VIA MEDICA

CASE REPORT

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A case of a patient treated with targeted therapy in brain metastases of melanoma with *BRAF V600* mutation

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ABSTRACT

The prognosis of patients diagnosed with melanoma with numerous metastatic lesions in the brain is poor, despite the use of modern techniques of radiotherapy, molecularly targeted therapies and immunotherapy. The author presents a case report of a 46-year-old patient with disseminated melanoma of the skin, who was diagnosed with asymptomatic brain metastases in screening tests for the clinical trial. During systemic treatment, binimetinib with encorafenib and pembrolizumab were used.

Keywords: melanoma, inhibitor BRAF, inhibitor MEK, immunotherapy

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Introduction

Melanoma is a highly malignant tumor derived from melanocytic cells, which most often affects the skin. The most common sites of metastasis are the lungs and brain. In Poland, melanoma is quite rare, but its incidence has increased almost threefold over the last 30 years, despite increased public awareness of the harmful effects of ultraviolet (UV) radiation [1].

The prognosis in patients with metastatic melanoma is poor. The infiltration thickness (according to Breslow scale) is the most important prognostic factor in patients without lymph node involvement. In recent years, an increase in the median survival time has been observed, which is associated with the introduction of modern treatment methods such as radiosurgery, molecularly targeted drugs and immunotherapy, but the average five-year survival is achieved only by 50% of patients with Breslow thickness > 4 mm [1]. Despite this, a significant percentage of patients do not achieve treatment response, which is associated with the need to search for the causes of resistance and new treatment options.

Case report

A 46-year-old male patient with no significant internal diseases reported to the Dermatosurgical Clinic in June 2016 due to a suspicious, dirty-gray lesion on the left calf. The lesion was removed, and the histopathological examination revealed: melanoma, mixed form with a predominance of spindle cell structure, nodular type, Breslow thickness 4 mm, Clark IV, with ulceration, pT3b, in the vertical growth phase, weak mitotic activity, infiltration of the reticular layer, without vascular invasion. Due to the narrow margin of healthy tissues (I — lateral 7 mm and 5 mm and II — polar 17 mm), it was decided to extend the resection with sentinel nodes removal. In July 2016, two sentinel lymph nodes measuring 25 mm and 20 mm in diameter were located

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and removed with use of lymphoscintigraphy, and the margin of healthy tissue was extended. Histopathological examination did not reveal melanoma cells.

The patient remained under close observation until September 2020, and no additional systemic treatment was undertaken. At that time, a control chest X-ray revealed the presence of numerous nodules disseminated in both lungs, which were confirmed by chest computed tomography. For this reason, in order of further diagnostics, the patient was qualified for resection of the largest lesion, which reached a size of up to 18 mm. The wedge resection of the left upper lobe nodule was performed in October 2020 by means of a video-assisted left mini-thoracotomy. The histopathological examination confirmed the spread of the disease, and complementary genetic tests showed the presence of the *BRAF* V600 mutation. PD-L1 expression level on tumor cells was 5%. The patient, in good general condition, without any complaints, including neurological ones, was referred to the Chemotherapy Outpatient Clinic of the Oncology Center in Bydgoszcz for further systemic treatment.

He was offered participation in a clinical trial with nivolumab and the investigated drug, however, due to the numerous focal lesions found in the screening magnetic resonance imaging of the central nervous system (CNS MRI), the patient was considered not eligible. In order to make further therapeutic decisions, the patient reported to the CNS treatment council, where he was qualified for radiotherapy at the Department of Neuro-oncology and Radiosurgery of the Oncology Center in Bydgoszcz.

In January 2021, stereotactic radiosurgery was conducted for 11 lesions located in the CNS, and then the patient was referred for further systemic treatment at the Chemotherapy Outpatient Clinic. In February 2021, after obtaining the necessary test results, including a control MRI of the CNS and an ophthalmological and cardiological consultation, the patient was qualified for a therapeutic program with binimetinib and encorafenib without contraindications. The patient received encorafenib (450 mg once daily) and binimetinib (45 mg twice daily). After a month, the first epileptic episode occurred. For this reason in April 2021, an MRI of the CNS was performed, which showed slightly larger metastatic lesions of up to 21 mm in size without increased perfusion, which suggested growth due to radiation necrosis. Anti-edematous treatment in the form of steroid therapy was used.

After another two months of therapy within drug program, in accordance with the guidelines, a follow-up computed tomography of the chest, abdomen and pelvis was performed, confirming the reduction in the size of all focal lesions in the lungs; however, based on RECIST 1.1 criteria the response was considered as disease stabilization. Until June 2021 treatment was well tolerated, no significant abnormalities were observed in complete blood count with smear and biochemical tests. However, in July, due to further epileptic episodes, an MRI of the CNS was performed, which showed new lesions in the left temporal lobe.

The patient was disqualified from further treatment within drug program. He was again referred to the Department of Neuro-oncology and Radiosurgery, where second stereotactic radiosurgery of new lesions in the CNS was performed. The patient was then qualified for second line treatment within drug program with pembrolizumab. After 3 months of therapy, due to progression in imaging studies, with new metastatic lesions in the skeletal system and the intensification of epileptic episodes, the treatment was discontinued. In addition, treatment tolerance deteriorated, and patient reported significant grade 3 weakness, according to the Common Terminology Criteria for Adverse Events (CTCAE). Steroid therapy was intensified and the patient was referred to oncology consultation to make further therapeutic decisions. The patient was qualified for palliative radiotherapy of metastatic lesions in L3 and L4 vertebrae. After palliative irradiation, the patient's condition deteriorated, and he was transferred to home palliative care.

Discussion

BRAF gene mutation is the most common molecular disorder in skin melanomas, and is detected in about 50–60% of all cases [1]. In recent years, many new therapeutic options have become available in Poland for patients with metastatic melanoma, the efficacy of which is confirmed by prolonging overall survival and progression-free survival [2]. Unfortunately, the use of BRAF and MEK inhibitors is associated with the risk of adverse events, most commonly affecting the skin [3, 4]. The effectiveness of oncological therapies and the prognosis is determined by disease clinical stage at the time of treatment commencement. Despite the median progression-free survival (PFS) of 14.9 months in patients treated with encorafenib and binimetinib [3, 4], in presented patient we observed a lack of treatment efficacy and rapid progression.

However, it should be noted, that the median PFS achieved in the COLUMBUS study concerned mainly the patients without CNS involvement. The change in therapy did not contribute to clinical improvement in the presented patient. The course of the disease in the presented patient was significantly influenced by resistance to both therapies and the primary location of brain metastases. Asymptomatic metastases to the CNS after surgery or radiotherapy do not constitute a contraindication to the use of drugs available within iBRAF and iMEK Therapeutic Program; however, they significantly worsen the prognosis, which is confirmed by the described case.

Conclusions

The clinical course of disease in presented patient and the experience of our center suggest the need for more frequent imaging of the CNS during follow-up, because a significant percentage of patients have asymptomatic brain metastases at diagnosis of metastatic disease. Stereotactic radiosurgery is more effective in the treatment of small metastatic brain lesions. The presented case indicates the high malignancy of melanoma and the need to search for new therapeutic options for patients with metastases to the CNS.

References

1. Rutkowski P, Kozak K, Świtaj T. Czerniak i inne nowotwory skóry. In: Krzakowski M, Potemski P, Wysocki P. ed. Onkologia kliniczna. Tom II. Via Medica, Gdańsk 2023: 957–961.
2. https://onkologia.org.pl/pl/czerniak-skory-leczenie#page-main-image (29.08.2023).
3. Charakterystyka Produktu Leczniczego INN-Encorafenib.
4. Charakterystyka Produktu Leczniczego INN-binimetinib.