VIA MEDICA

CASE REPORT

Łukasz Galus

Department of Clinical and Experimental Oncology, Institute of Oncology, Poznan University of Medical Sciences, Poland

Response to encorafenib and binimetinib therapy after prior treatment with targeted therapy and immunotherapy in melanoma patient with brain metastases

Address for correspondence:
Łukasz Galus, MD PhD
Department of Clinical and Experimental Oncology, Institute of Oncology, Poznan University of Medical Sciences, Poland
e-mail: lukasz.galus@usk.poznan.pl

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ABSTRACT

Brain metastases in melanoma patients are a serious therapeutic problem significantly worsening the prognosis. According to the literature, they occur in about 30–40% of patients. The subject of this study is a 53 year old patient with dissemination of melanoma to the central nervous system, who remains under systemic treatment at the Department of Clinical and Experimental Oncology in Poznań. The patient has been treated with targeted therapy with vemurafenib and cobimetinib, immunotherapy with pembrolizumab, and then again with targeted therapy (encorafenib with binimetinib) and immunotherapy with ipilimumab and nivolumab. Despite the poorer prognosis of patients with CNS metastases and less effective therapies, the patient remains in treatment for 6 years. Progression free survival (PFS) for targeted therapy in the first line of treatment and immunotherapy in the second line exceeded 20 months for each of these, while for rechallenge therapy with BRAF and MEK inhibitors (encorafenib with binimetinib) it was 15 months and nearly 3 times exceeded the median PFS obtained in retrospective analyzes of patients undergoing such treatment. In order to select patients with a poor prognosis (M1d) who nevertheless respond well and permanently to the therapy, it is advisable to find appropriate predictive biomarkers.

Keywords: melanoma, targeted therapy, BRAF inhibitors, MEK inhibitors, brain metastases, rechallenge

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Introduction

Brain metastases occur in about 30–40% of patients with advanced melanoma; however, according to autopsy data, their frequency is even higher. Despite the dynamic development of immunotherapy and targeted therapy, the presence of metastatic lesions in the central nervous system (CNS) still significantly worsens the prognosis, and the treatment results are often unsatisfactory.

Case report

In February 2018, a 53-year-old female patient with melanoma and metastases in the CNS was admitted to the Department of Clinical and Experimental Oncology in Poznań. In 2015, the patient underwent radical surgical treatment of trunk melanoma (stage IIc; pT4bpN0cM0). Since then, the patient has been under observation outside the clinic. After detection of 3 metastases in the CNS with a maximum size of 2 cm, the patient underwent stereotactic radiotherapy. After progression in the form of two new brain metastases, patient was referred to our center for qualification for systemic treatment. The patient's general condition was good, she did not report any complaints. The general medical history revealed only well-controlled arterial hypertension. In the molecular test of the archival histopathological block, *BRAF V600*E mutation was found. Blood tests revealed an elevated lactate dehydrogenase (LDH) level,

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i.e. 428 U/L (normal value up to 225 U/L). At that time, the patient had the option of immunotherapy with anti-PD-1 antibodies in monotherapy and targeted therapy with BRAF and MEK inhibitors. Due to the advanced M1d1 stage of disease, after presenting the patient with therapeutic options, a joint decision was made to start targeted therapy with vemurafenib and cobimetinib. A partial response (PR) was achieved, which lasted until December 2019, when a new lesion in the CNS and metastases in the spleen were detected in a control computed tomography (CT). Progression-free survival (PFS) for the first line treatment was 21 months. From December 2019 to July 2021, the patient received pembrolizumab in second treatment line, achieving disease stabilization. In September 2021, disease progression (PD) was detected in the form of a new metastasis in the cerebellum. PFS for immunotherapy as second line treatment was 20 months. The patient underwent stereotactic radiotherapy of the new CNS lesion and was then requalified for rechallenge targeted therapy this time with encorafenib (BRAF inhibitor) in combination with binimetinib (MEK inhibitor). The treatment was started in September 2021 and well tolerated. The only adverse effect during the therapy was grade 2 joint pain, according to the Common Terminology Criteria for Adverse Events (CTCAE). Therefore, the patient periodically took diclofenac 75 mg twice daily, orally. As a result, a partial remission was achieved, which lasted until December 2022, when a new metastatic lesion in the CNS was again detected in the control CT scan. PFS for rechallenge of BRAF and MEK inhibitors was 15 months and was slightly shorter than for the therapies previously used. As part of the fourth line treatment, the patient started immunotherapy with ipilimumab with nivolumab (commercial purchase). At the time of preparing manuscript, patient continued treatment, before the first scheduled efficacy assessment.

Discussion

Despite the dynamic development of therapeutic options in patients with advanced melanoma, the presence of brain metastases is still an important problem and reduces the chance of treatment success. The negative impact of CNS metastases on the prognosis is often the reason for excluding patients from pivotal clinical trials. The data regarding effectiveness of immunotherapy or targeted therapies in such populations is most often derived from studies dedicated only to such patients. One of them is the randomized phase II ABC study, comparing the effectiveness of nivolumab in combination with ipilimumab with nivolumab alone. The results of this study showed a clear benefit of combined therapy with ipilimumab and nivolumab as compared to nivolumab monotherapy in terms of intracranial response rate, 5-year PFS (52% *vs.* 14%) and 5-year overall survival (OS) (54% *vs.* 34%). The study indicates a potentially large benefit of using doublet immunotherapy with ipilimumab and nivolumab compared to nivolumab monotherapy [1, 2]. Another important study indicating the effectiveness of immunotherapy with ipilimumab and nivolumab in melanoma patients with CNS metastases is the Ca209-204 study, which shows a particular benefit of using this combination in patients with asymptomatic metastases [3]. The presented patient started the treatment in 2018, when in Poland the combination therapy with anti-CTLA-4 and anti-PD-1 antibodies was not reimbursed.

Another important study in melanoma patients with brain metastases is the multicenter, nonrandomized, open-label phase II Combi-MB study, which assessed the efficacy of targeted therapy with dabrafenib in combination with trametinib. Patients with meningeal metastases and with lesions larger than 4 cm in diameter were excluded from the study. In patients without neurological symptoms, not previously receiving local treatment, the objective response rate was 58%, in the group of asymptomatic patients who had additionally undergone local treatment it was 56%, while in patients with symptomatic CNS metastases (both previously treated and not treated locally) it was similar and amounted to 59%. The duration of response in the subgroups was 6.5 months, 7.3 months, and 4.5 months, respectively [4]. The duration of response in the presented patients was significantly shorter compared to the results of the COMBI-d and COMBI-v studies evaluating the efficacy of dabrafenib with trametinib in patients with advanced melanoma, but with exclusion of patients with CNS metastases. The median duration of response in the mentioned studies was about 11 months, and the response rate was 68% [5]. Similar results were obtained in the Ebrain-Mel study, in which the efficacy of encorafenib with binimetinib was evaluated in patients with stage M1d melanoma, both asymptomatic and symptomatic [6].

Despite the enormous progress in the treatment of patients with metastatic melanoma, both in targeted therapy and immunotherapy, most patients still experience resistance to the applied treatment at some stage and lack further possible therapeutic options. One of the attempts to deal with this situation is the re-use of BRAF and MEK inhibitors, also called rechallenge. The first reports of successful re-use of a BRAF inhibitor after previously documented progression during dabrafenib treatment in two patients were published in 2012. In both patients clinical response was observed after treatment reintroduction, complete response (CR) after 4 months and PR after 8 months, respectively [7]. In 2018, the results of a large retrospective study were published, assessing the efficacy of such a management in 116 patients. The objective response rate (ORR) after the reintroduction of BRAF and MEK inhibitors was 43.3%, 24.8% of patients had stable disease (SD),

while 31.9% of patients had disease progression (PD). The median PFS and OS was 5 and 9.8 months, respectively [8]. Similar results of rechallenge were obtained in the retrospective analysis of Polish population of 51 patients, i.e. ORR 63%, median PFS 5.9 months and OS 9.3 months [9]. It should be noted that the PFS after rechallenging with BRAF and MEK inhibitors in presented patient was almost three times higher than the median obtained in the above-mentioned analyses. Additionally, it should be emphasized that presented study included patients with all clinical stages of melanoma, whilst presented patient belongs to the M1d group, i.e. with the least favorable prognosis.

Conclusions

The presented description of the treatment of melanoma patient with brain metastases indicates the possibility of achieving a long-term disease remission even in the group of patients with the worst prognosis. It is also worth emphasizing the fact of over a year of response duration to reuse of BRAF and MEK inhibitors (encorafenib, binimetinib). Further studies defining biomarkers that indicate patients with CNS metastases who may benefit from immunotherapy, targeted therapy, and the so-called rechallenge are warranted.

References

1. Long G, Atkinson V, Lo S, et al. Five-year overall survival from the anti-PD1 brain collaboration (ABC Study): Randomized phase 2 study of nivolumab (nivo) or nivo+ipilimumab (ipi) in patients (pts) with melanoma brain metastases. Presented at: 2021 ASCO Annual Meeting Chicago, Illinois, June 4-8, 2021.
2. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Five-Year Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma. N Engl J Med. 2019; 381(16): 1535–1546, doi: 10.1056/NEJMoa1910836, indexed in Pubmed: 31562797.
3. Tawbi HA, Forsyth PA, Algazi A, et al. Combined Nivolumab and Ipilimumab in Melanoma Metastatic to the Brain. N Engl J Med. 2018; 379(8): 722–730, doi: 10.1056/NEJMoa1805453, indexed in Pubmed: 30134131.
4. Davies M, Saiag P, Robert C, et al. Dabrafenib plus trametinib in patients with BRAFV600-mutant melanoma brain metastases (COMBI-MB): a multicentre, multicohort, open-label, phase 2 trial. Lancet Oncol. 2017; 18(7): 863–873, doi: 10.1016/s1470-2045(17)30429-1.
5. Luther C, Swami U, Zhang J, et al. Advanced stage melanoma therapies: Detailing the present and exploring the future. Crit Rev Oncol Hematol. 2019; 133: 99–111, doi: 10.1016/j.critrevonc.2018.11.002, indexed in Pubmed: 30661664.
6. Marquez Rodas et al. Streszczenie 1038MO, ESMO 2021.
7. Seghers AC, Wilgenhof S, Lebbé C, et al. Successful rechallenge in two patients with BRAF-V600-mutant melanoma who experienced previous progression during treatment with a selective BRAF inhibitor. Melanoma Res. 2012; 22(6): 466–472, doi: 10.1097/CMR.0b013e3283541541, indexed in Pubmed: 22584957.
8. Valpione S, Carlino MS, Mangana J, et al. Rechallenge with BRAF--directed treatment in metastatic melanoma: A multi-institutional retrospective study. Eur J Cancer. 2018; 91: 116–124, doi: 10.1016/j.ejca.2017.12.007, indexed in Pubmed: 29360604.
9. Cybulska-Stopa B, Rogala P, Czarnecka AM, et al. BRAF and MEK inhibitors rechallenge as effective treatment for patients with metastatic melanoma. Melanoma Res. 2020; 30(5): 465–471, doi: 10.1097/CMR.0000000000000662, indexed in Pubmed: 32221131.