VIA MEDICA

CASE REPORT

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Treatment with encorafenib and binimetinib of elderly female patient with *BRAF*-mutated melanoma with central nervous system metastases

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ABSTRACT

Metastases in central nervous system are relatively common in patients with melanoma. Treatment of these patients should be carried out in multidisciplinary teams and may include systemic therapy, radiotherapy, neurosurgery and symptomatic management. About half of melanoma patients have a mutation in the *BRAF* gene. In its presence, the risk of brain metastases is slightly higher and the prognosis is worse. Currently, both immunotherapy and molecularly targeted anti-BRAF and anti-MEK therapies are available for the treatment of these patients. The treatment strategy should be based on the parameters related to the neoplastic disease as well as the patient's general condition, comorbidities and patient preferences. One of the treatment options with BRAF/MEK inhibitors is encorafenib with binimetinib. The following paper describes the case of an 81-year-old patient treated with this combination for about a year with good tolerance.

Keywords: melanoma, *BRAF* mutation, targeted therapy, brain metastases

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Introduction

Melanoma is the third most common malignant tumor, after breast and lung cancer, in terms of the frequency of brain metastases. The presence of brain metastases worsens the prognosis, and the treatment of these patients is a major challenge. Historical data indicate a short overall survival with a median of four months. Central nervous system (CNS) metastases develop in almost half of patients with advanced melanoma, and in almost 20% of melanoma patients, CNS is the first location of metastases. CNS lesions are often multifocal and initially asymptomatic, with a tendency to bleed. Factors associated with a higher risk include the location of the primary lesion in the head and neck, increased lactate dehydrogenase (LDH) level, presence of ulceration in the primary lesion and harboring of mutations in the *BRAF*, *NRAS*, and *PTEN* genes [1–3]. Brain lesions may be asymptomatic, especially at the beginning, but as they grow, neurological symptoms appear due to pressure on the surrounding structures and edema.

The introduction of new methods of local and systemic treatment has improved the prognosis and prolonged survival. Treatment should be carried out in multidisciplinary teams [4]. The choice and sequencing of individual treatment methods, including systemic, and local (radiotherapy +/– neurosurgery) therapy, as well as supportive care depends on many clinical factors. In the systemic treatment of melanoma, also with CNS metastases, immune checkpoint inhibitors (ICIs) (anti-PD-1, anti-LAG3, anti-CTL-A4) and BRAF and MEK inhibitors are currently used. In approximately 40–60% of melanomas, mutations are found in the *BRAF* gene. The most common mutation is *V600E* (80–90%), which involves replacing valine with glutamic acid at amino acid 600. The presence of mutations in the *BRAF* gene is associated with a worse prognosis and more frequent presence of CNS metastases [5, 6]. In patients with

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BRAF mutations, the choice of systemic treatment depends, among others, on clinical characteristics, including different factors, such as the curse of previous treatment, location and clinical characteristics of extracranial lesions, patient's performance status (PS), comorbidities, and concomitant drugs.

One of the regimens used in this therapy is encorafenib in combination with binimetinib. In a retrospective analysis of 24 patients with *BRAF*-mutated melanoma and CNS metastases treated with encorafenib and binimetinib, the objective response rate (ORR) in the CNS was 33%, and disease control rate (DCR) was 63%. This treatment also appeared to be effective in the group of patients previously treated with BRAF and MEK inhibitors, in whom ORR and DCR were 24% and 57%, respectively [7]. The results of this treatment seem to be even more promising in combination with radiotherapy, as indicated by the GEM1802/EBRAIN-MEL study [8, 9]. Unfortunately, during treatment with BRAF and MEK inhibitors, the risk of disease progression should be taken into account, including in the CNS, due to treatment resistance development.

Case report

In 2016, a 76-year-old female patient reported to the National Research Institute of Oncology after resection of skin melanoma of the left subcostal area (pT3a) in February 2016. The patient had post-flu myocarditis in medical history, but during qualification for surgery was without signs and symptoms of heart failure. Additionally, patient's medical history included treatment for epilepsy, previous cholecystectomy, controlled hypertension, and hypercholesterolemia.

After performing imaging tests that excluded the spread of the disease and an anesthetic assessment, the patient was qualified for sentinel node biopsy and cutting over a scar removal, to which she consented. In March 2016, a scar excision of the left subcostal region was performed (radicalization). As part of the preparation for sentinel node biopsy lymphoscintigraphy was performed, showing lymphatic drainage from the scar to the anterior mediastinal lymph nodes. Imaging studies did not show any signs of lymph nodes involvement, so the surgery was limited to scar resection only. No complications were observed in the postoperative course. Postoperative pathological examination did not reveal cancer cells in the scar. The patient remained under outpatient care, with physical examination and imaging tests regularly performed.

In November 2020, a control CT scan revealed suspicious, ambiguous lesions in the lungs, and after assessment at a multidisciplinary meeting, a follow-up in three months was recommended. A molecular test was ordered to assess the *BRAF* gene status, which gave a positive result. In January 2021, during a follow-up visit, the patient reported persistent hematuria for several months. The ultrasound examination and cystoscopy showed nodular infiltrates, from which samples were taken. The pathological examination revealed the presence of melanoma cells. Qualification for immunotherapy was planned. Imaging tests performed during qualification process revealed multiple metastases in CNS with the largest lesion measuring 20 × 15 mm, with edema around the largest lesions, but without mass effect (Fig. 1). A radiotherapist consultation was planned and after discussing the clinical situation and taking into account patient's history and age, the team made a decision to qualify for treatment with BRAF and MEK inhibitors.

In March 2021, tests were performed to qualify patient for the drug program with encorafenib and binimetinib. No contraindications to treatment were found based on the tests performed, including ophthalmological and cardiological consultation, left ventricular ejection fraction (LVEF) in echocardiography (ECHO) was 56%, and QTc interval in electrocardiogram (ECG) was < 450 ms. According to this treatment was introduced at a standard dose. The patient was qualified by the radiotherapy committee for radiotherapy of the two largest brain lesions due to age, burden and applied systemic treatment.

On April 13–17, 2021, patient received radiotherapy using the IMR-T + CBCT technique on the area of two brain lesions, at a fractional dose of 9 Gy/70%, up to a total dose of 27 Gy/70%, with fractionation every other day under steroid cover. During the treatment anemia (grade up to 2), seborrheic changes on forehead and chest skin, and slight lower limbs swelling were observed. Apart from that, no adverse effects of the treatment were noted. During the treatment, the control ECHO was normal, with LVEF of 55–60%, and ECG was without significant abnormalities.

In September 2021, due to a single episode of blood in the stool, the patient underwent a colonoscopy, which revealed the ulceration in the mucosa of the large intestine. Histopathological examination of the collected samples revealed changes that could correspond to inflammatory bowel disease. For this reason, the patient remained under the care of a family doctor. A control CT scan performed in June 2021 revealed a partial response to treatment, which was maintained in subsequent tests. A CNS scan performed in March 2022 revealed an increase in the size of previously detected lesions and the appearance of numerous new lesions (Fig. 2).

At the end of March 2022, the patient was hospitalized in the neurology department of the district hospital due to neurological symptoms including hemiplegia and aphasia, and deterioration of the general condition, re-

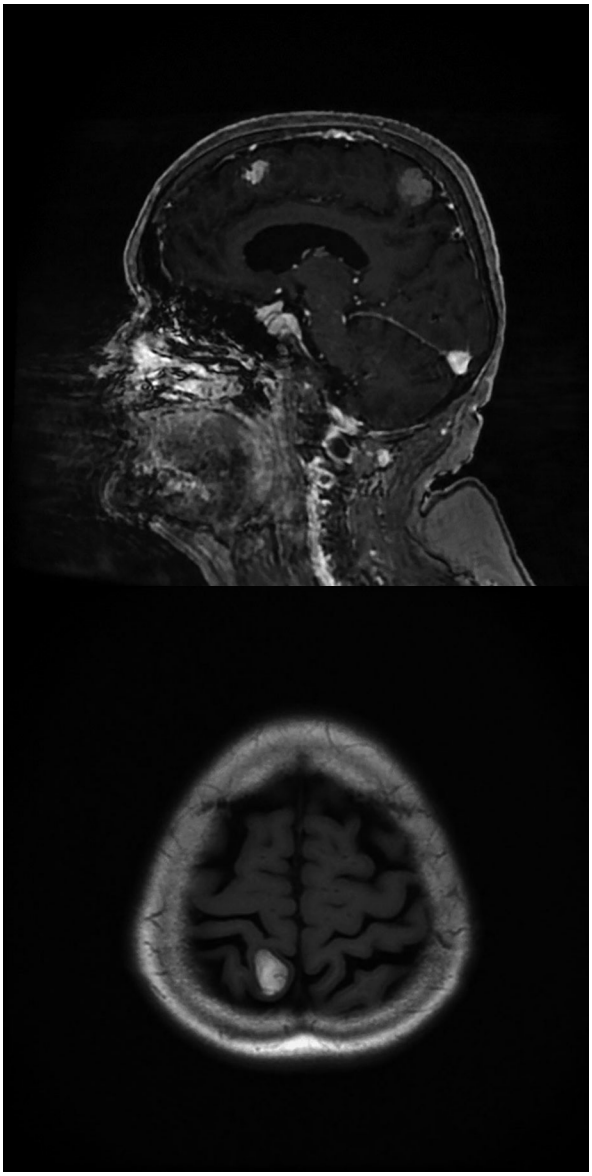

Figure 1. Changes in the central nervous system, March 2021 (material from Department of Soft-Tissue/Bone Sarcomas and Melanomas of the Maria Sklodowska-Curie National Research Institute of Oncology in Warsaw)

sulting from bleeding into CNS tumor. Despite the symptomatic treatment used at that time, the patient died.

Discussion

The choice of systemic treatment, which remains the backbone therapy in patients with *BRAF*-mutated melanoma with CNS metastases, is difficult. In elderly patients single-drug immunotherapy is more often chosen and it is definitely less effective than doublet targeted therapy in terms of CNS lesions control [10 –15].

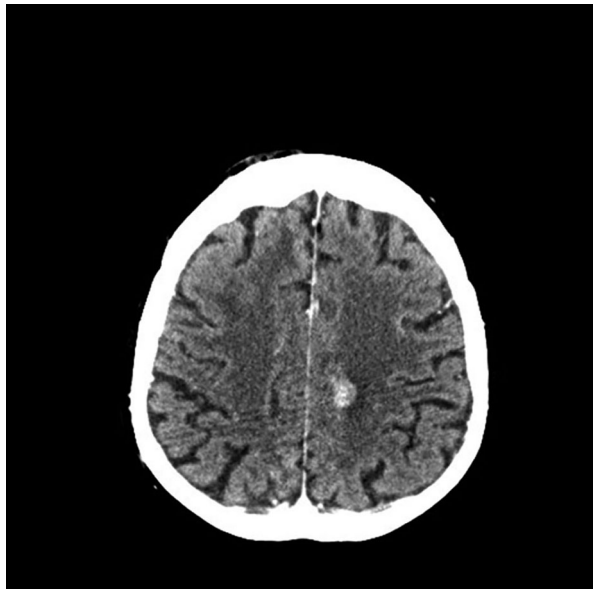

Figure 2. Changes in the central nervous system, March 2022 (material from Department of Soft-Tissue/Bone Sarcomas and Melanomas of the Maria Sklodowska-Curie National Research Institute of Oncology in Warsaw)

Molecularly targeted therapy allows for high intracranial response rates, with treatment outcomes definitely better in asymptomatic patients. Taking into account all these data, together with patient's preferences and informed consent to the treatment, patient started combined therapy with encorafenib and binimetinib. After that patient also received radiotherapy for the two largest CNS lesions.

Data on the combination of BRAF and MEK inhibitors with radiotherapy are not clear, but preclinical studies (*in vitro*) have shown their potential sensitizing effect [16]. Simultaneous use of these modalities may be associated with the risk of increased toxicity, but current data indicate that withholding BRAFi/MEKi during stereotactic radiotherapy is not required. This is only necessary during whole brain irradiation, three days before and three days after its completion.

However, the indications for whole brain radiotherapy are currently very limited, therefore this treatment method is used very rarely [17]. In presented 81-year-old patient, who underwent irradiation for the two largest CNS lesions, there was no need to interrupt systemic treatment during radiotherapy.

The treatment used resulted in almost 12 months of disease control, both intra- and extracranial, with a partial response as the best response. In a retrospective analysis of the results of encorafenib and binimetinib treatment in 24 patients with *BRAF*-mutated melanoma with CNS metastases, published by Holbrook et al., the objective response rate (ORR) in the CNS was 33%, with three patients achieving a complete response and five patients achieving a partial response.

The median time to response in the CNS was 6 weeks, and its duration was 22 weeks. In extracranial lesions, mainly disease stabilization was observed [7]. In presented patient, no significant toxicity was observed during radiotherapy or systemic treatment.

Conclusions

Melanoma patients with CNS metastases are treated with BRAF and MEK inhibitors in daily clinical practice. This treatment can be well tolerated, also when combined with local radiotherapy. This option should be considered in every patient with a *BRAF* mutation and brain metastases, especially symptomatic, in elderly patients or in the case of contraindications to immunotherapy.

In patients undergone concomitant whole brain radiotherapy, for which indications are currently significantly limited, systemic treatment should be interrupted for the duration of radiotherapy, starting 3 days before and ending 3 days after its completion. Local radiotherapy does not require BRAFi/MEKi discontinuation.

Due to common therapy resistance development, the risk of disease progression should be taken into account despite the response to treatment. It should also be remembered that melanoma metastases to the CNS are associated with a high risk of bleeding.

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