VIA MEDICA

CASE REPORT

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Patient with M1d melanoma treated with encorafenib and binimetinib with partial response in the second line

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ABSTRACT

The presence of brain metastases in patients diagnosed with melanoma is associated with a dismal prognosis. The implementation of modern therapies (a combination of BRAF-MEK inhibitors and anti-CTLA-4 with anti-PD-1), has resulted in unprecedented improvements in the treatment of such patients. The presented case of a 40-year-old patient diagnosed with melanoma disseminated to the brain, with negative prognostic factors, is an example of a milestone in oncology. The combination of systemic treatment and radio- therapy makes it possible to achieve disease control in the central nervous system. It is worth emphasizing that such a patient should be treated with a multidisciplinary approach in comprehensive cancer centers.

Keywords: melanoma, brain metastases, targeted therapy, radiotherapy

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Introduction

The brain metastases in patients diagnosed with melanoma are associated with a poor prognosis [1–3]. In recent years, significant progress has been made in the treatment of melanoma patients, and both targeted the rapies (BRAFi/MEKi combinations) and immune checkpoint inhibitors (anti-CTLA-4 and anti-PD-1 combinations) show impressive activity in the central nervous system [4–6]. Despite this, the duration of response is still shorter in patients with intracranial metastases compared to extracranial metastases [4, 5].

We presented a clinical case of a young female patient diagnosed with melanoma in the stage of multifocal spread, including brain metastases (stage M1d1). The high dynamics of the disease, significantly severe neurological symptoms and very high lactate dehydrogenase (LDH) level at baseline indicate a very unfavorable prognosis in this patient. Despite this, thanks to the use of modern therapeutic options, it was possible to achieve disease control.

Case report

A 40-year-old female patient diagnosed with melanoma of the neck (pT2a) reported to the outpatient clinic of the Department of Soft-Tissue/Bone Sarcomas and Melanomas in the Maria Sklodowska-Curie National Research Institute of Oncology in Warsaw for qualification for oncological treatment due to symptomatic brain metastases. The medical history included the status after the excision of neck melanoma (pT2a) on 13.04.2015 and biopsy of the sentinel node with scar removal on 11.08.2015. The histopathological examination did not reveal any metastases to the sentinel node. Since then, the patient has been under the care of the outpatient clinic and has undergone follow-up imag-

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ing tests, which did not show any suspicious lesions. On November 26, 2022, the patient was admitted to hospital due to a seizure, preceded by severe headache, nausea and vomiting. A computed tomography (CT) scan performed on November 27, 2022, revealed metastases to the brain (the largest lesion in the brain stem measuring 20 × 25 mm), lungs, right adrenal gland and suspected gallbladder infiltration.

On 07.12.2022, the patient was qualified for treatment with nivolumab and ipilimumab under the B.59 drug program. A molecular test detected a mutation in codon 600 of the *BRAF* gene. Due to numerous metastatic lesions to the brain, which were confirmed in contrast-enhanced magnetic resonance imaging (MRI) on 06.12.2022, radiotherapy using the RAD3D technique was performed on the brain area, at a fractional dose of 3 Gy, up to a total dose of 30 Gy. After the third course of combined immunotherapy, the treatment was discontinued due to grade 3 bloody diarrhea according to CTCAE v5.0. In addition, exacerbation of neurological symptoms was observed in the form of nausea, deterioration of cognitive processes, and weakening of muscle strength. Colonoscopy performed on 16.02.2023 revealed extensive, mild, active inflammatory changes in the form of blurred vascular pattern and hyperemia of the mucous membrane along the entire large intestine. After the use of methylprednisolone at a dose of 2 mg/kg b.w. with subsequent tapering the symptoms of diarrhea resolved. A follow-up imaging performed on 05.03.2023 revealed progression of the neoplastic disease in the form of new lesions in the lungs. The other lesions remained stable, but the patient's neurological status deteriorated significantly (ECOG 3). In laboratory tests after immunotherapy cessation, lactate dehydrogenase (LDH) level was 965 IU/L. On 10.03.2023, the patient was qualified for second line treatment with encorafenib and binimetinib. Due to symptomatic brain metastases, concomitant dexamethasone and levetiracetam were used. During the treatment with BRAF and MEK inhibitors, a gradual normalization of LDH level and improvement of the general condition were observed. On 18.05.2023, the patient was qualified for cyber knife radiotherapy of the metastatic lesion in the brain stem at a fractional dose of 6 Gy/t every other day to a total dose of 12 Gy/t. In the follow-up brain MRI scan from 30.06.2023, a partial response (PR) was obtained according to RECIST1.1 criteria, with 50% regression of the lesion in the brain stem. In the CT scan of the chest and pelvis from 14.07.2023, a partial regression was also obtained. The patient's neurological condition improved significantly, which allowed discontinuation of anti-edematous treatment. The patient continues the treatment with good tolerance.

Conclusions

In approximately 50–60% of patients diagnosed with advanced melanoma, the disease will spread to the brain (including multiple metastases in approximately 75% of patients, often initially asymptomatic) [2, 7]. The presence of metastases in the central nervous system is a negative prognostic factor and poses a major challenge in the context of oncological treatment [4]. Before 2011, local treatment (surgery and/or radiotherapy) and dacarbazine-based chemotherapy were used. At that time, the median overall survival was less than 6 months [2, 7]. Since 2011, targeted therapies (BRAF and MEK inhibitors) and immunotherapy (anti-PD-1 antibody in monotherapy or in combination with anti-CTLA-4) have been introduced to the treatment of metastatic disease [4, 8]. This has led to significant improvement in treatment outcomes in patients with metastatic disease. In patients with good performance status, dual immunotherapy based on anti-PD-1 and anti-CTLA-4 antibodies is the treatment of choice for asymptomatic brain metastases, while in the presence of *BRAF* mutations and symptomatic metastases, systemic treatment with BRAFi and MEKi may be used in a front line [8, 9]. The efficacy of molecularly targeted drugs (BRAFi/MEKi) in melanoma patients with brain metastases has been demonstrated in several prospective clinical trials. The COMBI-MB study investigated the role of dabrafenib + trametinib, with an intracranial response rate (icRR) of 58% for asymptomatic patients and 59% for symptomatic patients [10]. The efficacy of encorafenib and binimetinib was demonstrated in the single-arm, open-label phase II EBRAIN-MEL study, evaluating the efficacy of this combination administered prior to local treatment in patients with *BRAF*-mutated melanoma and brain metastases [11]. Encorafenib and binimetinib showed intracranial effects regardless of disease symptoms in patients with *BRAF*-mutant melanoma with brain metastases, although longer follow-up is needed and the effect of local radiotherapy is not yet clear [11, 12]. The use of encorafenib and binimetinib followed by radiotherapy in patients with brain metastases is safe and not associated with an increased number of adverse events [11, 13]. It should be emphasized that the qualification for treatment of patients with M1d melanoma should be carried out in multidisciplinary teams involving neurosurgeon, radiotherapist and clinical oncologist.

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