (25). Patient 2 had prostate cancer and received vismodegib treatment in our department based on an ongoing phase-II trial (NCT01163084) in combination with a GnRH agonist. The Hedgehog pathway was proved to have a significant role in oncogenesis and progression of prostate cancer (26). Vismodegib may also be effective in the treatment of prostate cancer (7). Due to the intracranial lesion of patient 3, the patient could not receive

Side effects of vismodegib therapy

The side effects first appeared after a mean of 6.45 ± 3.45 weeks (7 ± 3.94 vs. 5 ± 2 weeks; laBCC vs. NBCCS respectively; *p = 0.31*). The most frequent drug-related adverse events were dysgeusia, weight loss, muscle cramps and alopecia. The most common side effect, weight loss, was seen in 9 patients, followed by dysgeusia in eight patients. Muscle cramps and alopecia were seen in 7 and 6 patients, respectively.

Drug-related adverse events developed in both groups, and 10 patients had more than one side effect, no Grade 4 adverse event was observed. Twenty-nine percent of all side effects were Grade 2 and Grade 3 seen in six patients. In the case of the other five patients, Grade 1 side effects were observed. The occurrence of Grade 2 and Grade 3 side effects did not differ significantly between the laBCC and NBCCS patient groups (Table 3).

| Patient | Treatment (months) | Outcome | Number of tumors | Diameter of the biggest lesion (cm) | Time elapsed before improvement (months) |
|---------|-------------------|---------|------------------|------------------------------------|----------------------------------------|
|         |                   |         | before treatment  | after treatment                     | before treatment after treatment        |                                       |
| Patient 1 | 15                | improvement | 43               | 2                                  | 13                                     | 5.8                                    | 2                                      |
| Patient 2 | 16                | improvement followed | 1               | 1                                  | 0.8                                    | 2                                      | 3                                      |
| Patient 3 | 15                | deceased | 1                | 1                                  | 8                                      | 5.4                                    | 3                                      |
| Patient 4 | 3                 | complete remission | 0               | 0                                  | 0.3                                    | 0                                      | 2                                      |
| Patient 5 | 35               | improvement | 1                | 1                                  | 1.5                                    | 3.6                                    | 2                                      |
| Patient 6 | 5                 | deceased | 2                | 1                                  | 5.77                                   | 1                                      | 1                                      |
| Patient 7 | 6                 | improvement | 1                | 1                                  | 8                                      | 1                                      | 4                                      |
| Patient 8 | 2                 | deceased | 53               | n/a                                | 9.4                                    | 18.2                                   | 2                                      |
| Patient 9 | 54               | complete remission | 44               | 0                                  | 2.3                                    | 0                                      | 2                                      |
| Patient 10 | 13               | improvement | 65               | n/a                                | 1                                      | n/a                                    | 1                                      |
| Patient 11 | 11               | complete remission | 8                | 0                                  | 7                                      | 0                                      | 3                                      |

n/a: not available.

The clinical outcomes of vismodegib therapy in our patients.

Figure 9. Changes in the relative size of the tumors in five well-documented patients. A marked decrease in the size of the basal cell carcinoma lesions could be seen in 4 of the 5 patients after only 2 months. No increment of the size of the lesions was revealed during the observation period in any of these patients.

relapse was observed after the discontinuation of the drug therapy. Three patients showed remarkable improvement, but later passed away due to unrelated conditions. Even though two patients with laBCC initially showed remission, the treatment was suspended due to severe side effects as shown below (Table 2). After the re-introduction of vismodegib therapy, loss of efficacy was observed and their condition deteriorated. The rest of the patients showed good response to therapy, but have not reached full remission yet (Figure 9).

Table 2. The clinical outcomes of vismodegib therapy in our patients.
vismodegib as part of a clinical trial. The lesion was suspected to be a meningioma based on CT imaging and did not change in size during treatment. Patient 9 also had a verified meningioma. The Hedgehog pathway is often affected in the development of meningiomas, hence a Hh-pathway inhibitor target therapy holds promise in the treatment of aggressive meningeal tumors (27). An ongoing phase II trial currently investigates the effect of vismodegib combined with a focal adhesion kinase inhibitor in the treatment of progressive meningiomas (NCT02523014). In our limited experience, vismodegib treatment did not have a significant effect on regression.

The objective response rate (ORR) in clinical trials varied between 30–58%, similarly in our patient group, 7 patients showed complete or partial response to treatment (28). In our study group, the patients spent an average of 4.6 ± 5.3 months off the drug during treatment. In some cases, patients omitted a few doses of vismodegib on medical advice because of the side effects or the exacerbation of a disease. However, patients decided to skip doses in some cases without consultation, which was mainly due to the severity of the side effects. In the ERIVANCE BCC trial, 17% of the patients with locally advanced BCC had to discontinue the treatment due to adverse events (29), and with the side effects taken into consideration, the treatment was suspended permanently in 5 cases in our study group. It is crucial to avoid the unsupervised suspension of vismodegib, since drug resistance and disease progression can occur, as it was seen in patient 2. With the development of target therapies in oncology, the emergence of acquired resistance for the agent is one of the main obstacles. Acquired (secondary) resistance is characterized by initial good response to the drug followed by deterioration. The progression of the disease should be distinguished from primary resistance in which the tumor never responds to treatment. Both primary and secondary resistance has been reported in sporadic and NBCC patients (30–32). Resistance for vismodegib is hypothesized to account for mutations in the drug target Smo, the amplification of the downstream signaling, or the amplification of other interfering pathways (e.g. PI3 kinase pathway). As seen in this present study, 2 out of 7 patients with laBCC developed acquired resistance after the temporary withdrawal of the drug, while in another study, a lower acquired resistance rate of 13% was reported in this patient group (31). Contrary to data in the previously mentioned study, where 3 out of 5 patients with NBCCS developed resistance, in our study, the patients with Gorlin-Goltz syndrome remained sensitive to the drug even after suspension (31). Since patients with NBCCS harbor a germline mutation which predestines them for the occurrence of numerous BCCs, it can be hypothesized that vismodegib is effective to prevent the development of BCCs. Even with the selection of a drug-resistant subtype, continuous treatment could be beneficial in the case of the existing and de novo developing tumors, while local therapy could be considered for the drug-resistant lesion. Sporadic cases of BCC carry individual mutations, once the resistance has occurred, the tumor will remain insensitive to the drug, and change in the treatment modality needs to be considered. Neoadjuvant use of vismodegib has been reported to treat patients with NBCCS. In one of the reports, the patient developed de novo lesions resistant to the drug, and an already existing ulcer also deteriorated while undergoing treatment, later he underwent surgery (33). The initial shrinkage of the tumor can provide for a less drastic procedure, which can be the only curative therapeutic option once resistance has occurred. It has also been speculated that chemoresistance might occur more frequently in patients who received chemotherapy or radiation therapy previously (32). While NBCCS is most commonly associated with germline mutations in PTCH1, other mutations of the Hh pathway could result in a disease that is resistant to Smo-inhibitors especially in sporadic tumors. Thus, understanding the molecular genetics of BCC carcinogenesis and the identification of novel targets are of major importance.

The most common cause in our patients for temporary or permanent withdrawal of vismodegib was the appearance of drug-related adverse events. Most of the side effects of vismodegib are mechanism-related since the activity of the Hedgehog pathway impacts several cellular functions including stem cell renewal in adult tissues. Vismodegib was suggested to induce calcium channel activation by interfering with the hedgehog-pathway in

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**Table 3. The details of adverse events during vismodegib treatment.**

| Adverse events | First appearance of adverse events |
|----------------|----------------------------------|
| Alopecia       |                                  |
| Muscle cramps  |                                  |
| Dyseusia       |                                  |
| Weight loss    |                                  |
| Other          |                                  |

| Patient 1     | Grade 1 | Grade 2 | Grade 1 | Grade 3 | – | – | 6 weeks |
| Patient 2     | –       | –       | –       | –       | – | – | 12 weeks |
| Patient 3     | –       | –       | Grade 1 | Grade 1 | – | – | 12 weeks |
| Patient 4     | Already existing complaint | – | – | Grade 1 | Nausea (grade 1) | 8 weeks |
| Patient 5     | Grade 2 | Grade 3 | Grade 1 | Grade 1 | Numbness of toes | 2 weeks |
| Patient 6     | Grade 1 | Grade 1 | Grade 1 | Grade 3 | GERD (grade 1), nausea | 3 weeks |
| Patient 7     | –       | –       | Grade 1 | Grade 1 | – | – | 8 weeks |
| Patient 8     | –       | –       | Grade 1 | –       | – | – | 8 weeks |
| Patient 9     | Grade 2 | Grade 3 | Grade 2 | Grade 1 | GERD (grade 1), fatigue | 4 weeks |
| Patient 10    | Grade 2 | Grade 1 | Grade 2 | – | Change in bowel function (grade 1), continuous nausea (grade 2), infrequently vomiting (grade 1) | 4 weeks |
| Patient 11    | Grade 1 | Already existing, worsened after the administration (grade 2) | – | Grade 1 | Indigestion (grade 1) | 4 weeks |

GERD: gastroesophageal reflux disease.
muscle cells, causing muscle cramps. Hence, the voltage-dependent calcium channel blocker amloclidine was proposed in the treatment of vismodegib-related muscle cramps and according to an auxiliary study involving 43 patients, it decreased the frequency of muscle cramps (22). In our patient group, the combination of tizanidine and amloclidine was introduced in two cases; however, it did not improve muscle cramps considerably. Eventually, the combination of two different central muscle relaxants, tolperisone and tizanidine partially relieved severe muscle cramps. With the administration of central muscle relaxants in particular cases, blood pressure can decrease to such an extent that the administration of the antihypertensive drug could become obsolete. In the treatment of vismodegib-induced muscle cramps, given that the available agents can have an antihypertensive effect, the titration of the dose, the revision of the already existing antihypertensive treatment and the monitoring of blood pressure after dose advancement should be a priority. According to literature data, alopecia is observed in 46–66% of patients who receive vismodegib, since the Hedgehog pathway is crucial in the adult hair follicle morphogenesis (19). In our study, 3 out of 11 patients received vismodegib, since the Hedgehog pathway is crucial in the HH-pathway could result in a locally advanced disease that is resistant to Smo-inhibitors. Thus, understanding the molecular genetics of BCC carcinogenesis and the identification of novel targets are of major importance. The improvement of treatment combinations could allow us to overcome resistance and increase treatment efficacy.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

The project has been supported by EFOP-3.6.3-VEKOP-16-2017-00009.

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