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Treatment of advanced skin melanoma with *BRAF V600* mutation with central nervous system metastases with encorafenib in combination with binimetinib

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ABSTRACT

A case report of an 80-year-old patient treated with encorafenib and binimetinib due to metastatic melanoma to the brain, lungs, lymph nodes and subcutaneous tissue. Due to use of the latest forms of systemic therapy in combination with local therapy, the patient obtained a definite clinical benefit from the therapy. The presented data correlate with the results described in the literature.

Keywords: case report, melanoma, encorafenib, binimetynib, brain metastases

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Introduction

Metastasizing to the central nervous system (CNS) is associated with a poor prognosis regardless of cancer type. In the case of melanoma, it contributes directly to the death of about 50% of patients [1]. The treatment of metastatic lesions in the CNS is based on local therapy (surgery, radiotherapy) and systemic treatment. The introduction of BRAF inhibitors (BRAFi) and MEK inhibitors (MEKi) as well as immunotherapy, in particular the combination of anti-PD-1 with anti-CTLA-4 antibodies (nivolumab with ipilimumab) increased objective responses rate and prolonged overall survival. It should be noted that the responses in intracranial metastases are worse than in lesions located outside the cranial cavity, which is related to the blood-brain barrier and the specific microenvironment [2]. Identified factors associated with a higher risk of spread to the CNS include: high lactate dehydrogenase (LDH) level, primary site in the head and neck area, presence of mutations in the *BRAF*, *NRAS*, *PTEN* genes, and ulceration of the primary site [3]. A very important role in the treatment of brain metastatic plays supportive care, most often based on steroid therapy, which reduces the clinical symptoms of the disease associated with cerebral edema.

Case report

A 80-year-old female patient with hypertension, reported to the physician office in April 2018 due to

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a rapidly growing lesion on the skin of her back. After dermatoscopic evaluation, the patient was qualified for removal of the lesion. The histopathological result revealed a nodular form of melanoma, Breslow thickness 11 mm, pT4a, Clark V, no ulceration, a lesion in the vertical growth phase, abundant brisk tumour lymphocytic infiltration, no signs of angioinvasion nor neuroinvasion, no satellite foci, 4 mitoses/1 mm^2, melanoma infiltration was found in the lateral margin. The chest X-ray, ultrasound (US) of abdominal cavity and axillary and inguinal lymph nodes performed at that time did not reveal any suspicious lesions. In June 2018, the patient underwent a procedure of expanding scar excision with a sentinel node biopsy. The histopathological examination did not reveal any melanoma infiltration. Due to the advanced disease stage, pT4aN0M0, the patient remained under close observation. The imaging tests and the dermatoscopic examination did not reveal any spread or recurrence of melanoma.

During a routine check-up in the fall of 2021, a burgundy skin lesion on patient's right lower limb was observed. The patient's performance status according to the Eastern Cooperative Oncology Group (ECOG) score was good (ECOG 1), adequate for age and existing comorbidities. In a positron emission tomography (PET) scan a single lesion was found in the subcutaneous tissue of the right lower limb (SUV 8) suggesting a metastatic lesion. There were no other suspicious lesions. Identified lesion was resected in September 2021. The result of the histopathological examination confirmed a metastatic melanoma lesion that was radically removed. In addition *BRAF* mutation was found. Imaging tests were repeated, including computed tomography (CT) of the CNS, which did not confirm further spread of the disease. Due to the stage IVa and status after radical metastasectomy, the patient was qualified for adjuvant treatment with nivolumab in accordance with the current Polish Drug Program. The patient received the first dose of the drug at the end of October 2021. The treatment was well tolerated, without significant complications. Initial doses were administered every 2 weeks to allow for better monitoring of adverse events. A slow increase in LDH level was observed already from the second administration of nivolumab, without clinical deterioration of patient's general condition and without clinical signs of melanoma progression. In January 2022, the patient reported periodic coughing and increasing weakness, which correlated with an increase in LDH level, which at that time for the first time exceeded the upper limit of normal (LDH 275 U/L). The CT scan of the chest, abdomen and pelvis performed at that time revealed metastatic lesions in the lungs (in the LungCare option, about 20 lesions of up to 18 mm in size, infiltrating the pleura), and pathological lymph nodes of up to 42 mm in size in the mediastinum. In the subcutaneous tissue of the chest and trunk, minor metastatic lesions of up to 6 mm were also found. The spread was also visible in the left external oblique muscle. An urgent CT scan of the CNS was performed, which revealed a 3 mm enhancement focus on the outline of the cortex at the border of the base of frontal lobe and anterior part of the insula, and a linear band of enhancement in the lateral part of right temporal lobe – the image raised suspicion of early phase of spread to the meninges. The lesions were confirmed by magnetic resonance imaging (MRI).

Due to the rapid disease progression during immunotherapy, and considering patient's good general condition and lack of clinical symptoms of dissemination to the CNS, the patient was qualified for BRAFi + MEKi treatment combined with radiotherapy of CNS lesions. In accordance with the current Drug Program, a cardiology (EF 64%, no cardiological contraindications to systemic treatment were found) and an ophthalmology consultation were performed (without significant deviations in the fundus of the eye, field of vision and visual acuity). In mid-February 2022, the patient received the first course of encorafenib + binimetinib and was qualified for whole brain irradiation. During the first treatment course, no significant complications were observed, apart from pain in the trunk at the site of subcutaneous tissue lesions. After 2 weeks of therapy, the patient reported a decrease in cough intensity. The second course of BRAFi/MEKi therapy was started in mid-March, with a decrease in LDH level to 145 U/L. At that time, whole brain palliative radiotherapy was also performed (Dc = 20 Gy). Dexamethasone was introduced at a dose of 2 mg per day. Encorafenib and binimetinib were stopped during radiotherapy and 3 days before and 2 days after treatment. The patient reported for the 3rd course of therapy with significant clinical improvement. The cough completely disappeared, no deviations were found in laboratory tests, LDH level was 156 U/L. The patient received the 3rd and 4th course of treatment without significant complications. The first follow-up imaging was performed in May 2022. The CT scan revealed regression of metastatic lesions in the CNS at the cortex outline at the border of the frontal lobe base and anterior part of the insula and in the lateral part of the right temporal lobe. CT scan of the chest, abdomen and pelvis also confirmed significant regression of all previously described metastatic lesions. The patient was qualified for therapy continuation. In June, the patient reported grade1 diarrhea. The anticancer treatment was continued with concomitant use of symptomatic drugs resulting in diarrhea resolution. In July 2022, the patient reported weakness and vomiting food. An urgent CNS imaging test was performed. CT scan revealed complete remission of metastatic lesions in the CNS. The patient did not consent to an endoscopic examination. Laboratory tests showed no significant deviations. Due to the deterioration of the patient's general condition, the therapy was stopped, intravenous fluids were administered, resulting in a significant improvement. After 7 days, the therapy was resumed and continued until August 2022. At that time, a follow-up CT scan of the chest, abdomen and pelvis was performed, which revealed stable residual lesion in the lungs and an increase in the dimensions of one right hilar lymph node to 11 mm — the lesion requires further observation. Due to the relatively good patient's general condition, disease stabilization in imaging tests and a normal LDH level, it was decided to continue the therapy. Subsequent drug administrations were well tolerated apart from slight weakness. In November 2022, another imaging follow-up was performed, confirming the stabilization of extracranial metastatic lesions. Based on brain CT scan a disease progression was suspected. In the cortex of the right frontal lobe at its base, on the border with the temporal lobe, a contrast enhancement focus measuring 5 × 4 mm was identified. The lesion was not observed previously. Magnetic resonance imaging was indicated. Additionally, based on laboratory tests a grade 3 hepatotoxicity according to CTCAE was identified. The patient's general condition was moderate. Increasing weakness was observed, the LDH level oscillated around the upper normal limits. The next treatment course was withheld. The patient reported after 10 days in poor general condition with significant weakness. The liver parameters decreased to G1 according to CTCAE, however, MRI of the CNS revealed progression of the neoplastic disease: meningeal metastatic lesion described in CT was confirmed. Additionally, numerous metastases appeared in the right hemisphere (9 lesions in total, the largest measuring up to 10 mm) and in the left hemisphere (5 lesions up to 5 mm). In February 2023 systemic treatment was discontinued due to progression of the disease in the central nervous system, the poor performance status (WHO 3). The patient was also disqualified from repeated radiotherapy to the CNS due to general condition and numerous new metastatic lesions occurring several months after whole brain irradiation. The patient remains under the care of the palliative medicine clinic.

Discussion

Dissemination of cancer to CNS is one of the poor prognostic factors. In the past, the median overall survival of patients with symptomatic brain metastases was about 2.5 months and of patients with asymptomatic CNS lesions about 6 months [3]. The pivotal phase III Columbus study with encorafenib and binimetinib did not include patients with CNS dissemination. However, the results of retrospective analysis of data from patients treated for stage IVd melanoma with encorafenib and binimetinib in 3 centers in the United States are available [4]. The analysis included 24 patients, the mean age was 58 years and 58% of the study group were men. In 54% of the patients, 1 to 10 metastatic lesions were found in the CNS, the median size of metastatic lesions was 10 mm. In 88% of patients (n = 21) local treatment (surgery, stereotactic radiotherapy) was used first. The median number of previous treatment lines was 2.5. The most commonly used were dabrafenib with trametinib (88%) and anti-PD-1 monoclonal antibodies (46%). Intracranial objective response rate was 33%. The median time to intracranial response was 6 weeks and the median duration of response was 22 weeks.

Another phase II study, COMBI-MB, investigated the use of dabrafenib plus trametinib in 125 melanoma patients with brain metastases. Primary local treatment was not required. The intracranial response rate was approximately 56%. The median duration of response was 6 months [5]. Of note, combined immunotherapy based on nivolumab with ipilimumab in the first-line treatment was used in melanoma patients with brain metastases. The CheckMate 204 study analyzed the use of combined immunotherapy in this patients population. The objective intracranial response rate was 55% and 6-month progression-free survival rate was 67% [6].

The choice of therapy sequence in patients with *BRAF*-mutated melanoma is determined by the patient's general condition, disease progression, and comorbidities. However, it should be remembered that combined immunotherapy in patients with good performance status, without organ crisis, should be considered as the first-line treatment.

Conclusions

The treatment results achieved in the presented patient treated at the Lower Silesian Center of Oncology, Pulmonology and Hematology were comparable with the literature. After 3 months of treatment, an objective response was achieved, with complete remission as the best response in the CNS, and the progression-free survival was 10 months. Thanks to the use of the latest treatment methods, the patient has lived for over a year since the diagnosis of dissemination to the central nervous system.

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