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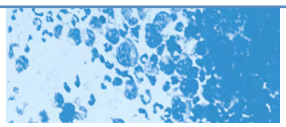

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Metastases of melanoma to the central nervous system

edited by
Piotr Rutkowski

Under the patronage of

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Introduction

Melanoma is one of the malignant tumors that most frequently metastasize to the central nervous system. New treatment methods introduced into daily clinical practice have significantly improved the prognosis of this group of patients [1]. Metastases in the central nervous system are increasingly diagnosed at an asymptomatic stage. Currently, most of the new systemic therapies are available in Poland under drug programs (vemurafenib with cobimetinib, dabrafenib with trametinib, encorafenib with binimetinib, ipilimumab with nivolumab, nivolumab and relatlimab, pembrolizumab, and nivolumab). Data from clinical trials indicate, that the median overall survival in patients with metastatic melanomas with *BRAF* mutations receiving anti-PD-1 immunotherapy or combined treatment with BRAF and MEK inhibitors is currently about 2 years, which is about 4 times longer than 7 years ago [2]. In each patient with confirmed metastases to the central nervous system, it is mandatory to assess *BRAF* gene status, if it has not been done before, in order to select the appropriate therapy.

The presented educational issue of Oncology in Clinical Practice includes review article and a series of clinical case reports concerning the efficacy of molecularly targeted therapies in the treatment of patients with melanoma with the V600 mutation in the *BRAF* gene and metastases to the central nervous system, with particular emphasis on the use of the latest combination of BRAF and MEK inhibitors — encorafenib with binimetinib. It should be noted, that according to current guidelines, in patients with *BRAF*-mutant melanoma and metastases in the central nervous system (especially asymptomatic and less than 3 cm in size), dual immunotherapy with nivolumab and ipilimumab is recommended; however, depending on the clinical situation, the use of BRAFi and MEKi should be considered in the first line treatment (especially in symptomatic cases) [1]. Recently published real-world evidence and the results of clinical trials also confirm that in patients with metastatic melanoma with *BRAF* mutations, the use of anti-PD-1 with anti-CTLA-4 combination as frontline therapy leads to a reduced rate and delay in the occurrence of central nervous system metastases compared to BRAF and MEK inhibitors in first line treatment [3, 4]. The basic principle in the management of patients with melanoma metastases to the central nervous system should be providing care by multidisciplinary teams whose members are experienced in the diagnosis and treatment of patients with melanoma.

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REVIEW ARTICLE

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Efficacy of targeted therapies in the treatment of patients with melanoma harboring *BRAF V600* mutation with central nervous system metastases

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ABSTRACT

Brain metastases develop in almost half of patients with advanced melanoma, and in about 20% of patients, they are the first location of disseminated disease. In the past, the median survival of these patients was about four months, and one-year survival rate was only 10–20%. The implementation of new treatments, including stereotactic radiosurgery, immunotherapy and targeted therapy has significantly improved the prognosis. Approximately 50–60% of melanomas harbor mutations in the *BRAF* gene, so the use of BRAF/MEK inhibitors, which allow for a high rate of intracranial responses, is one of the management options. Many melanoma patients with brain metastases require various therapeutic methods, including local and systemic therapy and their selection and sequence depend on many clinical parameters. Diagnostic and therapeutic management in this group of patients is currently a great challenge. The aim of this publication is to summarize the effectiveness of targeted therapies in the treatment of melanoma patients with a mutation in the *BRAF* gene and central nervous system metastases.

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

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Introduction

Incidence of melanoma is increasing worldwide. It is the third most common malignant tumor, after breast and lung cancer, in terms of the frequency of brain metastases. The central nervous system (CNS) is a common site of disease recurrence and progression in melanoma patients. The presence of brain metastases significantly worsens the prognosis. CNS lesions develop in almost half of patients with advanced melanoma, with 30–40% of patients having them already at diagnosis of disseminated disease, and 80% of patients with disseminated melanoma have CNS metastases at the time of death. In almost 20% of melanoma patients, CNS is the first location of metastases. In 3% of melanoma patients with brain metastases, the primary site cannot be determined.

CNS metastases are often multifocal and initially asymptomatic, with a tendency to bleed. In the past, the prognosis in melanoma patients with brain metastases was very poor, the median survival was four months and only 10–20% of patients had a chance to survive a year. The introduction of new methods of local and systemic treatment has improved the prognosis and allowed for survival prolongation. Due to characteristic for melanoma spreading of disease to CNS, the last update, 8th edition of the American Joint Committee on Cancer (AJCC) staging classification distinguishes brain metastases as a separate stage IV category (M1d) [1]. Predictors of CNS involvement in melanoma patients have not been established yet.

The risk of brain metastases increases with melanoma stage. Factors associated with a higher risk include

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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 [2]. Brain lesions may be asymptomatic, especially at the beginning. Their growth is usually accompanied by symptoms resulting from pressure and edema, including speech impediments, swallowing disorders, paresis and paralysis, epilepsy, headaches and dizziness, nausea, vomiting and bradycardia. These symptoms adversely affect the patient's general condition. Awareness of the high risk of melanoma metastases to the brain and related diagnostics consisting of routine brain imaging as part of the follow-up and during qualification for systemic treatment, allow for detection of CNS metastases at the asymptomatic stage, when both the patient's condition and systemic treatment outcomes are better.

Metastasizing to the brain is a major challenge in the management of melanoma. Patients' care should be provided by multidisciplinary team (MDT) with the participation of specialists experienced in the diagnosis and treatment of this disease, including a neurosurgeon, radiotherapist and clinical oncologist, because the therapy may include both local (radiotherapy, neurosurgery) and systemic treatment as well as supportive (symptomatic) care [3]. The choice and sequencing of individual treatment methods depends on many clinical factors. In the systemic treatment of melanoma, also with metastases to the CNS, 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, and in this group of patients, treatment with targeted therapies, BRAF and MEK inhibitors, is justified.

A mutation in the gene encoding the BRAF protein leads to constitutive activation of MAP kinase signaling pathway. In 80–90% of these cases, the activating mutation consists of replacing valine with glutamic acid at amino acid 600 (V600E). The presence of mutations in the *BRAF* gene is associated with a worse prognosis and distinct clinical characteristics of melanoma. In a case series including 197 melanoma patients, Long et al. [5, 6] demonstrated that *BRAF* mutations were associated with high-risk melanoma features, including location in the trunk, disease onset at a younger age, lack of chronic skin damage, and shorter survival [4]. *BRAF*-mutated melanomas more frequently metastasize to the CNS. In patients with *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.

A review and meta-analysis published in 2019 showed that dual immunotherapy and doublet targeted therapy allow to achieve similar intracranial response rates, while dual immunotherapy allows for longer progression-free survival (PFS) and overall survival (OS) compared to single-drug immunotherapy and targeted therapy [7]. According to current guidelines (NCCN, ESMO), in patients with *BRAF*-mutated melanoma with brain metastases, especially asymptomatic and less than 3 cm in size, not requiring corticosteroids, dual immunotherapy is recommended, which shows the greatest activity in CNS lesions, unless contraindicated. Its efficacy is higher in *BRAF*-positive melanomas compared to *BRAF*-negative ones.

However, depending on the clinical situation, the use of BRAF and MEK inhibitors in the first line treatment should be also considered. BRAF and MEK inhibitors are more often used as treatment of choice in symptomatic brain metastases or in the case of progression after immunotherapy. Therapeutic decisions should be individualized, based on clinical features such as LDH level, involvement of other organs, tumor mass, patient's performance status, course of the disease, comorbidities, size and location of CNS lesions, leptomeningeal carcinomatosis and its treatment, as well as patient preferences and treatment goals (short-term versus long-term benefits). All decisions should be made within multidisciplinary team [8–10].

The use of targeted therapies in the treatment of patients with *BRAF V600*-mutated melanoma with central nervous system metastases

Systemic treatment is well established as a backbone therapy in patients with *BRAF*-mutated melanoma with CNS metastases, which significantly improves prognosis. The choice of treatment regimen depends on many factors, including the presence of the V600 mutation in the *BRAF* gene, patient's performance status, clinical characteristics of intra- and extracranial disease, previous melanoma treatment, comorbidities and concomitant drugs, and patient's preferences. Systemic treatment is usually supplemented with appropriate local treatment.

The efficacy of molecularly targeted drugs (BRAF and MEK inhibitors) in melanoma patients with brain metastases has been demonstrated in prospective clinical trials. The first of these studies evaluated the efficacy of BRAF inhibitors in monotherapy. The largest of them was the phase II BREAK-MB study (n = 172) with dabrafenib in melanoma patients with asymptomatic CNS metastases. The intracranial response rate (IRR) was 39.2% in patients without previous local treatment for CNS metastases and 30.8% in patients with progression after prior local treatment. The median OS in both groups was more than 8 months [11]. In a phase II study

with vemurafenib (n = 146), the IRR was 18% regardless of the previous local treatment, and the median OS was about 9 months [12]. In independent review the IRR in both studies was about 18%, and the disease control rate (DCR) was about 70–80%.

The efficacy of vemurafenib in monotherapy was also assessed in a small study in patients with symptomatic brain metastases not eligible for neurosurgery and requiring corticosteroids (n = 24) [13]. The IRR was 16%, and the median OS was 5.3 months. Whilst performance status and pain improved, with decreased need for corticosteroids, disease progression in the CNS was relatively rapid, despite the initial improvement. The combination of BRAF inhibitors with MEK inhibitors was associated with targeted therapy outcomes, also in melanoma patients with brain metastases.

In the prospective phase II COMBI-MB clinical trial with dabrafenib and trametinib (n = 125) in patients with good performance status (ECOG PS 0–2) and CNS metastases, previously treated and not treated locally for CNS lesions, the IRR was 56–59%, regardless of previous local treatment and presence of clinical signs and symptoms [14]. In asymptomatic patients, the treatment response maintained longer than in symptomatic patients. The duration of response was approximately six months (median) and was significantly shorter than in phase III studies in patients without CNS metastases (12–14 months) [14–16]. The most frequently observed adverse events were fever and gastrointestinal disorders, similarly to other studies with dabrafenib and trametinib.

In an analysis of patients after first line treatment for metastatic melanoma without CNS metastases (n = 1704), published in 2023, the authors retrospectively analyzed the treatment outcomes depending on *BRAF* mutation status. In melanoma patients with *BRAF* mutation treated with anti-PD-1 and anti-CTLA4 immunotherapy in the first line, brain metastases occurred less frequently and later than in patients receiving anti-BRAF and anti-MEK therapy. In addition, the use of dual immunotherapy was associated with a longer OS. Interestingly, no differences in OS were shown between dual immunotherapy and anti-PD-1 monotherapy in melanoma patients without *BRAF* mutations [17].

In 2023 Derks et al. [18] published real-world evidence (RWE) from melanoma patients with brain metastases treated at Rotterdam center from 2005 to 2021 (n = 430), comparing the outcomes achieved before and after the introduction of new therapies (cutoff year 2015). Overall survival was assessed before and after 2015, when ICIs and targeted therapies were used much more frequently. The analysis included 152 melanoma patients with CNS metastases treated before 2015 and 278 patients treated after 2015. The median OS in patients treated after 2015 was significantly longer compared to patients treated before 2015 (6.9 *vs*. 4.4 months, HR 0.67, $p < 0.001$). Median OS was shorter in patients who received systemic therapy before detection of brain metastases. Immunotherapy administered immediately after diagnosis of CNS metastases was associated with prolongation of median OS from 4.2 months to 21.5 months ($p < 0.001$) [18]. As BRAF and MEK inhibitors can induce a rapid treatment response, these drugs were frequently used (> 70%) in patients with symptomatic melanoma brain metastases (MBM) and poor performance status.

BRAF and MEK inhibitors allow for a response in most patients, usually after a short period of use, which may improve the quality of life, especially in symptomatic patients. Unfortunately, the response to targeted drugs is relatively short-term and resistance develops over time.

The results of the studies conducted so far, that confirmed the activity of BRAF and MEK inhibitors in melanoma patients with brain metastases, are summarized in Table 1.

The efficacy of BRAF and MEK inhibitors has also been confirmed in clinical practice, including patients previously treated with these drugs. 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%, disease control rate (DCR) was 63%, as compared to 24% and 57%, respectively, in patients previously treated with BRAF and MEK inhibitors. Only 3 of the 24 patients had not been previously treated with BRAF and MEK inhibitors, and they achieved a partial treatment response in CNS, while two of them achieved a complete CNS response. Among 21 patients, who had previously been treated with BRAF and MEK inhibitors, 11 patients discontinued previous therapy due to poor tolerance and 10 due to disease progression. Encorafenib and binimetinib were well tolerated. Adverse events were observed in 16 patients (67%), the most common of which were fatigue (17%) and myalgia (13%), as well as retinal detachment (8%), arthritis (8%), and nausea (8%). Adverse events were grade 1 or 2, except for two patients who experienced grade 3 myalgia. Pyrexia was observed in one patient [23].

The results of treatment of melanoma patients with brain metastases have significantly improved thanks to the use of new systemic therapies. In many cases systemic therapy is combined with local treatment, which may include both neurosurgery and radiotherapy. In selected patients local treatment includes both of these modalities. Currently, radiotherapy is often used during treatment with BRAF and MEK inhibitors. The combined use of radiotherapy and targeted therapy allows for sensitization of melanoma cells to radiation through the use of BRAF inhibitors, but at the same time may increase the risk and severity of potential adverse effects,

Table 1. Clinical trials evaluating the efficacy of BRAF and MEK inhibitors in the treatment of patients with *BRAF*--mutated melanoma with brain metastases

Study	Type of analysis, phase	Treatment	n	IC ORR % (CR + PR)	mPFS [months]	mOS [months]
Dummer R. [13]	2.	vemurafenib	24	16	3.9	5.3
Falchook GS [19]	1.	dabrafenib	10	NA	4.2	NA
Arance AM [20]	3.	vemurafenib	66	18	NA	NA
BREAK-MB [11] (dabrafenib) (Cohort A: no prior local treatment; Cohort B: progression after prior local treatment)	2.	Cohort A *BRAF V600*E	74	39.2	3.7	7.6
		Cohort A *BRAF V600*K	15	6.7	1.9	3.8
		Cohort B *BRAF V600*E	65	30.8	3.8	7.2
		Cohort B *BRAF V600*K	18	22.2	3.7	5.1
McArthur GA [12] (Vemurafenib (Cohort 1: no prior treatment for brain metastases; Cohort 2: patients previously treated for brain metastases)	2.	Cohort 1	90	18	3.7	8.9
		Cohort 2	56	18	4.0	9.6
Geukes Foppen MH [21]	Retrospective analysis	dabrafenib + trametinib	30	NA	5.8	11.2
Drago JZ [22]	Retrospective analysis	dabrafenib + trametinib, vemurafenib + cobimetinib, encorafenib + binimetinib, vemurafenib + trametinib	65	NA	5.3	9.5
Holbrook K [23]	Retrospective analysis	encorafenib + binimetinib	24	33	NA	NA
COMBI-MB [14] (dabrafenib + trametinib) (Cohort A: asymptomatic untreated brain metastases; Cohort B: asymptomatic previously treated brain metastases; Cohort C: asymptomatic brain metastases of *BRAF V600*K/D/R mutation-positive melanoma; Cohort D: symptomatic brain metastases)	2.	Cohort A	76	58	5.6	10.8
		Cohort B	16	56	7.2	24.3
		Cohort C	16	44	4.2	10.1
		Cohort D	17	59	5.5	11.5
GEM1802/EBRAIN-MEL (encorafenib and binimetinib in combination with radiotherapy) [24, 25] (Cohort 1: asymptomatic brain metastases; Cohort 2: symptomatic brain metastases)	2.	Cohort 1	14	64	7.1	NA
		Cohort 2	15	73	9.3	18.4

IC ORR — intracranial objective response rate; CR — complete response; PR — partial response; PFS — progression-free survival; OS — overall survival; NA — data not available; n — number of patients

e.g., skin toxicity during whole brain radiation therapy (WBRT). It is recommended to withhold BRAFi/MEKi therapy for at least three days before starting WBRT and to resume no earlier than three days after completing radiotherapy.

Currently, stereotactic radiosurgery (SRS) is increasingly used, which allows for a high local control rate. In the case of SRS, systemic therapy is not required to be withhold [8, 24–27]. Concomitant use of BRAF and MEK inhibitors with concurrent radiotherapy is well tolerated and safe, as proven in the phase II GEM1802/ /EBRAIN-MEL clinical trial (NCT03898908), in which encorafenib and binimetinib were used in combination with radiotherapy [24, 25, 28]. The results of this study suggest that outcomes of treatment with novel BRAF and MEK inhibitors combined with radiotherapy may be improved without increased toxicity related to addition of radiotherapy. GEM1802 was a prospective phase II clinical trial in which melanoma patients with CNS metastases received encorafenib (450 mg daily) and binimetinib (45 mg BID) for 56 days, followed by CNS radiotherapy (local or WBRT) and continued encorafenib plus binimetinib until disease progression. The study included 27 patients without signs and symptoms of CNS metastases and 15 symptomatic patients.

The primary endpoint was ICR after 56 days of systemic therapy, i.e., before the start of radiotherapy. Only patients with disease stabilization or partial response to systemic treatment were qualified for radiotherapy. During the median follow-up of 12.3 months, disease progression was not observed in patients receiving systemic treatment. ICR after 56 days of therapy was 66.7% in asymptomatic patients and 73.3% in symptomatic patients. Radiotherapy was administered to 30 patients, including local irradiation in 15 patients and WBRT in 15 patients. In symptomatic patients who did not achieve a complete intracranial response and received radiotherapy, the duration of response was longer compared to patients who did not receive radiotherapy (8.6 months *vs*. 5.6 months). No significant increase in systemic toxicity was observed after radiotherapy use [28].

Unfortunately, the treatment response in melanoma patients with CNS metastases is often unsatisfactory or short-term. Further clinical trials are being conducted to evaluate potential systemic treatments with the aim of improving these outcomes. Among others, trials are currently underway to combine BRAF and MEK inhibitors with other kinase inhibitors or immunotherapy or local treatments. Published results of studies on combination therapies are summarized in Table 2.

Table 2. Clinical trials evaluating the efficacy of targeted therapy combined with immunotherapy in the treatment of patients with BRAF-mutated melanoma with brain metastases.

Study	Phase	Treatment	n	IC ORR % (CR + PR)	mPFS (months)	mOS (months)
TRIDeNT [31] Patients with anti-PD1 resistance (n = 17) or with previous or current brain metastases, including active, asymptomatic or mildly symptomatic/requiring steroids metastases (n = 10)	2.	nivolumab + dabrafenib + trametinib	10	4/7 patients (57%)	8.0	NA
IMSpire 150 [29, 30] Exploratory analysis	3.	vemurafenib + cobimetinib + atezolizumab *vs.* vemurafenib + cobimetinib	244 *vs.* 247	Cumulative incidence of brain metastases as first site of progression: at 12 months: 16% *vs.* 19% at 24 months: 24% *vs.* 26% at 36 months: 25% *vs.* 28% at 48 months: 28% *vs.* 29% Stratified HR: 0.91; 95%: 0.64–1.29)		
TRICOTEL [32] (Cohort 1: *BRAF V600*--negative melanoma patients with brain metastases; n = 15; Cohort 2: *BRAF V600*-mutated melanoma patients with brain metastases)	2.	atezolizumab + vemurafenib + cobimetinib	65	42 in IRC assessment (51 in investigator assessment)	5,3 in the IRC assessment (5.8 in investigator assessment)	13.7

IC ORR — intracranial objective response rate; CR — complete response; PR — partial response; PFS — progression-free survival; OS — overall survival; NA — data not available; ICR — independent review committee; HR — hazard ratio; n — number of patients

Table 3. Currently conducted clinical trials with targeted therapies in melanoma patients with central nervous system metastases

NCT number	Title and phase	Endpoints
NCT04074096 [33]	Randomized phase II clinical trial of adding upfront stereotactic radiosurgery to binimetinib, encorafenib, and pembrolizumab versus binimetinib, encorafenib, and pembrolizumab in patients with *BRAF V600*-mutant melanoma with brain metastases	CNS progression-free survival
NCT04511013 [34]	Phase II clinical trial comparing encorafenib plus binimetinib plus nivolumab versus ipilimumab plus nivolumab in patients with *BRAF V600*-mutated melanoma with brain metastases	Progression-free survival based on RECIST 1.1 criteria
NCT03332589 [35]	Phase 1 clinical trial of E6201 (MEK inhibitor) plus dabrafenib in the treatment of patients with BRAF-mutant melanoma with central nervous system metastases	Intracranial response rate based on RANO-BM criteria

The results of the IMSpire 150 study, in which patients receiving atezolizumab and vemurafenib in combination with cobimetinib achieved ICR of 42% and median OS of 13.7 months [29, 30] show that in selected cases combination of targeted therapy with immunotherapy may be an option; however, it is not a current standard of care. Selected ongoing clinical trials are presented in Table 3.

Conclusions

Melanoma is a malignant tumor often associated with brain metastases, which significantly worsens the prognosis. Treatment should be carried out in a multidisciplinary team, with the participation of experienced specialists. Whilst systemic therapy is backbone therapy, neurosurgery and radiotherapy are also used. Treatment should be individualized and based on clinical characteristics of disease, patient general condition, comorbidities and patient preferences. There are no results of head-to-head studies comparing the available systemic therapies, also in combination with local treatment.

Currently, dual immunotherapy is recommended for asymptomatic patients with CNS metastases smaller than 3 cm, regardless of *BRAF* mutation status. In approximately 40–50% of melanomas, the *V600E* mutation in the *BRAF* gene is found. In patients with melanoma with *BRAF* gene mutation, BRAF and MEK inhibitors should be considered, as their efficacy in terms of intracranial response rate is similar to dual immunotherapy.

The decision regarding systemic treatment should take into account the patient's preferences. Patients should also be qualified for local treatment. BRAF and MEK inhibitors may also be used in subsequent treatment lines in patients who have previously received these drugs. Whilst prognosis in patients treated with modern therapies has improved significantly, many patients still experience disease progression despite their use. Clinical trial participation, if available, remains a valuable option in melanoma patients with CNS metastases.

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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-

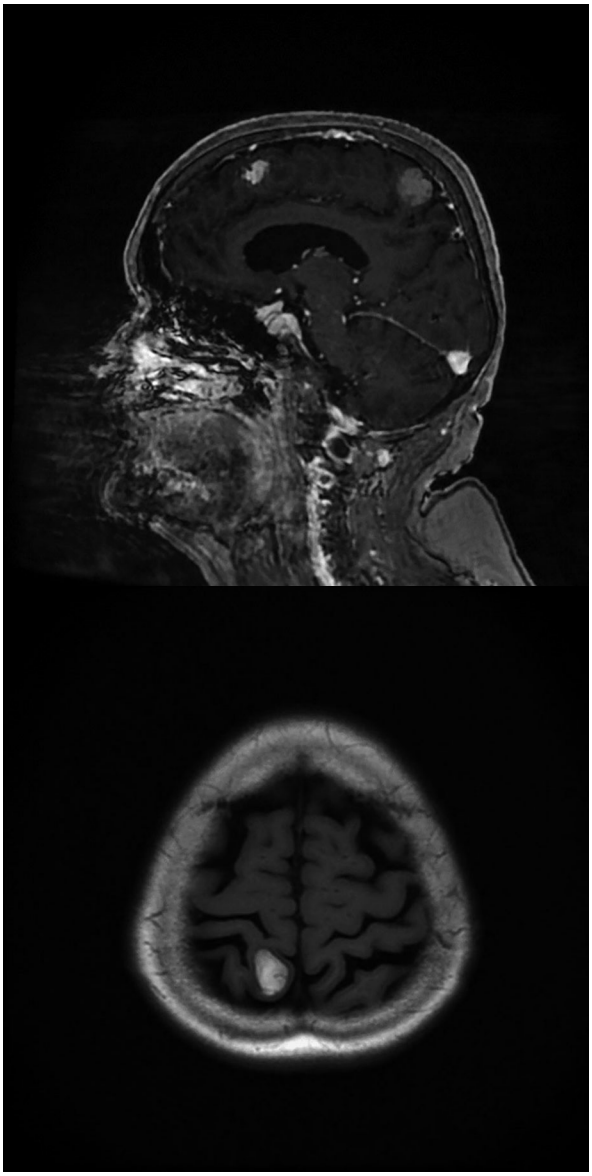

Figure 1. Changes in the central nervous system, March 2021 (material from Department of Soft-Tissue/Bone Sarcomas and Melanomas of the Maria Sklodowska-Curie National Research Institute of Oncology in Warsaw)

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].

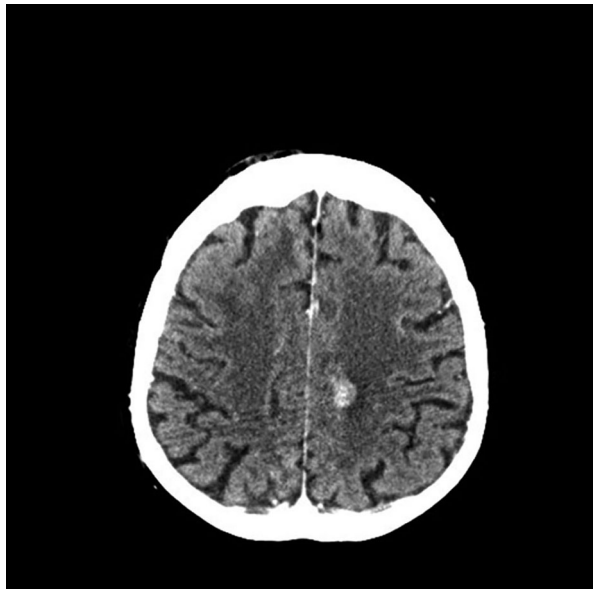

Figure 2. Changes in the central nervous system, March 2022 (material from Department of Soft-Tissue/Bone Sarcomas and Melanomas of the Maria Sklodowska-Curie National Research Institute of Oncology in Warsaw)

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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VIA MEDICA

CASE REPORT

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Melanoma of unknown origin with central nervous system metastases

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ABSTRACT

Melanoma is a tumor with high affinity for metastasis within the central nervous system (CNS). Brain metastases indicate a poor prognosis for the patient, often causing deterioration of neurological functions, and thus the patient's quality of life. We present a case of a 72-year-old patient with diagnosed melanoma of unknown origin in clinical stage IV with metastases to the brain, liver and lymph nodes with the current BRAF *V600E* mutation. The patient underwent stereotactic radiotherapy to the area of changes within the central nervous system and combined therapy involving encorafenib with binimetinib under the drug program of the National Health Fund with a very good response. Despite the initial poor prognosis and the appearance of skin toxicities, the patient is still undergoing oncological therapy, is in good general condition and has obtained a clear therapeutic benefit from the use of anti-BRAF/MEK therapy.

Keywords: melanoma, CNS metastasis, focus primarus ignotus

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Introduction

Therapeutic decisions regarding the treatment of melanoma patients are currently made based on the eighth edition of the American Joint Committee on Cancer (AJCC) staging system. According to this classification, location of distant metastases has the greatest prognostic impact in patients with stage IV disease. Patients with metastases to subcutaneous tissue and skin or nonregional lymph nodes (stage M1a), or metastases to the lungs (stage M1b) have a better prognosis compared to patients with metastases to other organs outside the central nervous system (stage M1c). However, dissemination to the central nervous system (CNS) (stage M1d) is associated with the worst prognosis [1]. Melanoma is the third most common cause of brain metastases after lung and breast cancer. It is estimated that approximately 7% of melanoma patients have lesions in the central nervous system at diagnosis, and 40–50% of patients with advanced melanoma will develop brain metastases during the course of disease [2].

Case report

The 72-year-old female patient, a farmer by profession, with a history of frequent exposure to ultraviolet radiation (UVR) due to the nature of her work, was admitted to the Emergency Department of the Voivodeship Multi-Specialist Center for Oncology and Traumatology in Lodz due to abdominal pain for several days, feeling unwell and chronic fatigue for the last 2 months. Laboratory tests revealed a reduced hemoglobin concentration (Hb 6.3 g/dL) and low ferritin concentration < 8 ng/mL, which corresponds to iron deficiency anemia. A year before the patient had been diagnosed by a general practitioner due to reduced complete blood count (CBC) parameters and a positive fecal occult blood test. No significant abnormalities were found in

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colonoscopy and gastroscopy performed at that time. The test for *Helicobacter pylori* was negative. A contrast-enhanced computed tomography (CT) of the chest, abdomen and pelvis performed urgently revealed a mass occluding duodenal lumen, measuring 13 × 10.6 × 6.9 cm, with several slightly enlarged mesenteric lymph nodes, the largest of which measured 18 mm in the short axis. The patient received 3 units of irradiated leukocyte-depleted red cell concentrate compatible with patient's blood group with good tolerance, and after that patient was qualified for urgent esophagogastroduodenoscopy. Intraoperatively, a friable 12 cm tumor was found in the duodenum narrowing its lumen without signs of active bleeding.

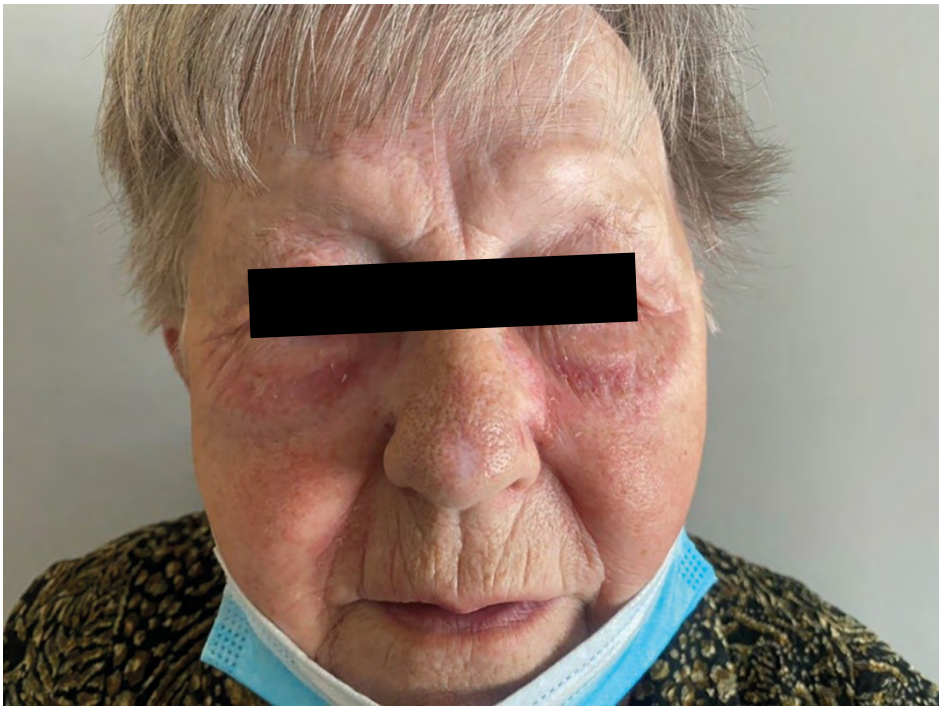
Postoperative histopathological examination showed the presence of poorly differentiated neoplastic cells with immunohistochemically positive staining for HMB-45, S100, Melan-A and SOX10, suggesting metastasis of melanoma.

Skin and mucous membranes dermatoscopy did not reveal any atypic pigmented lesions, which could correspond to a primary melanoma. The patient had never had any skin lesions removed before.

Molecular analysis revealed the presence of a valine-glutamic acid substitution in codon *600* of the *BRAF* gene (*BRAF V600*E mutation). After surgery, the patient reported weakness, periodic headaches, and loss of appetite. Positron emission tomography revealed three metastatic intracerebral lesions, several minor liver lesions, and significantly enlarged mesenteric lymph nodes. Magnetic resonance imaging (MRI) of the brain confirmed the presence of intracerebral metastases in the right parietal lobe and right occipital lobe measuring up to 8 mm. The patient was qualified for stereotactic radiotherapy of both lesions. One fraction of stereotactic radiotherapy was administered at a dose of 22.5 Gy to both brain lesions with a good clinical response. Laboratory tests showed elevated lactate dehydrogenase (LDH) level, i.e. 404 U/L (normal value below 250 U/L).

After ophthalmological consultation and performing an echocardiography, the patient was qualified for first-line treatment with encorafenib and binimetinib in standard doses as part of the drug program, which began in October 2022. During the treatment, the patient observed an improvement in well-being, a reduction in pain and better appetite. In follow-up imaging performed in January 2023, a partial response of hepatic and nodal lesions was obtained.

After more than half a year of therapy, in May 2023, the patient reported to the attending physician due to redness around the eyes (Fig. 1). The patient admitted that she had not followed the recommendations for photoprotection and had spent the last few days in the sun planting vegetables. Due to characteristic clinical picture, current treatment with BRAF and MEK inhibitors and intensive exposure to UVR, the patient was diagnosed with a grade 1 phototoxic reaction according to the Common Terminology Criteria for Adverse Events (CTCAE). Local treatment with weak-potency steroids



Rycina 1. Grade 1 phototoxicity during treatment with encorafenib and binimetinib

and antihistamines was used with a good response. The patient is still undergoing oncological therapy, is in good general condition and has obtained a clear therapeutic benefit from the use of BRAFi/MEKi therapy without other side effects.

Discussion

Melanoma is an aggressive cancer with rapidly increasing incidence worldwide. In the vast majority of patients, the primary lesion is known, located mainly on the skin. In rare cases disseminated disease is diagnosed without a visible primary lesion. These are melanomas of unknown origin (FPI, focus primarius ignotus). It is estimated that they account for 2 to 6% of all melanomas [3].

We consider and treat such patients as diagnosed with skin melanoma, assuming one of the hypotheses that the primary lesion has undergone spontaneous regression, which is why it cannot be detected at diagnosis [4].

Melanoma shows a high predisposition to metastasize to the CNS. Brain metastases are associated with a poor prognosis, and often cause deterioration of neurological functions and quality of life. In asymptomatic patients, they are often detected accidentally during observational radiological studies or during qualification for systemic treatment. It happens that, as in presented patient, the first symptoms of brain metastases are frequent periodic headaches. As in presented case, in patients with single or few mainly asymptomatic brain metastases, stereotactic radiotherapy is recommended. However, depending on the clinical situation, management of melanoma patients with brain metastases includes local and/or systemic treatment, as well as supportive care. The treatment of melanoma patients with brain metastases is currently one of the greatest challenges in the care of patients with advanced melanoma, and therapeutic decisions should be made in teams or specially created units, which should include a clinical oncologist, neurosurgeon, radiotherapist. In patients diagnosed with stage IV melanoma with a *BRAF* mutation, both immunotherapy and three combinations of anti-BRAF and anti-MEK targeted therapies approved for this indication can be used: vemurafenib with cobimetinib, dabrafenib with trametinib, and encorafenib with binimetinib, which have similar efficacy but slightly different toxicity profiles.

Phototoxic reactions are common side effects of anticancer drugs. Indeed, the first BRAF inhibitor introduced into the clinical practice, vemurafenib, was associated with significantly more skin toxicities, and their frequency was reduced by adding the MEK inhibitor, cobimetinib. Phototoxicities observed in patients receiving therapy with other anti-BRAF and anti-MEK drugs: dabrafenib with trametinib or encorafenib with binimetinib are much less frequent. Phototoxic reactions in COLUMBUS pivotal study for combination of encorafenib with binimetinib concerned only 5% of patients in the group receiving the studied combination, while the same skin adverse effect occurred in as many as 30% of patients treated with vemurafenib monotherapy [5]. Although these dermatoses have a very diverse clinical manifestation and can present as polymorphic rashes, erythematous lesions, discolorations or edema, the management patterns of these toxicities have been well known and described. It is essential to inform the patient before starting the therapy about the need for photoprotection throughout the treatment period.

Conclusions

Based on available clinical and laboratory factors, the presented patient could be classified in group with poor prognosis due to the location of metastatic lesions (brain, liver — unfavorable locations), initially elevated LDH level and the observed sign and symptoms of the disease. Despite this, the patient achieved a good therapeutic effect in the form of partial remission (according to RECIST 1.1) of metastatic lesions, which was accompanied by a reduction in pain and improvement in performance status.

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VIA MEDICA

CASE REPORT

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

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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,

Translation and republished by permission from: Galus Ł. Odpowiedź na terapię enkorafenibem z binimetynibem po wcześniejszym leczeniu terapią celowaną i immunoterapią u chorej z przerzutami czerniaka w mózgowiu. Onkol Prakt Klin Edu 2023; 9(supl. E): E20–E22.

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.

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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-

Translation and republished by permission from: Jagodzińska-Mucha P. Pacjentka z rozpoznaniem czerniaka M1d leczona enkorafenibem i binimetynibem w II linii z częściową odpowiedzią na leczenie. Onkol Prakt Klin Edu 2023; 9(supl. E): E23–E25.

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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VIA MEDICA

CASE REPORT

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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

Translation and republished by permission from: Kempa-Kamińska N. Leczenie zaawansowanego czerniaka skóry z mutacją *BRAF V600* z przerzutami do ośrodkowego układu nerwowego z zastosowaniem enkorafenibu skojarzonego z binimetynibem. Onkol Prakt Klin Edu 2023; 9(supl. E): E26–E29.

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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VIA MEDICA

CASE REPORT

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Encorafenib in combination with binimetinib in second line palliative treatment in 44-year patient with symptoms of spinal cord compression

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ABSTRACT

The described case concerns a 44-year-old patient with metastatic skin melanoma and the presence of *BRAF* mutation, who was treated with combined immunotherapy (nivolumab and ipilimumab) with the result of hyperprogression. The first signs of spinal cord compression were observed before the treatment with encorafenib and binimetinib was started. Despite a poor prognosis related to fast progression, the presence of CNS metastases and the presence of *BRAF* mutations, the treatment allowed for a good control of the symptoms of the disease for about six months and improved the quality of patient's life. The combination of BRAF/MEK inhibitors was well tolerated and there was no need for a dose reduction.

Keywords: advanced melanoma, *BRAF* mutation, encorafenib, binimetinib, brain metastases

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Introduction

In recent decades, an alarming increase in the number of newly diagnosed skin melanomas has been observed in Poland. The standardized incidence is approximately 6/100,000, which corresponds to nearly 4,000 new cases per year [1].

A five-year survival rate for patients with metastatic disease ranges from 20% to 40%. Melanoma patients with dissemination in the central nervous system constitute a subgroup with a particularly poor prognosis. It is estimated that in approximately 50% to 60% of patients with advanced melanoma brain metastases will develop (in approximately 75% patients in this subgroup multiple metastases will be detected).

One of unfavorable prognostic factors associated with a higher risk of metastases to the CNS is the presence of an activating mutation in the *BRAF* gene, which is found in about half of patients with advanced melanoma [2].

Case report

A 44-year-old male patient with no significant comorbidities presented for his first visit to the dermatology clinic in August 2021, due to a skin lesion in the left breast area. On August 12, 2021, an excisional biopsy of the suspicious lesion was performed. Histopathological examination revealed invasive melanoma, nodular type; maximum depth of invasion (Breslow thickness) 3 mm; without accompanying ulceration. Subsequently, on August 31, 2021, a wide scar excision procedure and a sentinel node biopsy were performed. Histopathological examination revealed a skin fragment with a scar without

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atypical changes and a lymph node with a melanoma metastasis of 8 mm in diameter with infiltration, but without crossing nodal capsule.

Due to the confirmed metastasis in the sentinel lymph node of the left axilla, the patient was qualified for left axillary lymph node dissection, which was performed on October 28, 2021. Histopathological examination confirmed metastases of melanoma to two of the twelve examined lymph nodes (2/12). In the positron emission tomography-computed tomography (PET-CT) examination performed after the surgery distant melanoma metastases were excluded. The clinical disease stage was finally determined as pT3aN2aM0 = IIIB.

In January 2022, the patient was consulted for the first time at the Krakow branch of the National Research Institute of Oncology. The molecular tests detected an activating mutation in codon *V600* of the *BRAF* gene. Computed tomography performed on January 28, 2022, before the planned qualification for adjuvant treatment, revealed local recurrence in the subcutaneous tissue of the left breast (heterogenous, enhancing after contrast agent administration, numerous nodules up to 25 mm) and dissemination in the lymph nodes, lungs (multiple lesions up to 8 mm in diameter) and liver (multiple lesions up to 53 mm in diameter).

On February 15, 2022, the patient was admitted to the Department of Clinical Oncology to qualify for first line palliative systemic treatment. On admission patient was in good performance status according to the Eastern Cooperative Oncology Group (ECOG) score (ECOG 0), without any significant complaints. The physical examination revealed a painless nodular lesion of approximately 5 cm in diameter on the border of the left breast and the left axilla. Laboratory tests did not reveal any significant abnormalities, lactate dehydrogenase (LDH) level at baseline was 519.6 U/L. After a team consultation, the patient was qualified for doublet immunotherapy (ipilimumab, nivolumab) under the Ministry of Health drug program. Therapy was started on February 11, 2022. The patient received a total of four series of immunotherapy in appropriate doses, every 21 days, with acceptable tolerance. During the treatment, only grade 1 elevation of the transaminases level according to CTCAE (Common Terminology Criteria for Adverse Events) v 5.0 was noted. Due to the appearance of pain from the persistent lesion in the area of the anterior border of the left axillary fossa, after three series of systemic treatment, hypofractionated irradiation was performed to the area of infiltration in the left axilla with a dose of 30 Gy in 5 fractions, using the V-MAT technique (df 6 Gy).

Approximately four weeks after the last dose of dual immunotherapy, the patient reported to the chemotherapy clinic concerned about fevers of up to 39°C lasting for approximately one week, unresponsive to antipyretics, and the appearance of severe pain in the lumbar-sacral spine. Laboratory tests revealed elevated inflammatory parameters — CRP 210 mg/L, procalcitonin 0.87 ng/mL, further increase in LDH level — 623 U/L, increase in transaminases level to G2 according to CTCAE. Empirical antibiotic therapy with ciprofloxacin and steroid therapy with prednisone at a dose of 1 mg/kg bw/d was implemented and the pain management was modified. The patient was referred for control imaging tests. During the planned regular outpatient follow-ups, the fever resolved, the transaminase levels decreased, while the pain symptoms in the lumbar-sacral spine continued to intensify (the patient required high doses of strong opioids) with the appearance of gradual difficulties in independent movement resulting from the paresis of proximal muscles of the lower limbs.

In the computed tomography performed on May 04, 2022, massive progression of metastases in the lungs, subcutaneous tissue, liver and the appearance of multiple new lesions in the skeletal system were revealed [PD according to Response Evaluation Criteria In Solid Tumors (RECIST) v 1.1 criteria]. In the L1 body, a lytic lesion with a mass protruding into the spinal canal to a depth of 4–5 mm with its narrowing was seen. Similar changes with a slight protrusion into the spinal canal were visible at other levels of the thoracic and lumbar spine. In addition, numerous smaller lesions were visible in all bones.

In addition, the magnetic resonance imaging of the head revealed new, quite numerous zones of increased signal in T1-weighted images of up to 2 mm in size in both cerebral hemispheres, in the cortex and subcortex, suggesting metastatic lesions. The lesions in the brain structures were asymptomatic. Considering previously excluded ophthalmological and cardiological contraindications to anti-BRAF/MEK targeted therapy, the patient was qualified for therapy with encorafenib/binimetinib as a second line palliative systemic treatment. Therapy under the drug program was commenced on May 11, 2023. At the same time, radiotherapy was planned for the lumbar spine. However, the planned radiotherapy was abandoned due to the rapid symptoms improvement during applied systemic treatment. Metastatic lesions in the spine were operated in a planned mode by performing vertebroplasty on the L1 and L4 vertebrae and then L4-5 and Th12 vertebrae.

During the follow-up at the beginning of the 3rd series of anti-BRAF/MEK treatment, the LDH level normalized. The patient also stopped taking painkillers without symptoms recurrence. The doses of glucocorticosteroids used were gradually reduced. CT after 14 weeks of therapy revealed partial regression (reduction of the sum of dimensions by over 50% compared to the baseline examination). Therapy with glucocorticosteroids were discontinued. The patient in very good general

condition, without any complaints, decided to return to professional activity (occupation performed — teacher/ /tutor). The treatment was very well tolerated, no side effects of targeted therapy were observed.

The therapy was continued without interruptions, in maximum doses until November 03, 2023, when the patient experienced the first epileptic episode in his life with a transient loss of consciousness. The patient was transported by the emergency medical team to the Emergency Department of the District Hospital. The CT scan of the head showed progression in the form of numerous disseminated metastatic lesions, the largest in the medial part of the right frontal lobe measuring 14 ×10 mm surrounded by a zone of edema.

Steroid therapy (dexamethasone 8 mg/d) was reintroduced with antiepileptic drugs. However, the patient's general and neurological condition deteriorated rapidly, with occurrence of balance disorders, dizziness and slowed speech. The patient was referred for an urgent radiotherapy consultation and then was qualified for CSN radiotherapy. The patient and authorized family members reported on the scheduled date, but the patient did not consent to the proposed palliative CSN radiotherapy. The patient was referred for further supportive care under the supervision of a home hospice.

Discussion

The results of phase III COLUMBUS study led to the registration of the combined therapy with encorafenib and binimetinib in 20218 by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of patients with unresectable/metastatic melanoma with *BRAF* mutations. The median progression-free survival (PFS) in patients receiving this therapy was 14.9 months, and the median overall survival (OS) was 33.6 months [3, 4]. In addition to its efficacy, this therapy is also characterized by very good tolerance.

In presented patient, hyperprogression occurred after four courses of doublet immunotherapy. This phenomenon, described relatively recently [5], reflects unexpectedly rapid progression of disease in patients receiving immunotherapy. The important parameter is tumor growth rate (TGR), which may significantly accelerate after immunotherapy, leading to significant deterioration of patient's general condition. The more than two-fold increase in TGR in the latest evaluation compared to the growth rate in previous evaluations raises the suspicion of hyperprogression. This aggressive and unfavorable mechanism of response to immunotherapy has been described in 9% of patients treated for various cancer types [6, 7].

Fast implementation of encorafenib/binimetinib therapy enabled rapid control of disease symptoms and significantly improved patient's quality of life.

Conclusions

Targeted therapy with BRAF/MEK inhibitors in patients with advanced melanomas with *BRAF* mutations allows for rapid response and tumor control in most patients, with limited response duration associated with the activation of resistance mechanisms. These drugs are considered the preferred therapeutic option in patients with significant disease dynamics and/or high tumor burden.

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VIA MEDICA

CASE REPORT

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Effectiveness of rechallenge with BRAF/ /MEK inhibitors in patient with advanced melanoma with *BRAF V600* mutation

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ABSTRACT

Rechallenge with BRAF/MEK inhibitors is currently a recognized option that improves treatment outcomes in terms of response and survival. This paper presents the case of a 54-year-old female patient with metastatic melanoma and a positive *BRAF* mutation status. The patient received first line targeted therapy. After disease progression, immunotherapy was administered. After another progression, with a good performance status, targeted therapy was reintroduced. A good response was achieved with a statistically significant prolongation of survival. The patient, without progression, in a good performance status, is alive 52 months after the start of the first line therapy and 23 months after the start of rechallenge.

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Introduction

The prognosis in patients with inoperable stage III and metastatic stage IV melanoma was very poor in the past decade. Historically, the overall survival (OS) in these patients was 7.5 months, while approximately 6% of patients survived 5 years. Available therapies were ineffective, with a short response to chemotherapy or unacceptable toxicity of high-dose interleukin 2 therapy [1]. The use of new therapeutic strategies has significantly improved the prognosis in patients with metastatic melanoma. Targeted therapy with BRAF/MEK inhibitors targets the MAPK signaling pathway, activated in melanomas with the *BRAF V600* mutation. Immunotherapy with anti-CTLA-4 and/ /or anti-PD-1 monoclonal antibodies modulates immune response checkpoints. Currently, the median OS in patients with skin melanoma is in the range of 12–24 months, and 20–40% of patients survive 5 years [2].

Approximately 50% of melanoma patients harbor *BRAF* mutation, which is a predictive factor for BRAF/ /MEK inhibitor therapy. Despite a high response rate of nearly 70% to the initial therapy, more than half of patients experience disease progression within 1 year. Immunotherapy with immune checkpoint inhibitors (ICIs), as second line treatment, is the treatment of choice in patients with progression during targeted therapy. This treatment involves monotherapy with an anti-PD-1 monoclonal antibody (nivolumab or pembrolizumab) or a combination of anti-PD-1 (nivolumab) and anti-CTLA-4 (ipilimumab) antibodies. The use of this therapy is associated with response rates of approximately 50% with 1-year survival rate of 70%. However, half of patients will not respond to immunotherapy, and most of them will experience progression [3].

Rechallenge with BRAF/MEK inhibitors is a promising therapeutic option in patients who have previously progressed on targeted therapy and then progressed on immunotherapy (anti-CTLA-4 or anti-PD-1).

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Case report

A 54-year-old female patient with no significant medical history was diagnosed at the Oncological Surgery Outpatient Clinic of the Voivodeship Hospital Centre of the Jelenia Gora Valley in April 2019 due to a tumor in the area of the left scapula that had been growing for two years. In a histopathological examination of the material collected by core needle biopsy, melanoma was diagnosed with a mutation in the *V600* codon of the *BRAF* gene.

The patient did not seek treatment at that time and used alternative therapy, despite growing tumor. The patient reported to the Oncology Outpatient Clinic of the Voivodeship Hospital Centre of the Jelenia Gora Valley in July 2019 due to worsening well-being and increasing pain in the area of the lesion. Patient's performance status according to the Eastern Cooperative Oncology Group (ECOG) score was assessed as 1. The physical examination revealed an ulcerating, spherical tumor in the area of the left scapula, 9 cm in diameter, with extensively infiltrated skin and subcutaneous tissue up to 20 cm in diameter, nodal packages up to 5 cm in both axillary fossae. Computed tomography of the chest, abdomen and pelvis, in addition to the previously mentioned nodular lesion, revealed bilateral metastatic lesions in the axillary nodes, left supraclavicular and subclavicular nodes, lymph nodes of the lower part of the neck on the left side, as well as micronodular dissemination to the lungs and liver. CT scans of the head did not reveal any pathology.

Taking into account the presence of *BRAF* mutation, disseminated nature and high dynamics of the neoplastic process, as well as high tumor burden and good performance status, the patient was qualified for palliative systemic therapy with vemurafenib and cobimetinib, in accordance with the provisions of the drug program B.59 "Treatment of melanoma of the skin and mucous membranes". Treatment was started in July 2019.

The first follow-up CT scan performed in November 2019 revealed complete remission of the primary lesion, metastatic lesions in the lungs and liver, and significant regression in the previously involved lymph nodes. In the physical examination, a very rapid regression of the lesion in the scapular region was observed, with residual flat, scabbed thickening with a diameter of 4 cm. The treatment was continued, and complete remission of neoplastic lesions was confirmed in subsequent imaging studies and physical examinations. Locally, the evolution of the lesion was observed through a black flat thickening to a completely discolored indentation in the place of the initially described tumor.

During the therapy, the patient reported recurrent itching of the skin, minor abdominal pain, and diarrhea with intensity assessed as grade 1 according to CTCAE. In addition, poor vision and a stinging sensation of the upper eyelids occurred periodically. The patient was consulted by an ophthalmologist several times, but no significant pathologies were found. The reported complaints were treated symptomatically, with good results and a stable performance status.

Since July 2020, the patient has been experiencing mild headaches and dizziness. A magnetic resonance imaging (MRI) scan of the head performed in August 2020 showed the presence of numerous metastatic lesions in the brain — the largest with a diameter of 15 mm in the left hemisphere of the cerebellum. After a radiotherapy consultation, the patient was qualified for palliative radiotherapy of the central nervous system (CNS) in the branch of the Radiotherapy Department of the Lower Silesian Oncology Center in Jelenia Góra. In the period from August 31 to September 4, 2020, palliative brain radiotherapy was performed with a total dose of 20 Gy in five fractions.

The patient returned to the Department of Clinical Oncology/Chemotherapy of the Voivodeship Hospital Centre of the Jelenia Gora Valley in September 2020. In the medical history, she reported stable dizziness and periodically occurring headaches of mild intensity. The patient's performance status was assessed as ECOG 1. Laboratory tests showed signs of grade 1 hypothyroidism according CTCAE, and for this reason appropriate supplementation was started.

Taking into account the previous course of the disease and treatment, the currently observed progression in the CNS, previous radiotherapy, stable CNS symptoms for 1 month (CTCAE grade 1), the performance status and organ efficiency, the patient was qualified for palliative second line treatment with nivolumab under the drug program. The therapy started in October 2020.

Follow-up imaging studies performed in December 2020 and March 2021 showed partial remission of the lesion in the right frontal lobe and complete remission of the remaining metastatic lesions in the brain, with continued complete remission (CR) of peripheral lesions. The patient reported sporadic paroxysmal tremors of the upper and lower left limbs, slight dizziness, with a continuous subjective improvement in well-being. Laboratory tests did not reveal any significant abnormalities. There was no deterioration in the patient's performance status.

In May 2021, the patient experienced epileptic seizures, with transient left-sided paresis, fainting, and a feeling of pressure in the head. Imaging tests performed in June 2021 showed significant progression of a single metastatic lesion in the left frontal lobe, accompanied by severe swelling, with persistent remission of peripheral lesions. After a neurosurgical consultation, the patient was qualified for surgical treatment. On June 22, 2021, a right parietal-frontal craniotomy

was performed at the Neurosurgery Department of the Voivodeship Hospital Centre of the Jelenia Gora Valley, with complete tumor resection. The histopathological examination confirmed a metastasis of melanoma.

In July 2021, the patient was readmitted to the Department of Clinical Oncology/Chemotherapy. She reported periodic sensations of pressure and pain in the area of the right temple without epileptic seizures. The performance status was still assessed as ECOG 1. Considering the persistent CR on the periphery, the radical neurosurgical procedure and good performance status, the patient was qualified for continued treatment with nivolumab.

Imaging tests performed in October 2021 showed postoperative changes in the right hemisphere of the brain, with persistent regression of other lesions in the CNS and the periphery. Treatment was well tolerated; no additional symptoms were found.

During the next follow-up visit in December 2021, a physical examination and imaging revealed progression in the right neck lymph nodes. A CT scan performed on December 28 showed pathological right neck lymph nodes, group IIB, measuring 17.5 × 13 mm. Due to the progression found on the periphery, immunotherapy was discontinued. Echocardiography was also performed, and an ophthalmological consultation was carried out. Laboratory tests did not reveal any significant abnormalities.

Taking into account the current course of the disease and treatment, good performance status, and no CNS symptoms, the patient was qualified for the third line treatment, with re-use of BRAF/MEK inhibitors (encorafenib + binimetinib), in accordance with the provisions of the drug program. The treatment was started on December 30, 2021.

In March 2022, the patient was urgently admitted to the Department of Clinical Oncology/Chemotherapy due to grade 4 diarrhea according to CTCAE. Laboratory tests showed grade 2 deterioration of renal parameters according to CTCAE and a negative result of a stool test for *Clostridium difficile*. The treatment with BRAF/MEK inhibitors was interrupted, intravenous fluids were introduced and symptomatic treatment was started. Within three days, the patient's general condition improved, renal parameters normalized, and diarrhea resolved.

The follow-up imaging tests performed at that time showed CR of the neck lesions, with continued regression of the remaining peripheral lesions and brain lesions. In April 2022, treatment with BRAF/MEK inhibitors (encorafenib + binimetinib) was resumed.

In May, during the visit, the patient had an epileptic seizure with transient left hemiplegia. Laboratory tests revealed grade 1 elevated creatinine level according to CTCAE. Antiepileptic treatment was modified under neurological control. MRI of the head performed in April did not reveal progression of the neoplastic process. It was decided to continue the treatment. Since July 2022, the patient has complained of alternating constipation with loose stools and paroxysmal, crampy abdominal pain. In addition, she reported a lack of appetite, general weakness, and dizziness when bending down. The ECOG performance status deteriorated to 2. The physical examination indicated pressure pain in the epigastric fossa. Laboratory tests revealed grade 1 elevated creatinine level according to CTCAE, without other significant abnormalities.

Due to the patient's complaints and poor well-being, the next course of encorafenib + binimetinib treatment was postponed. On July 11, 2022, gastrofiberoscopy and abdominal ultrasound were performed, which did not show any significant pathologies. After the applied symptomatic treatment, the patient's condition improved. It was decided to continue the treatment.

The patient reported recurrent moderate abdominal pain. Laboratory test indicated grade 1 creatinine level elevation according to CTCAE and grade 1 decrease in the estimated glomerular filtration rate (eGFR) according to CTCAE. A CT scan of the chest, abdomen and pelvic performed on September 6, 2022, did not reveal any signs of cancer progression.

A circular infiltration was described in the terminal section of the small intestine, requiring further diagnostics.

Due to maintaining treatment response it was decided to continue systemic therapy. The patient was also referred to the Oncological Surgery Department, where on October 4, 2022, a colonoscopy was performed, revealing a small, hard infiltration at the Bauhin valve level. Samples were taken for histopathological examination, in which features of non-specific inflammation were found, without neoplastic changes.

On October 17, 2022, a laparoscopic right hemicolectomy was performed. Due to the planned procedure, BRAF/MEK encorafenib + binimetinib treatment was suspended for a week before the procedure and three weeks after the procedure. Postoperative histopathological examination revealed non-specific inflammatory changes, without neoplastic changes.

The next whole-body imaging, performed on December 12, 2022, did not show any signs of tumor progression. Therefore, it was decided to continue targeted therapy.

In February 2023, epileptic seizures reappeared. The MRI image showed stable lesions in the CNS. Under the supervision of the Neurological Outpatient Clinic of the Voivodeship Hospital Centre of the Jelenia Gora Valley, antiepileptic treatment was modified, which resulted in a gradual improvement in the patient's condition.

The patient reported to the hospital on March 30, 2023, with diarrhea, periodically worsening to 2 degree according to CTCAE, and low blood pressure. Dizziness and significant weakness were also reported. The clinical assessment showed a deterioration of the performance status to 3 degree according to the ECOG score. Laboratory tests showed: increased CRP level (27), deterioration of renal parameters – grade 1 creatinine and eGFR according to CTCAE. On March 29, a CT scan of the chest, abdomen and pelvis was performed, which revealed asymmetry of glandular tissue in the right breast, without signs of progression of neoplastic lesions. Due to the deterioration of the patient's general condition and the previously mentioned symptoms, it was decided to temporarily interrupt BRAFi/MEKi therapy. Symptomatic treatment was used. Both tests — MMG and ultrasound — excluded focal lesions in the breasts.

During the follow-up visit on April 20, 2023, the patient reported resolution of previously existing symptoms and significant improvement of well-being. Performance status was assessed as ECOG 1. Laboratory tests showed normalization of renal parameters and CRP level. Due to the deteriorating treatment tolerance it was decided to resume BRAFi/MEKi therapy (encorafenib + binimetinib) in reduced doses — first dose reduction (in accordance with the SPC) from the current, 15th course: BRAF 75 mg, 4 tablets once daily; MEK 15 mg, 1 tablet twice daily.

In June 2023, the patient was consulted by an ophthalmologist due to visual disturbances, flashes in the eyes and darkening of the field of vision. The patient received local medications, with good results.

Since June 2023, an increasing number of pigmented lesions have been observed on the skin of the entire body. Therefore, the patient has been systematically undergoing dermatoscopy. To date, no suspicious lesions have been found.

Subsequent imaging studies performed according to the planned scheme showed stabilization of the neoplastic disease. The last CT scan of the chest, abdominal cavity and pelvis was performed on November 23, 2023, and the MRI of the head on September 4.

The patient's next visit took place on December 19, 2023. The patient continues treatment, and at the time of manuscript preparation, she is in the middle of her 25th course. The patient currently reports no symptoms. Performance status was assessed as ECOG 1. The patient functions normally.

Discussion

Progression during treatment with BRAF/MEK inhibitors occurs as a result of acquired resistance associated with reactivation of the MAPK/ERK pathway or at the level of the *BRAF* mutation itself. BRAF/MEK inhibitor resistance has also been shown to induce mechanisms of tumor escape from immune control. In turn, immunotherapy may increase the response to targeted therapy in *BRAF*-mutated melanomas.

Mechanisms of resistance to targeted therapy may be reversible. Tumors are heterogeneous and dominant cell clones change due to new mutations acquired by dividing cells, depending on changes in the tumor microenvironment or external factors such as systemic or local treatment. Hence, after initial exposure to targeted therapy and achieving treatment response, some cell clones may develop resistance, leading to disease progression.

Cessation of exposure to targeted therapy allows for the growth of other tumor cell clones, which were sensitive to it. This phenomenon may result in reversal of resistance to BRAF/MEK inhibitors [2].

The results of review of 238 patients, published in 2019, showed responses to re-challenge in this population, even in patients with previous progression on targeted therapy. The objective response rate (ORR) was 47% with progression-free survival (PFS) of 6.4 months, which was shorter than after first line treatment (9.2 months) [4].

A multicenter retrospective analysis conducted by a Polish group in 2020 included 51 patients who were rechallenged with BRAFi/MEKi therapy. Median overall survival (OS) from the initiation of first line targeted treatment and from rechallenge was 29.7 and 9.3 months, respectively, median progression-free survival (PFS) was 10.5 and 5.9 months, respectively. 6-month survival rates were 98% and 55%, 1-year: 92% and 29%, and 2-year: 69% and 2%, respectively. ORR was higher in first line treatment compared to rechallenge and was 72% and 27%, respectively. The duration of break between the end and start of BRAFi/MEKi therapy did not affect OS. Lower treatment toxicity was observed during rechallenge. The efficacy of rechallenge was better in patients with good performance status, normal lactate dehydrogenase level, and no brain metastases [5].

In August 2023, a meta-analysis was published, including a group of 400 patients with advanced *BRAF*-mutated melanoma, receiving in the first or second line BRAFi/MEKi combined therapy or BRAFi monotherapy. The majority of patients (83%) received immunotherapy, 10% had a break in treatment. During rechallenge, 79% of patients received BRAFi/MEKi combination. The median PFS in this subgroup was 5 months, median OS was 9.8 months, 1-year survival rate 42.6%, and ORR 34%. The presence of brain metastases was not associated with a higher risk of progression or death [2].

At the 2023 ASCO Annual Meeting, Polish and Spanish studies were presented. The Polish study presented the results of a multicenter analysis, which

included 86 patients. The median OS from the start of BRAFi/MEKi therapy and from the start of rechallenge was 34 and 9 months, respectively, and median PFS was 10.5 and 4.4 months, respectively. The half-year, 1-year and 2-year survival rates for first-line treatment were 99%, 93% and 70%, respectively, and for rechallenge 65%, 40% and 2%, respectively. The ORR for first line BRAFi/MEKi therapy and rechallenge was 57% and 28%, respectively [6].

The Spanish study reported the results of a subgroup analysis of 30 of 893 melanoma patients in the GEM 1801 study. The objective response rate (ORR) for the rechallenge group (n = 26), was 38.5%, median PFS and OS 11.1 and 22.1 months, respectively. A positive correlation was found between the depth of response to first line treatment and the duration of PFS [3].

Conclusions

We presented a case report of 54-year-old female patient, treated for disseminated melanoma since July 2019, who achieved a rapid and complete response to first line BRAFi/MEKi combined treatment. Multiple CNS metastases occurred in the 11th month of therapy. After radiotherapy to the CNS, the patient was qualified for immunotherapy with nivolumab, as second line treatment. After 8 months of therapy, progression of one brain lesion was observed, which was surgically removed. Immunotherapy was conducted for a total of 15 months, until progression in the cervical, supraclavicular and subclavicular lymph nodes. Since December 30, 2021, the patient has been undergoing third line treatment with BRAF/MEK inhibitors (encorafenib + + binimetinib). During follow-up, until this manuscript preparation, no signs of cancer recurrence have been observed. The patient is currently during 25th course of therapy. The patient does not report any significant complaints and functions normally.

Rechallenge with BRAF/MEK inhibitors after second line immunotherapy provides significant clinical benefit and is a valuable treatment option for patients with advanced melanoma. Third line therapy should be offered to patients in good performance status. Presented patient is in good performance status, without disease progression, alive 52 months after first treatment initiation and 23 months after the start of rechallenge.

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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.

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Médicament