VIA MEDICA

CASE REPORT

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Encorafenib in combination with binimetinib in second line palliative treatment in 44-year patient with symptoms of spinal cord compression

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ABSTRACT

The described case concerns a 44-year-old patient with metastatic skin melanoma and the presence of *BRAF* mutation, who was treated with combined immunotherapy (nivolumab and ipilimumab) with the result of hyperprogression. The first signs of spinal cord compression were observed before the treatment with encorafenib and binimetinib was started. Despite a poor prognosis related to fast progression, the presence of CNS metastases and the presence of *BRAF* mutations, the treatment allowed for a good control of the symptoms of the disease for about six months and improved the quality of patient's life. The combination of BRAF/MEK inhibitors was well tolerated and there was no need for a dose reduction.

Keywords: advanced melanoma, *BRAF* mutation, encorafenib, binimetinib, brain metastases

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Introduction

In recent decades, an alarming increase in the number of newly diagnosed skin melanomas has been observed in Poland. The standardized incidence is approximately 6/100,000, which corresponds to nearly 4,000 new cases per year [1].

A five-year survival rate for patients with metastatic disease ranges from 20% to 40%. Melanoma patients with dissemination in the central nervous system constitute a subgroup with a particularly poor prognosis. It is estimated that in approximately 50% to 60% of patients with advanced melanoma brain metastases will develop (in approximately 75% patients in this subgroup multiple metastases will be detected).

One of unfavorable prognostic factors associated with a higher risk of metastases to the CNS is the presence of an activating mutation in the *BRAF* gene, which is found in about half of patients with advanced melanoma [2].

Case report

A 44-year-old male patient with no significant comorbidities presented for his first visit to the dermatology clinic in August 2021, due to a skin lesion in the left breast area. On August 12, 2021, an excisional biopsy of the suspicious lesion was performed. Histopathological examination revealed invasive melanoma, nodular type; maximum depth of invasion (Breslow thickness) 3 mm; without accompanying ulceration. Subsequently, on August 31, 2021, a wide scar excision procedure and a sentinel node biopsy were performed. Histopathological examination revealed a skin fragment with a scar without

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atypical changes and a lymph node with a melanoma metastasis of 8 mm in diameter with infiltration, but without crossing nodal capsule.

Due to the confirmed metastasis in the sentinel lymph node of the left axilla, the patient was qualified for left axillary lymph node dissection, which was performed on October 28, 2021. Histopathological examination confirmed metastases of melanoma to two of the twelve examined lymph nodes (2/12). In the positron emission tomography-computed tomography (PET-CT) examination performed after the surgery distant melanoma metastases were excluded. The clinical disease stage was finally determined as pT3aN2aM0 = IIIB.

In January 2022, the patient was consulted for the first time at the Krakow branch of the National Research Institute of Oncology. The molecular tests detected an activating mutation in codon *V600* of the *BRAF* gene. Computed tomography performed on January 28, 2022, before the planned qualification for adjuvant treatment, revealed local recurrence in the subcutaneous tissue of the left breast (heterogenous, enhancing after contrast agent administration, numerous nodules up to 25 mm) and dissemination in the lymph nodes, lungs (multiple lesions up to 8 mm in diameter) and liver (multiple lesions up to 53 mm in diameter).

On February 15, 2022, the patient was admitted to the Department of Clinical Oncology to qualify for first line palliative systemic treatment. On admission patient was in good performance status according to the Eastern Cooperative Oncology Group (ECOG) score (ECOG 0), without any significant complaints. The physical examination revealed a painless nodular lesion of approximately 5 cm in diameter on the border of the left breast and the left axilla. Laboratory tests did not reveal any significant abnormalities, lactate dehydrogenase (LDH) level at baseline was 519.6 U/L. After a team consultation, the patient was qualified for doublet immunotherapy (ipilimumab, nivolumab) under the Ministry of Health drug program. Therapy was started on February 11, 2022. The patient received a total of four series of immunotherapy in appropriate doses, every 21 days, with acceptable tolerance. During the treatment, only grade 1 elevation of the transaminases level according to CTCAE (Common Terminology Criteria for Adverse Events) v 5.0 was noted. Due to the appearance of pain from the persistent lesion in the area of the anterior border of the left axillary fossa, after three series of systemic treatment, hypofractionated irradiation was performed to the area of infiltration in the left axilla with a dose of 30 Gy in 5 fractions, using the V-MAT technique (df 6 Gy).

Approximately four weeks after the last dose of dual immunotherapy, the patient reported to the chemotherapy clinic concerned about fevers of up to 39°C lasting for approximately one week, unresponsive to antipyretics, and the appearance of severe pain in the lumbar-sacral spine. Laboratory tests revealed elevated inflammatory parameters — CRP 210 mg/L, procalcitonin 0.87 ng/mL, further increase in LDH level — 623 U/L, increase in transaminases level to G2 according to CTCAE. Empirical antibiotic therapy with ciprofloxacin and steroid therapy with prednisone at a dose of 1 mg/kg bw/d was implemented and the pain management was modified. The patient was referred for control imaging tests. During the planned regular outpatient follow-ups, the fever resolved, the transaminase levels decreased, while the pain symptoms in the lumbar-sacral spine continued to intensify (the patient required high doses of strong opioids) with the appearance of gradual difficulties in independent movement resulting from the paresis of proximal muscles of the lower limbs.

In the computed tomography performed on May 04, 2022, massive progression of metastases in the lungs, subcutaneous tissue, liver and the appearance of multiple new lesions in the skeletal system were revealed [PD according to Response Evaluation Criteria In Solid Tumors (RECIST) v 1.1 criteria]. In the L1 body, a lytic lesion with a mass protruding into the spinal canal to a depth of 4–5 mm with its narrowing was seen. Similar changes with a slight protrusion into the spinal canal were visible at other levels of the thoracic and lumbar spine. In addition, numerous smaller lesions were visible in all bones.

In addition, the magnetic resonance imaging of the head revealed new, quite numerous zones of increased signal in T1-weighted images of up to 2 mm in size in both cerebral hemispheres, in the cortex and subcortex, suggesting metastatic lesions. The lesions in the brain structures were asymptomatic. Considering previously excluded ophthalmological and cardiological contraindications to anti-BRAF/MEK targeted therapy, the patient was qualified for therapy with encorafenib/binimetinib as a second line palliative systemic treatment. Therapy under the drug program was commenced on May 11, 2023. At the same time, radiotherapy was planned for the lumbar spine. However, the planned radiotherapy was abandoned due to the rapid symptoms improvement during applied systemic treatment. Metastatic lesions in the spine were operated in a planned mode by performing vertebroplasty on the L1 and L4 vertebrae and then L4-5 and Th12 vertebrae.

During the follow-up at the beginning of the 3rd series of anti-BRAF/MEK treatment, the LDH level normalized. The patient also stopped taking painkillers without symptoms recurrence. The doses of glucocorticosteroids used were gradually reduced. CT after 14 weeks of therapy revealed partial regression (reduction of the sum of dimensions by over 50% compared to the baseline examination). Therapy with glucocorticosteroids were discontinued. The patient in very good general

condition, without any complaints, decided to return to professional activity (occupation performed — teacher/ /tutor). The treatment was very well tolerated, no side effects of targeted therapy were observed.

The therapy was continued without interruptions, in maximum doses until November 03, 2023, when the patient experienced the first epileptic episode in his life with a transient loss of consciousness. The patient was transported by the emergency medical team to the Emergency Department of the District Hospital. The CT scan of the head showed progression in the form of numerous disseminated metastatic lesions, the largest in the medial part of the right frontal lobe measuring 14 ×10 mm surrounded by a zone of edema.

Steroid therapy (dexamethasone 8 mg/d) was reintroduced with antiepileptic drugs. However, the patient's general and neurological condition deteriorated rapidly, with occurrence of balance disorders, dizziness and slowed speech. The patient was referred for an urgent radiotherapy consultation and then was qualified for CSN radiotherapy. The patient and authorized family members reported on the scheduled date, but the patient did not consent to the proposed palliative CSN radiotherapy. The patient was referred for further supportive care under the supervision of a home hospice.

Discussion

The results of phase III COLUMBUS study led to the registration of the combined therapy with encorafenib and binimetinib in 20218 by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of patients with unresectable/metastatic melanoma with *BRAF* mutations. The median progression-free survival (PFS) in patients receiving this therapy was 14.9 months, and the median overall survival (OS) was 33.6 months [3, 4]. In addition to its efficacy, this therapy is also characterized by very good tolerance.

In presented patient, hyperprogression occurred after four courses of doublet immunotherapy. This phenomenon, described relatively recently [5], reflects unexpectedly rapid progression of disease in patients receiving immunotherapy. The important parameter is tumor growth rate (TGR), which may significantly accelerate after immunotherapy, leading to significant deterioration of patient's general condition. The more than two-fold increase in TGR in the latest evaluation compared to the growth rate in previous evaluations raises the suspicion of hyperprogression. This aggressive and unfavorable mechanism of response to immunotherapy has been described in 9% of patients treated for various cancer types [6, 7].

Fast implementation of encorafenib/binimetinib therapy enabled rapid control of disease symptoms and significantly improved patient's quality of life.

Conclusions

Targeted therapy with BRAF/MEK inhibitors in patients with advanced melanomas with *BRAF* mutations allows for rapid response and tumor control in most patients, with limited response duration associated with the activation of resistance mechanisms. These drugs are considered the preferred therapeutic option in patients with significant disease dynamics and/or high tumor burden.

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