VIA MEDICA

CASE REPORT

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Effectiveness of rechallenge with BRAF/ /MEK inhibitors in patient with advanced melanoma with *BRAF V600* mutation

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ABSTRACT

Rechallenge with BRAF/MEK inhibitors is currently a recognized option that improves treatment outcomes in terms of response and survival. This paper presents the case of a 54-year-old female patient with metastatic melanoma and a positive *BRAF* mutation status. The patient received first line targeted therapy. After disease progression, immunotherapy was administered. After another progression, with a good performance status, targeted therapy was reintroduced. A good response was achieved with a statistically significant prolongation of survival. The patient, without progression, in a good performance status, is alive 52 months after the start of the first line therapy and 23 months after the start of rechallenge.

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Introduction

The prognosis in patients with inoperable stage III and metastatic stage IV melanoma was very poor in the past decade. Historically, the overall survival (OS) in these patients was 7.5 months, while approximately 6% of patients survived 5 years. Available therapies were ineffective, with a short response to chemotherapy or unacceptable toxicity of high-dose interleukin 2 therapy [1]. The use of new therapeutic strategies has significantly improved the prognosis in patients with metastatic melanoma. Targeted therapy with BRAF/MEK inhibitors targets the MAPK signaling pathway, activated in melanomas with the *BRAF V600* mutation. Immunotherapy with anti-CTLA-4 and/ /or anti-PD-1 monoclonal antibodies modulates immune response checkpoints. Currently, the median OS in patients with skin melanoma is in the range of 12–24 months, and 20–40% of patients survive 5 years [2].

Approximately 50% of melanoma patients harbor *BRAF* mutation, which is a predictive factor for BRAF/ /MEK inhibitor therapy. Despite a high response rate of nearly 70% to the initial therapy, more than half of patients experience disease progression within 1 year. Immunotherapy with immune checkpoint inhibitors (ICIs), as second line treatment, is the treatment of choice in patients with progression during targeted therapy. This treatment involves monotherapy with an anti-PD-1 monoclonal antibody (nivolumab or pembrolizumab) or a combination of anti-PD-1 (nivolumab) and anti-CTLA-4 (ipilimumab) antibodies. The use of this therapy is associated with response rates of approximately 50% with 1-year survival rate of 70%. However, half of patients will not respond to immunotherapy, and most of them will experience progression [3].

Rechallenge with BRAF/MEK inhibitors is a promising therapeutic option in patients who have previously progressed on targeted therapy and then progressed on immunotherapy (anti-CTLA-4 or anti-PD-1).

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Case report

A 54-year-old female patient with no significant medical history was diagnosed at the Oncological Surgery Outpatient Clinic of the Voivodeship Hospital Centre of the Jelenia Gora Valley in April 2019 due to a tumor in the area of the left scapula that had been growing for two years. In a histopathological examination of the material collected by core needle biopsy, melanoma was diagnosed with a mutation in the *V600* codon of the *BRAF* gene.

The patient did not seek treatment at that time and used alternative therapy, despite growing tumor. The patient reported to the Oncology Outpatient Clinic of the Voivodeship Hospital Centre of the Jelenia Gora Valley in July 2019 due to worsening well-being and increasing pain in the area of the lesion. Patient's performance status according to the Eastern Cooperative Oncology Group (ECOG) score was assessed as 1. The physical examination revealed an ulcerating, spherical tumor in the area of the left scapula, 9 cm in diameter, with extensively infiltrated skin and subcutaneous tissue up to 20 cm in diameter, nodal packages up to 5 cm in both axillary fossae. Computed tomography of the chest, abdomen and pelvis, in addition to the previously mentioned nodular lesion, revealed bilateral metastatic lesions in the axillary nodes, left supraclavicular and subclavicular nodes, lymph nodes of the lower part of the neck on the left side, as well as micronodular dissemination to the lungs and liver. CT scans of the head did not reveal any pathology.

Taking into account the presence of *BRAF* mutation, disseminated nature and high dynamics of the neoplastic process, as well as high tumor burden and good performance status, the patient was qualified for palliative systemic therapy with vemurafenib and cobimetinib, in accordance with the provisions of the drug program B.59 "Treatment of melanoma of the skin and mucous membranes". Treatment was started in July 2019.

The first follow-up CT scan performed in November 2019 revealed complete remission of the primary lesion, metastatic lesions in the lungs and liver, and significant regression in the previously involved lymph nodes. In the physical examination, a very rapid regression of the lesion in the scapular region was observed, with residual flat, scabbed thickening with a diameter of 4 cm. The treatment was continued, and complete remission of neoplastic lesions was confirmed in subsequent imaging studies and physical examinations. Locally, the evolution of the lesion was observed through a black flat thickening to a completely discolored indentation in the place of the initially described tumor.

During the therapy, the patient reported recurrent itching of the skin, minor abdominal pain, and diarrhea with intensity assessed as grade 1 according to CTCAE. In addition, poor vision and a stinging sensation of the upper eyelids occurred periodically. The patient was consulted by an ophthalmologist several times, but no significant pathologies were found. The reported complaints were treated symptomatically, with good results and a stable performance status.

Since July 2020, the patient has been experiencing mild headaches and dizziness. A magnetic resonance imaging (MRI) scan of the head performed in August 2020 showed the presence of numerous metastatic lesions in the brain — the largest with a diameter of 15 mm in the left hemisphere of the cerebellum. After a radiotherapy consultation, the patient was qualified for palliative radiotherapy of the central nervous system (CNS) in the branch of the Radiotherapy Department of the Lower Silesian Oncology Center in Jelenia Góra. In the period from August 31 to September 4, 2020, palliative brain radiotherapy was performed with a total dose of 20 Gy in five fractions.

The patient returned to the Department of Clinical Oncology/Chemotherapy of the Voivodeship Hospital Centre of the Jelenia Gora Valley in September 2020. In the medical history, she reported stable dizziness and periodically occurring headaches of mild intensity. The patient's performance status was assessed as ECOG 1. Laboratory tests showed signs of grade 1 hypothyroidism according CTCAE, and for this reason appropriate supplementation was started.

Taking into account the previous course of the disease and treatment, the currently observed progression in the CNS, previous radiotherapy, stable CNS symptoms for 1 month (CTCAE grade 1), the performance status and organ efficiency, the patient was qualified for palliative second line treatment with nivolumab under the drug program. The therapy started in October 2020.

Follow-up imaging studies performed in December 2020 and March 2021 showed partial remission of the lesion in the right frontal lobe and complete remission of the remaining metastatic lesions in the brain, with continued complete remission (CR) of peripheral lesions. The patient reported sporadic paroxysmal tremors of the upper and lower left limbs, slight dizziness, with a continuous subjective improvement in well-being. Laboratory tests did not reveal any significant abnormalities. There was no deterioration in the patient's performance status.

In May 2021, the patient experienced epileptic seizures, with transient left-sided paresis, fainting, and a feeling of pressure in the head. Imaging tests performed in June 2021 showed significant progression of a single metastatic lesion in the left frontal lobe, accompanied by severe swelling, with persistent remission of peripheral lesions. After a neurosurgical consultation, the patient was qualified for surgical treatment. On June 22, 2021, a right parietal-frontal craniotomy

was performed at the Neurosurgery Department of the Voivodeship Hospital Centre of the Jelenia Gora Valley, with complete tumor resection. The histopathological examination confirmed a metastasis of melanoma.

In July 2021, the patient was readmitted to the Department of Clinical Oncology/Chemotherapy. She reported periodic sensations of pressure and pain in the area of the right temple without epileptic seizures. The performance status was still assessed as ECOG 1. Considering the persistent CR on the periphery, the radical neurosurgical procedure and good performance status, the patient was qualified for continued treatment with nivolumab.

Imaging tests performed in October 2021 showed postoperative changes in the right hemisphere of the brain, with persistent regression of other lesions in the CNS and the periphery. Treatment was well tolerated; no additional symptoms were found.

During the next follow-up visit in December 2021, a physical examination and imaging revealed progression in the right neck lymph nodes. A CT scan performed on December 28 showed pathological right neck lymph nodes, group IIB, measuring 17.5 × 13 mm. Due to the progression found on the periphery, immunotherapy was discontinued. Echocardiography was also performed, and an ophthalmological consultation was carried out. Laboratory tests did not reveal any significant abnormalities.

Taking into account the current course of the disease and treatment, good performance status, and no CNS symptoms, the patient was qualified for the third line treatment, with re-use of BRAF/MEK inhibitors (encorafenib + binimetinib), in accordance with the provisions of the drug program. The treatment was started on December 30, 2021.

In March 2022, the patient was urgently admitted to the Department of Clinical Oncology/Chemotherapy due to grade 4 diarrhea according to CTCAE. Laboratory tests showed grade 2 deterioration of renal parameters according to CTCAE and a negative result of a stool test for *Clostridium difficile*. The treatment with BRAF/MEK inhibitors was interrupted, intravenous fluids were introduced and symptomatic treatment was started. Within three days, the patient's general condition improved, renal parameters normalized, and diarrhea resolved.

The follow-up imaging tests performed at that time showed CR of the neck lesions, with continued regression of the remaining peripheral lesions and brain lesions. In April 2022, treatment with BRAF/MEK inhibitors (encorafenib + binimetinib) was resumed.

In May, during the visit, the patient had an epileptic seizure with transient left hemiplegia. Laboratory tests revealed grade 1 elevated creatinine level according to CTCAE. Antiepileptic treatment was modified under neurological control. MRI of the head performed in April did not reveal progression of the neoplastic process. It was decided to continue the treatment. Since July 2022, the patient has complained of alternating constipation with loose stools and paroxysmal, crampy abdominal pain. In addition, she reported a lack of appetite, general weakness, and dizziness when bending down. The ECOG performance status deteriorated to 2. The physical examination indicated pressure pain in the epigastric fossa. Laboratory tests revealed grade 1 elevated creatinine level according to CTCAE, without other significant abnormalities.

Due to the patient's complaints and poor well-being, the next course of encorafenib + binimetinib treatment was postponed. On July 11, 2022, gastrofiberoscopy and abdominal ultrasound were performed, which did not show any significant pathologies. After the applied symptomatic treatment, the patient's condition improved. It was decided to continue the treatment.

The patient reported recurrent moderate abdominal pain. Laboratory test indicated grade 1 creatinine level elevation according to CTCAE and grade 1 decrease in the estimated glomerular filtration rate (eGFR) according to CTCAE. A CT scan of the chest, abdomen and pelvic performed on September 6, 2022, did not reveal any signs of cancer progression.

A circular infiltration was described in the terminal section of the small intestine, requiring further diagnostics.

Due to maintaining treatment response it was decided to continue systemic therapy. The patient was also referred to the Oncological Surgery Department, where on October 4, 2022, a colonoscopy was performed, revealing a small, hard infiltration at the Bauhin valve level. Samples were taken for histopathological examination, in which features of non-specific inflammation were found, without neoplastic changes.

On October 17, 2022, a laparoscopic right hemicolectomy was performed. Due to the planned procedure, BRAF/MEK encorafenib + binimetinib treatment was suspended for a week before the procedure and three weeks after the procedure. Postoperative histopathological examination revealed non-specific inflammatory changes, without neoplastic changes.

The next whole-body imaging, performed on December 12, 2022, did not show any signs of tumor progression. Therefore, it was decided to continue targeted therapy.

In February 2023, epileptic seizures reappeared. The MRI image showed stable lesions in the CNS. Under the supervision of the Neurological Outpatient Clinic of the Voivodeship Hospital Centre of the Jelenia Gora Valley, antiepileptic treatment was modified, which resulted in a gradual improvement in the patient's condition.

The patient reported to the hospital on March 30, 2023, with diarrhea, periodically worsening to 2 degree according to CTCAE, and low blood pressure. Dizziness and significant weakness were also reported. The clinical assessment showed a deterioration of the performance status to 3 degree according to the ECOG score. Laboratory tests showed: increased CRP level (27), deterioration of renal parameters – grade 1 creatinine and eGFR according to CTCAE. On March 29, a CT scan of the chest, abdomen and pelvis was performed, which revealed asymmetry of glandular tissue in the right breast, without signs of progression of neoplastic lesions. Due to the deterioration of the patient's general condition and the previously mentioned symptoms, it was decided to temporarily interrupt BRAFi/MEKi therapy. Symptomatic treatment was used. Both tests — MMG and ultrasound — excluded focal lesions in the breasts.

During the follow-up visit on April 20, 2023, the patient reported resolution of previously existing symptoms and significant improvement of well-being. Performance status was assessed as ECOG 1. Laboratory tests showed normalization of renal parameters and CRP level. Due to the deteriorating treatment tolerance it was decided to resume BRAFi/MEKi therapy (encorafenib + binimetinib) in reduced doses — first dose reduction (in accordance with the SPC) from the current, 15th course: BRAF 75 mg, 4 tablets once daily; MEK 15 mg, 1 tablet twice daily.

In June 2023, the patient was consulted by an ophthalmologist due to visual disturbances, flashes in the eyes and darkening of the field of vision. The patient received local medications, with good results.

Since June 2023, an increasing number of pigmented lesions have been observed on the skin of the entire body. Therefore, the patient has been systematically undergoing dermatoscopy. To date, no suspicious lesions have been found.

Subsequent imaging studies performed according to the planned scheme showed stabilization of the neoplastic disease. The last CT scan of the chest, abdominal cavity and pelvis was performed on November 23, 2023, and the MRI of the head on September 4.

The patient's next visit took place on December 19, 2023. The patient continues treatment, and at the time of manuscript preparation, she is in the middle of her 25th course. The patient currently reports no symptoms. Performance status was assessed as ECOG 1. The patient functions normally.

Discussion

Progression during treatment with BRAF/MEK inhibitors occurs as a result of acquired resistance associated with reactivation of the MAPK/ERK pathway or at the level of the *BRAF* mutation itself. BRAF/MEK inhibitor resistance has also been shown to induce mechanisms of tumor escape from immune control. In turn, immunotherapy may increase the response to targeted therapy in *BRAF*-mutated melanomas.

Mechanisms of resistance to targeted therapy may be reversible. Tumors are heterogeneous and dominant cell clones change due to new mutations acquired by dividing cells, depending on changes in the tumor microenvironment or external factors such as systemic or local treatment. Hence, after initial exposure to targeted therapy and achieving treatment response, some cell clones may develop resistance, leading to disease progression.

Cessation of exposure to targeted therapy allows for the growth of other tumor cell clones, which were sensitive to it. This phenomenon may result in reversal of resistance to BRAF/MEK inhibitors [2].

The results of review of 238 patients, published in 2019, showed responses to re-challenge in this population, even in patients with previous progression on targeted therapy. The objective response rate (ORR) was 47% with progression-free survival (PFS) of 6.4 months, which was shorter than after first line treatment (9.2 months) [4].

A multicenter retrospective analysis conducted by a Polish group in 2020 included 51 patients who were rechallenged with BRAFi/MEKi therapy. Median overall survival (OS) from the initiation of first line targeted treatment and from rechallenge was 29.7 and 9.3 months, respectively, median progression-free survival (PFS) was 10.5 and 5.9 months, respectively. 6-month survival rates were 98% and 55%, 1-year: 92% and 29%, and 2-year: 69% and 2%, respectively. ORR was higher in first line treatment compared to rechallenge and was 72% and 27%, respectively. The duration of break between the end and start of BRAFi/MEKi therapy did not affect OS. Lower treatment toxicity was observed during rechallenge. The efficacy of rechallenge was better in patients with good performance status, normal lactate dehydrogenase level, and no brain metastases [5].

In August 2023, a meta-analysis was published, including a group of 400 patients with advanced *BRAF*-mutated melanoma, receiving in the first or second line BRAFi/MEKi combined therapy or BRAFi monotherapy. The majority of patients (83%) received immunotherapy, 10% had a break in treatment. During rechallenge, 79% of patients received BRAFi/MEKi combination. The median PFS in this subgroup was 5 months, median OS was 9.8 months, 1-year survival rate 42.6%, and ORR 34%. The presence of brain metastases was not associated with a higher risk of progression or death [2].

At the 2023 ASCO Annual Meeting, Polish and Spanish studies were presented. The Polish study presented the results of a multicenter analysis, which

included 86 patients. The median OS from the start of BRAFi/MEKi therapy and from the start of rechallenge was 34 and 9 months, respectively, and median PFS was 10.5 and 4.4 months, respectively. The half-year, 1-year and 2-year survival rates for first-line treatment were 99%, 93% and 70%, respectively, and for rechallenge 65%, 40% and 2%, respectively. The ORR for first line BRAFi/MEKi therapy and rechallenge was 57% and 28%, respectively [6].

The Spanish study reported the results of a subgroup analysis of 30 of 893 melanoma patients in the GEM 1801 study. The objective response rate (ORR) for the rechallenge group (n = 26), was 38.5%, median PFS and OS 11.1 and 22.1 months, respectively. A positive correlation was found between the depth of response to first line treatment and the duration of PFS [3].

Conclusions

We presented a case report of 54-year-old female patient, treated for disseminated melanoma since July 2019, who achieved a rapid and complete response to first line BRAFi/MEKi combined treatment. Multiple CNS metastases occurred in the 11th month of therapy. After radiotherapy to the CNS, the patient was qualified for immunotherapy with nivolumab, as second line treatment. After 8 months of therapy, progression of one brain lesion was observed, which was surgically removed. Immunotherapy was conducted for a total of 15 months, until progression in the cervical, supraclavicular and subclavicular lymph nodes. Since December 30, 2021, the patient has been undergoing third line treatment with BRAF/MEK inhibitors (encorafenib + + binimetinib). During follow-up, until this manuscript preparation, no signs of cancer recurrence have been observed. The patient is currently during 25th course of therapy. The patient does not report any significant complaints and functions normally.

Rechallenge with BRAF/MEK inhibitors after second line immunotherapy provides significant clinical benefit and is a valuable treatment option for patients with advanced melanoma. Third line therapy should be offered to patients in good performance status. Presented patient is in good performance status, without disease progression, alive 52 months after first treatment initiation and 23 months after the start of rechallenge.

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