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Case Report

Hedgehog Pathway and Programmed Cell Death Protein-1 Inhibitors for Advanced Basal Cell Carcinoma

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Keywords

Basal cell carcinoma · Locally advanced basal cell carcinoma · Metastatic disease · Hedgehog pathway inhibitor · Programmed cell death protein-1 inhibitors · Checkpoint inhibitors

Abstract

Introduction: Basal cell carcinoma (BCC) is treated with local surgery or noninvasive treatment modalities. If a BCC remains untreated, it can develop into a locally advanced BCC or a metastatic BCC. ***Case Presentation:*** Here we report in detail the management of three complex advanced BCC (aBCC) after treatment failure with vismodegib. On all tumors, next generation DNA sequencing in the Center for Personalized Cancer Treatment-02 (CPCT-02) study was performed; subsequently, patients were included in the Drug Rediscovery Protocol (DRUP) trial, in which treatment was started with commercially available targeted anticancer drugs based on the molecular tumor profile. All patients showed partial response or stable disease following treatment with second line PD-1 inhibitors with an average duration of response of 12.3 months. ***Discussion/Conclusion:*** Immunotherapy can be a treatment option for aBCC resistant to hedgehog pathway inhibitor treatment. However, despite the high tumor mutational burden of aBCCs, immunotherapy does not always lead to a long response. Rechallenge or combining treatment of hedgehog inhibitors and PD-1 inhibitors by parallel or alternating cycles may be a strategy to lengthen the treatment response.

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Introduction

Basal cell carcinoma (BCC) is treated with local surgery or noninvasive treatment modalities. If a BCC remains untreated, it can develop into a locally advanced BCC (laBCC) or a metastatic BCC (mBCC). In those relatively rare cases, local surgery or radiotherapy may not be possible or desirable due to extensive morbidity and functional impairment. The first approved systemic treatment options for advanced BCC (aBCC) were hedgehog pathway inhibitors, but disease progression during or after treatment is very common [1]. Before hedgehog inhibitors became available, aBCC cases were sometimes treated with different chemotherapy regimens with low efficacy rates [2]. Due to the high tumor mutational load in BCCs, immune checkpoint inhibitors were expected to be very effective. The effectiveness of cemiplimab was recently confirmed in an open-label trial in 84 patients with laBCC who progressed during or were intolerant to treatment with smoothened inhibitors [3]. The objective response rate of cemiplimab treatment was 31% (26/84 patients, 95% confidence interval (CI); 21–42). Here we report in detail the management of three complex aBCC cases treated with nivolumab and pembrolizumab after vismodegib failure. The CARE Checklist has been completed by the authors for this case report, attached as online suppl. material (for all online suppl. material, see https://doi.org/10.1159/000539592). All patients were treated with PD-1 inhibitors before cemiplimab was approved by the FDA and EMA. On all tumors, next generation DNA sequencing in the Center for Personalized Cancer Treatment-02 (CPCT-02) study was performed; subsequently, patients were included in the Drug Rediscovery Protocol (DRUP) trial, in which treatment was started with commercially available targeted anticancer drugs based on the molecular tumor profile [4, 5].

Case 1

A 68-year-old woman presented to our clinic with progressive left arm dysfunction and pain, four-and-a-half years after treatment of an aBCC on the left scapula with neoadjuvant vismodegib and surgical excision. There were no visible or palpable abnormalities in and around the scar. Computed tomography (CT) and magnetic resonance imaging (MRI) showed a soft tissue mass with bone destruction and widespread tumor invasion of the shoulder girdle muscles, a solitary lung mass in the right lower lobe and pathologic lymph nodes in the left axilla, left para-iliac region, and among the left anterior chest wall. Histological biopsy of the lung nodule showed a non-small cell carcinoma with basaloid and squamous morphology. Genetic analysis of this material confirmed clonality with the previous laBCC; therefore, the patient was diagnosed with mBCC [6]. A second biopsy was obtained for the CPCT-02 study, and genetic analysis revealed multiple gene mutations including *PTCH1*, a vismodegib-resistant *SMO* mutation, and a high tumor mutational burden (TMB) (693/Mb) (Table 1). Vismodegib retreatment was already started before these results were available and resulted in stable disease for 6 more months. After a slight increase in functional impairment of the left arm, MRI and CT of the thorax-abdomen revealed progressive disease in the shoulder with bone destruction after 6 months of treatment. Based on the high TMB, treatment with nivolumab 240 mg intravenously once every 2 weeks was started in the DRUP trial, resulting in partial response after 4 months of treatment. However, the patient developed grade three immune-mediated colitis and the treatment had to be discontinued after seven cycles. Oral prednisone 1 mg/kg/day was given for 5 months, as relapsing diarrhea prevented faster tapering. Ten months after nivolumab discontinuation, pain was no longer under control with morphine, and the arm function was almost lost. As retreatment with nivolumab was not

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Table 1. Clinical and tumor characteristics

	Case 1	Case 2	Case 3
Location primary BCC	Left scapula	Right abdomen	Midface
Location histology proven metastasis	Lungs	Left axillary lymph node	–
Genetic syndrome	No	No	No
Immunosuppression	No	No	No
Clonal relationship BCC and metastasis	Confirmed with mutational analysis	Confirmed with mutational analysis	–
Mutational analysis performed on before/after vismodegib	Metastasis after vismodegib	Metastasis before vismodegib	aBCC after vismodegib
TMB[a]	693	Classified as high, number unknown[b]	1,249
Gene mutations in	[d]DDR2, DDR2, MYCN, ERBB4, CTNNB1, CTNNB1, PDGFRA, APC, ESR1, SMO[c], PTCH1, TSC1, ARAF	[e]PTCH1, TP53, KDR	[d]MTOR, RAD54L, CTNNA2, APC, APC, CSFR1, ROS1, FGFR1, PTCH1, TSC1, NOTCH1, CTNNA3, BRCA2. FANCM, FANCI, TP53, TP53, CDK12, GNA11, GNA11, FANCB
PD-1 inhibitor	Nivolumab 240 mg intravenously 1×/2 weeks	Pembrolizumab 200 mg intravenously 1×/3 weeks	Nivolumab 220 mg intravenously 1×/2 weeks for 2 months and 480 mg 1×/4 weeks thereafter
Treatment duration	4 months	6 months	18 months
Reason discontinuation	Immune-related adverse event (colitis)	Progressive disease	Death unrelated to aBCC
Outcome	Partial response for 11 months	Stable disease for 8 months	Near complete response for 18 months

[a]The tumor mutational burden represents the total number of somatic missense variants across the whole genome of the tumor. Patients with a mutational load over 140 could be eligible for immunotherapy within the Drug Rediscovery Protocol study. Tumor purity was >20% in all cases, mutational analysis was based on reference genome version GRCh37. [b]Original report dates from 2016. [c]A known vismodegib-resistant *SMO* mutation: c.722C>T p.Thr241Met. [d]Gene panel tested: ABL1, AKT1, ALK, APC, AR, ARAF, ATM, ATR, AXL, BARD1, BRAF, BRCA1, BRCA2, BRIP1, CCND1, CDH1, CDK12, CDK4, CDK6, CDKN2A, CHEK1, CHEK2, CRKL, CSF1R, CTNNA1, CTNNA2, CTNNA3, CTNNB1, EGFR, ERBB2, ERBB3, ERBB4, ERCC1, ESR1, EZH2, FANCA, FANCB, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, FBXW7, FGFR1, FGFR2, FGFR3, FGFR4, FLT1, FLT3, FLT4, GNA11, GNAQ, GNAS, HNF1A, HRAS, IDH1, IDH2, JAK2, JAK3, KDR, KIT, KRAS, MAP2K1, MAP2K2, MAP2K4, MAP3K1, MAPK1, MCPH1, MDM2, MET, MLH1, MPL, MRE11A, MSH2, MSH6, MST1R, MTOR, MYC, MYCN, NBN, NF1, NOTCH1, NPM1, NRAS, NRG1, NTRK1, NTRK2, NTRK3, PALB2, PDGFRA, PDGFRB, PIK3CA, PIK3CB, PMS2, PPP2R2A, PTCH1, PTEN, PTPN11, RAD50, RAD51, RAD51B, RAD51C, RAD51D, RAD54L, RAF1, RB1, RET, RNF43, ROS1, RUNX1, SLX4, SMAD4, SMARCB1, SMO, SRC, STK11, TOP2A, TP53, TSC1, TSC2, VHL. [e]Gene panel tested: ABL1, AKT1, ALK, APC, ATM, BRAF, BRCA1, BRCA2, CDH1, CDKN2A, CSF1R, CTNNB1, EGFR, ERBB2, ERBB4, EZH2, FBXW7, FGFR1, FGFR2, FGFR3, FLT3, GNA11, GNAQ, GNAS, HNF1A, HRAS, IDH1, IDH2, JAK2, JAK3, KDR, KIT, KRAS, MET, MLH1, MPL, NOTCH1, NPM1, NRAS, PDGFRA, PIK3CA, PTEN, PTPN11, RB1, RET, SMAD4, SMARCB1, SMO, SRC, STK11, TP53, VHL.

permitted in the DRUP trial and no other trials were available, we treated the patient with palliative radiotherapy (35 × 2 Gy) on the shoulder. Palliative radiotherapy led to a decrease in pain, but shortly after, the disease progressed further and the patient deceased 40 months after presentation with metastatic disease.

Case 2

A 63-year-old woman presented to our clinic with a 20-year existing, ulcerating tumor on the abdomen and a smaller, ulcerating tumor in the left axilla (Fig. 1a, b). Histologic examination of punch biopsies of both lesions showed basaloid tumors with undifferentiated, infiltrating growth that were considered to be BCC. Mutational analysis of tumor material obtained from both lesions revealed the same *PTCH1* mutation and confirmed the diagnosis aBCC with axillary metastasis (Table 1) [6]. With additional staging with a f-18 fluorodeoxyglucose (FDG) positron emission tomography/CT scan, multiple FDG-avid lymph nodes were seen in the left iliac, infraclavicular, retroperitoneal, and inguinal regions. Because of the widespread BCC localization, systemic treatment with vismodegib 150 mg/day was started, but after 7 months, a CT scan showed progressive disease of the abdominal BCC and axillary lymph nodes. After inclusion in the CPCT-02 and DRUP trials, genetic analysis revealed multiple gene mutations including *PTCH1*, and a high TMB (exact number unknown) (Table 1). Pembrolizumab treatment was started with 200 mg intravenously once every 3 weeks, resulting in stable disease for 8 months monitored both clinically and with 3-month CT scan evaluation. However, after 8 months, the patient developed more pain from the axillary mass, and CT scan showed an increase in size of the axillary mass and an increase in lymphadenopathy in the left axillary region. Pembrolizumab treatment was discontinued because of the progressive disease. As there were no other systemic treatment options available, vismodegib treatment was restarted, and the clinical visible tumors on the abdomen and axilla remained stable. After 7 months of retreatment with vismodegib, the axillary metastasis evolved in a painful, ulcerating tumor. Vismodegib treatment was temporarily stopped and radiotherapy with 15 fractions of 2.67 Gy directed to the axillary metastasis led to a partial response. Vismodegib therapy was restarted, but 4 months after termination of radiotherapy, the axillary metastasis and abdominal tumor progressed, and vismodegib therapy was discontinued. Palliative radiotherapy was given for both the abdominal BCC (15 × 2.67 Gy) and axillary metastasis (5 × 4 Gy), leading to a decrease in pain. Forty-five months after the first presentation with metastatic disease the patient deceased.

Case 3

A 60-year-old woman presented with an irresectable, histopathological, confirmed nodular and infiltrative BCC on the nose, both cheeks, left medial eye corner, and upper lip, present for 20 years. Staging with CT revealed an additional mass in the oropharynx. After histological examination of this mass and an FDG-positron emission tomography/CT scan, the patient was diagnosed with a stage II diffuse large cell B-cell lymphoma, with localization in the oropharynx and cervical lymph nodes. Treatment of the lymphoma was initiated with rituximab, cyclophosphamide, hydroxydaunorubicin, vincristine (Oncovin), and prednisolone chemotherapy (R-CHOP), resulting in complete remission of the lymphoma. Interestingly, also the BCC showed a complete clinical response, but it recurred 9 months after R-CHOP discontinuation. Vismodegib treatment 150 mg/day was started, resulting in partial response,

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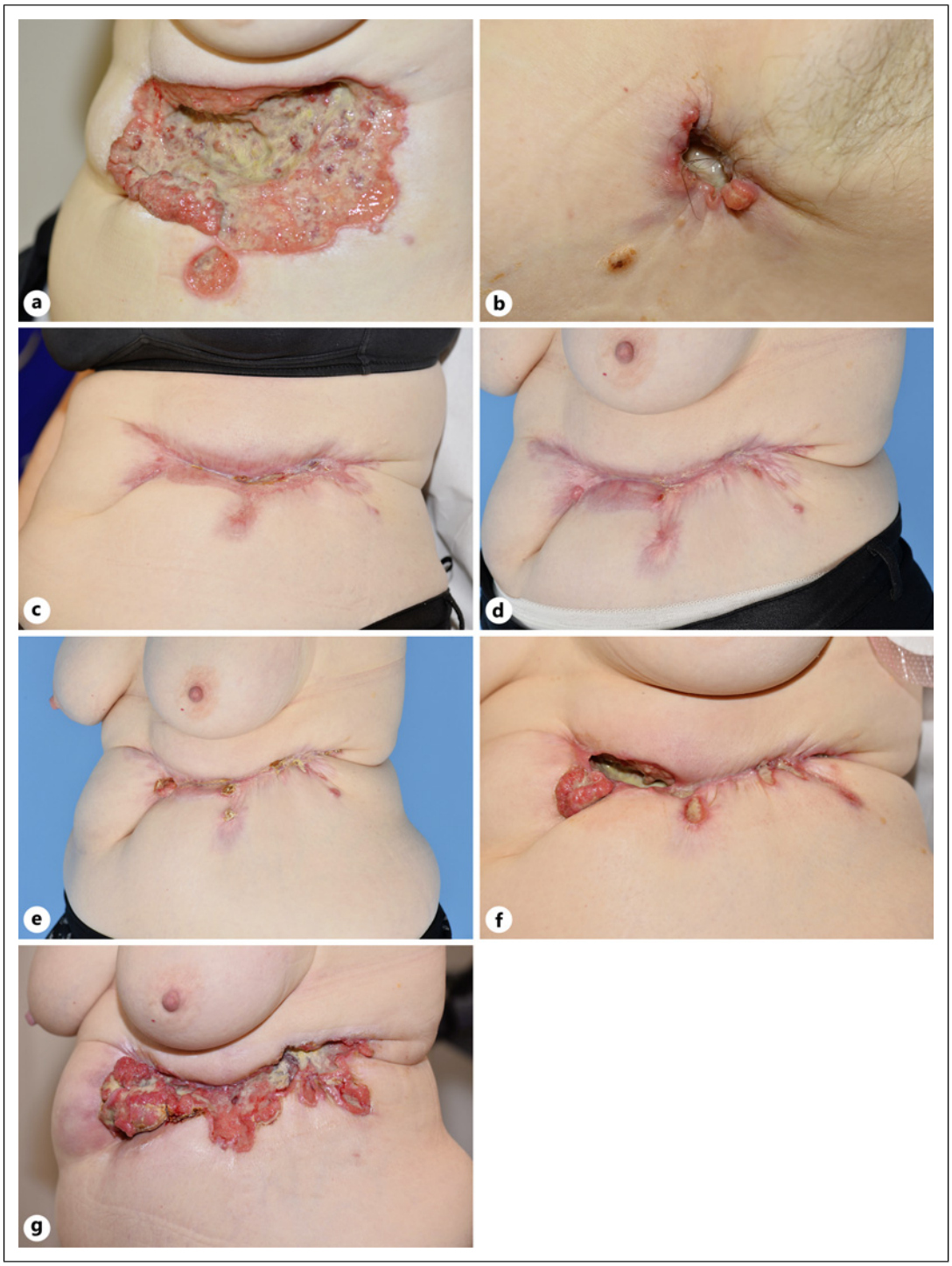

Fig. 1. Clinical photograph of advanced basal cell carcinoma on the left abdomen before and during the complete treatment course (case 2). **a** aBCC on the left side of the abdomen at first presentation. **b** Axillary metastasis in the left axilla at first presentation. **c** aBCC on the abdomen after 4 months of vismodegib treatment. Clinically visible good response to vismodegib treatment. **d** aBCC on the abdomen after 6 months of vismodegib treatment. Several tumor nodules visible in the scar. **e** aBCC on the abdomen during treatment with pembrolizumab. Several tumor nodules are still visible. **f** aBCC on the abdomen after discontinuing pembrolizumab treatment. Clinically visible disease progression. **g** aBCC on the abdomen during the second cycle of vismodegib treatment. Disease progression is clinically visible.

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but it had to be discontinued after 6 months due to side effects (alopecia, dysgeusia, and muscle cramps). Only 20 months after vismodegib discontinuation, the aBCC progressed, and retreatment with vismodegib again led to a partial response. However, after 6 months, the aBCC progressed during treatment, and the patient was included in the CPTC-02 and DRUP trials. Genetic analysis revealed a broad spectrum of gene alterations in the BCC and a high TMB (1,249/Mb) and nivolumab treatment was started with 240 mg intravenously once every 2 weeks for 2 months and 480 mg intravenously once every 4 weeks thereafter. Seven months after the start of nivolumab treatment, an MRI scan showed partial response, eventually leading to near complete response (unmeasurable disease on MRI) ongoing for at least 18 months during which the patient did not experience side effects and had no signs of recurrence of the lymphoma. However, the patient died suddenly of an unknown cause, 69 months after the first presentation with aBCC.

Discussion

We described three vismodegib resistant aBCC patients whom were treated with different PD-1 inhibitors before cemiplimab was approved as only PD-1 inhibitor for the treatment of aBCC by the FDA and EMA. All patients showed partial response or stable disease following treatment with second line PD-1 inhibitors with an average duration of response of 12.3 months. A high TMB was found in all tumors, which is consistent with findings in the literature and known to correlate with good response to checkpoint inhibitors [7, 8].

Evidence regarding PD-1 therapy in hedgehog pathway inhibitor treatment resistance aBCC is scarce. A large open-label, multicenter, single-arm study investigated the use of the PD inhibitor cemiplimab in 84 patients with laBCC who progressed during or were intolerant to treatment with smoothened inhibitors [3]. Treatment with cemiplimab 350 mg intravenously once every 3 weeks led to a found objective response rate of 31% (26/84 patients) following a median exposure to cemiplimab of 47 weeks, with five patients (6%) complete response and 21 patients (25%) partial response. Furthermore, a proof-of-concept study was published in which 16 aBCC patients were included to evaluate the response to either pembrolizumab monotherapy (n = 9) or pembrolizumab and vismodegib combination therapy (n = 7) [9]. Monotherapy with pembrolizumab 200 mg intravenously every 3 weeks was given to patients who showed progressive disease during vismodegib treatment, whereas patients with no tumor progression during vismodegib treatment continued vismodegib 150 mg orally daily, while pembrolizumab 200 mg intravenously every 3 weeks was added. The overall response rate was 38% (6/16 patients) at 18 weeks with no statistical difference between both groups [9]. The duration of response was 67.6 (95% CI, 31.4–82.0) months in the pembrolizumab monotherapy group and 52.8 (95% CI, 28.0–77.6) months in the pembrolizumab plus vismodegib group. A third multicenter study retrospectively analyzed 29 patients with aBCC treated with PD-1 inhibitor therapy (nivolumab, pembrolizumab, or cemiplimab), of whom twenty-four (82.8%) had been treated with a hedgehog pathway inhibitor before, among which 18 (75.0%) discontinued therapy due to disease progression [10]. After a median follow-up of 11 months, the objective response rate was 31.0%, and the median progression free survival was 12.2 months in the complete group. Results per different PD-1 inhibitor were not described.

In the second case described, vismodegib retreatment after pembrolizumab discontinuation still led to stable disease, whereas the previous vismodegib treatment was discontinued after progressive disease. This may imply that a refractory tumor can turn responsive again after a treatment holiday, a phenomenon that is also observed in several other

tumors [11]. On the other hand, it can be debated whether the 6 months of stable disease can be attributed to vismodegib treatment or whether mBCC itself grows so slowly that changes are difficult to detect. For instance, the lung metastasis of case 1 harbored a vismodegib-resistant *SMO* mutation but still remained stable for 6 months on vismodegib treatment. As studies investigating vismodegib treatment in mBCC were not placebo-controlled, and no other data on the growth of BCC metastases over time are available, there is no information on the natural behavior of untreated mBCC.

One of our patients experienced grade three immune-mediated colitis which resulted in early treatment discontinuation despite a good tumor response. Toxicity is commonly seen in the use of PD-1 inhibitors with often described immunologic side effects such as colitis, hepatitis, endocrine toxicity, dermatitis, and pneumonia [12]. In melanoma, toxicity to PD-1 inhibitors is known to be positively correlated to a good and durable response to PD-1 inhibitors, but it is unknown whether this correlation can also be found in patients treated for aBCC [13]. Our patient had a stable disease for 7 months after discontinuing treatment with immunotherapy. After disease progression, retreatment with nivolumab might have evoked a partial response again, but due to restrictions of the study protocol and insurance companies, we could not prescribe this therapy again.

In conclusion, immunotherapy can be a treatment option for aBCC resistant to hedgehog pathway inhibitor treatment. However, despite the high TMB of aBCCs, immunotherapy does not always lead to a long response. Rechallenge or combining treatment of hedgehog inhibitors and PD-1 inhibitors by parallel or alternating cycles may be a strategy to lengthen the treatment response.

Statement of Ethics

Ethical approval is not required for this study in accordance with local or national guidelines. Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images. Consent for the publication of all patient photographs and medical information was provided by the authors at the time of article submission to the journal stating that all patients or their next of kin gave consent for their photographs and medical information to be published in print and online and with the understanding that this information may be publicly available.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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None.

Author Contributions

B.V.: writing draft of the article; design; and data collection and interpretation; A.R. and M.A.: revision of the article and data collection and interpretation; and K.M.: writing draft of the article and revision of the article; design; and data collection and interpretation.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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