VIA MEDICA

CASE REPORT

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Patient with stage IV melanoma with *BRAF* mutation — immunotherapy or BRAF and MEK inhibitors?

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ABSTRACT

Treatment of patients with non-operative or metastatic melanoma has changed. New therapies (immunotherapy, targeted therapies — BRAF/MEK inhibitors) significantly prolonged the survival of melanoma patients. The therapy sequence has not been determined, especially in the group of patients with *BRAF* mutation-positive melanoma. We present a case of a 44-year-old patient with *BRAF* mutation-positive metastatic. Due to the slow current course of the disease, normal LDH activity, lack of metastases to the central nervous system, it was decided to use nivolumab immunotherapy in the first line of treatment. After 24 weeks of treatment, a partial remission was observed. The treatment was without complications. Currently, the patient continues immunotherapy. Treatment with nivolumab in the described case proved to be effective.

The decision about the choice of a particular procedure must be consistent with dynamic of cancer, the patient's current condition and should always be discussed with the patient.

Key words: melanoma, immunotherapy, treatment line, nivolumab

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Introduction

The treatment of patients with metastatic or unresectable melanomas has undergone a huge change in recent years. The emergence of new therapies (immunotherapy, targeted therapies using BRAF/MEK inhibitors) has significantly prolonged the survival of melanoma patients.

A major challenge remains, however: the sequence used in therapy, especially in patients with the presence of mutations in the *BRAF* gene. There is no unequivocal evidence for improved survival in *BRAF*(+) patients depending on the application in the first line of immunotherapy or targeted therapies. We are still looking for the factors that can help in the selection of patients for the best treatment options.

This paper presents the case of a patient with metastatic skin melanoma with the presence of the *BRAF* mutation, in whom immunotherapy in the first line of treatment was successfully applied.

Case report

The patient, aged 44 years, was treated for cutaneous melanoma. In the medical history there were no accompanying diseases, no medication, and family history of cancer was negative.

The onset of the disease occurred in August 2012: a nodule was removed from the scalp of the patient's head, histopathological examination (hist-pat) revealed melanoma malignum — 0.5 mm thickness according to Breslow. In September 2012, another nodule from the forehead on the left side was removed, in a hist-pat examination melanoma malignum was found — thickness according to Breslow 2.5 mm. Further standard treatment was applied — removal of the scar and a sentinel lymph node biopsy were performed on the left neck lymph node (October 2012); in the hist-pat examination no melanoma cells were found within the scar and the sentinel node.

In June 2013, a recurrence in the scar was found — the lesion was removed, confirming the melanoma

in the hist-pat examination. PET-CT (positron emission tomography) was performed, not confirming metastatic spread. In September 2013, another relapse in the scar was removed and the hist-pat examination showed melanoma malignum. In October 2013, three consecutive lesions appeared on the skin of the scalp, which were removed. In the hist-pat examination all lesions showed the presence of melanoma cells. He underwent radiotherapy for the lodge after the removed lesions (December 2013). Afterwards the patient remained under surveillance.

In April 2015 a physical examination revealed enlargement of the left cervical lymph nodes, and PET-TK examination confirmed isolated metastatic spread in this area. Left-sided neck lymphadenectomy (May 2015) was performed, hist-pat examination showed metastatic melanoma 4/40 nodes. Due to the number of positive lymph nodes it was decided that adjuvant radiotherapy would be applied (July 2015) to the surrounding left side lymph nodes in the neck, parotid, and behind the ear.

In July 2015 another relapse was diagnosed, this time in the scar in the fronto-parietal area on the left side. The lesion was removed, and hist-pat examination confirmed melanoma malignum. Subsequently, the site was irradiated (50 Gy in 25 fractions). The patient remained under surveillance.

In July 2016 a physical examination revealed an enlarged lymph node in the left submandibular region. The PET-CT exam showed metastases to the left submandibular node and subcutaneous tissue of the right popliteal region and single metastases to the right lung. Due to isolated spread possible for radical excision of lesions it was decided that the lobe of the right lung should be removed (September 2016; hist-pat — *melanoma malignum*). Also the tumour from the left submandibular region was removed (October 2016) and within the right knee (October 2016; hist-pat — *melanoma malignum*). Then in December 2016 adjuvant radiotherapy to the right knee joint (50 Gy in 25 fractions) was applied.

In February 2017, a physical examination showed a nodule on the scalp in the right parietal region (2 cm), a lump on the scalp in the left parietal region (1 cm), enlarged lymph nodes on the right side (2 cm), and enlarged cervical lymph nodes on the left side (1 cm) (Fig. 1). The PET-CT scan performed in February 2017 revealed melanoma metastases to the subcutaneous tissue of the right parietal (12 mm) and left (5 mm) right head and the right (12 mm) and left right (13 mm) lymph nodes (Fig. 2).

In genetic testing, mutation in the V600 codon of the *BRAF* gene was detected. The patient was in very good general condition (PS/ECOG 0), and lactate dehydrogenase activity (LDH) remained normal.

Due to the lack of the possibility to radically resect the metastatic lesions, and very good general condition of the patient and normal LDH activity, after discussion

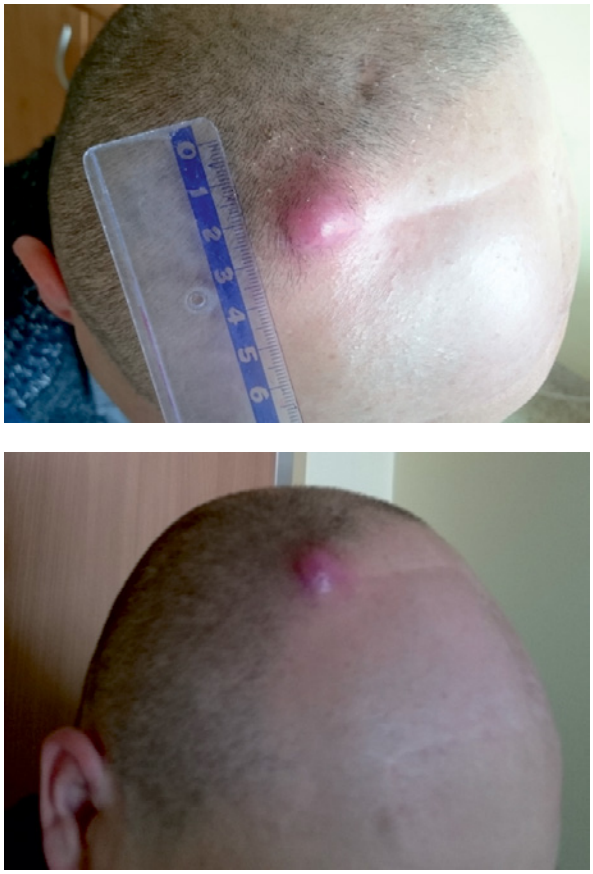

Figure 1. Metastatic lesions on the scalp — February 2017

with the patient it was decided to initiate immunotherapy with nivolumab.

In March 2017 the first immunotherapy cycle was administered: nivolumab 3 mg/kg every 2 weeks. The patient continues the treatment; in December 2017 the 21st cycle of therapy was given. So far there have been no complications related to nivolumab treatment. In imaging studies after 12 weeks of treatment, a small remission of cutaneous and nodal lesions was found. In subsequent studies performed after 24 weeks, a partial remission of lesions was noted (Fig. 3). The patient continues immunotherapy.

Discussion

Treatment of patients with unresectable or metastatic melanoma poses considerable problems, despite the fact that in recent years we have witnessed remarkable progress in this regard. The most controversy and debate is raised by the management of patients with the presence of *BRAF* mutations in melanoma cells because the optimal sequence of therapy in this group of patients is unknown. At present, in Poland, targeted therapies with

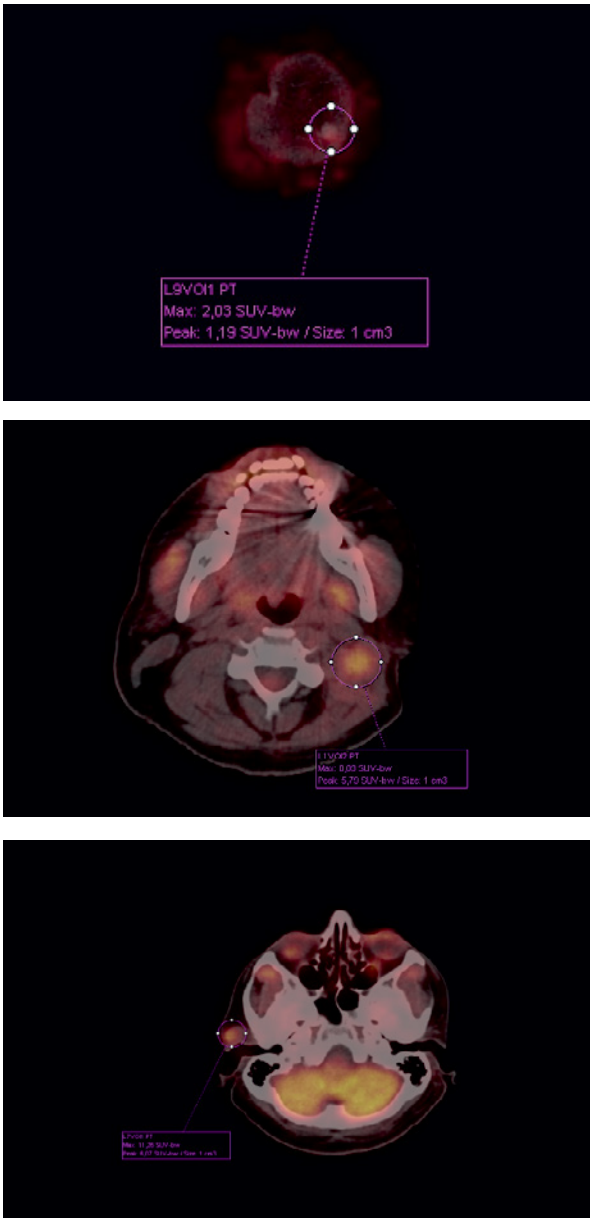

Figure 2. PET-CT — February 2017

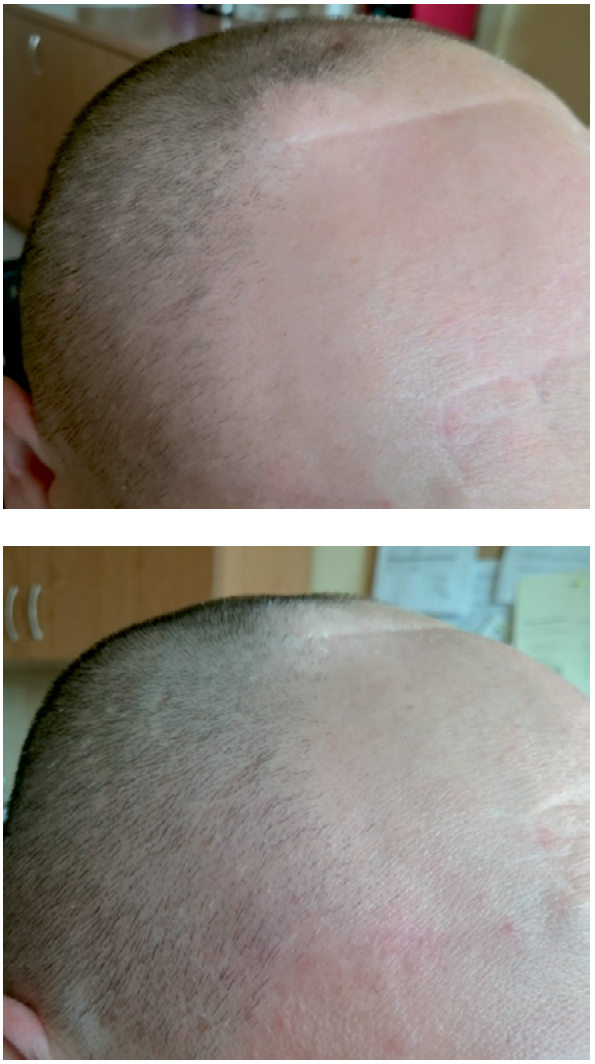

Figure 3. Remission of metastatic lesions on the head — November 2017

BRAF/MEK inhibitors (vemurafenib with cobimetinib and dabrafenib with trametinib) and anti-PD-1 immunotherapy (nivolumab and pembrolizumab) are available in the first and second treatment lines, while in the second line anti-CTLA-4 (ipilimumab) immunotherapy is used, which gives a great opportunity and freedom in the care of patients with unresectable or metastatic melanoma with the presence of *BRAF* mutation.

The use of molecular-targeted therapies with *BRAF* or BRAF/MEK inhibitors results in rapid response to treatment in the majority of patients — lesions are reduced within a few days of the start of medication and responses to monotherapy are observed in more than 50% of patients and in combination in more than 75% of patients [1–6]. The responses last about 12 months in combination therapy — median progression-free survival is 5–12 months for BRAF inhibitors/BRAF and MEK inhibitors, and progression of the disease occurs in the majority of patients and may have a rapid course [1–6]. It is different when using immunotherapy, in which the response to treatment occurs after a few (sometimes even several) weeks. Depending on the type of therapy (anti-CTLA-4, anti PD-1) and treatment line, the response to therapy is recorded in 10–45% of patients, and if it occurs, it is usually long-lasting [1]. Another important issue is the possibility of a completely different profile of complications during targeted therapy or immunotherapy. For this reason, during the qualification of patients for treatment they should always be asked about additional diseases, in particular

autoimmune ones, which may be a contraindication to the use of immunotherapy.

In each case, the patient's qualification for treatment should be approached individually. The rapid dynamics of the disease, the significantly elevated LDH level, and the presence of metastases to the central nervous system (CNS) support the use of targeted therapies in the first line of treatment. In patients with a slow course of disease, normal LDH activity, without CNS metastases, immunotherapy in the first line of treatment should be considered [1, 6].

In our case, the decision on the use of immunotherapy in the first line of treatment was dictated by the free course of the disease, normal LDH activity, lack of CNS metastases, and the attitude of the patient regarding further treatment. During the discussion, the patient was presented with available treatment options and related complications. The patient was extremely motivated to start immunotherapy. It can be concluded that the initiation of nivolumab treatment in the described case was a good decision.

At the moment, there are no clear data on the advantage of one therapy over another in the first line of treatment [1, 6]; therefore, the decision on the choice of a particular procedure must be consistent with the patient's current condition and should be discussed with the patient.

References

1. Luke JJ, Flaherty KT, Ribas A, et al. Targeted agents and immunotherapies: optimizing outcomes in melanoma. Nat Rev Clin Oncol. 2017; 14(8): 463–482, doi: 10.1038/nrclinonc.2017.43, indexed in Pubmed: 28374786.
2. Chapman PB, Hauschild A, Robert C, et al. BRIM-3 Study Group. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med. 2011; 364(26): 2507–2516, doi: 10.1056/NEJMoa1103782, indexed in Pubmed: 21639808.
3. Hauschild A, Grob JJ, Demidov LV, et al. Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. Lancet. 2012; 380(9839): 358–365, doi: 10.1016/S0140-6736(12)60868-X, indexed in Pubmed: 22735384.
4. Flaherty KT, Robert C, Hersey P, et al. METRIC Study Group. Improved survival with MEK inhibition in BRAF-mutated melanoma. N Engl J Med. 2012; 367(2): 107–114, doi: 10.1056/NEJMoa1203421, indexed in Pubmed: 22663011.
5. Flaherty KT, Infante JR, Daud A, et al. Combined BRAF and MEK inhibition in melanoma with BRAF V600 mutations. N Engl J Med. 2012; 367(18): 1694–1703, doi: 10.1056/NEJMoa1210093, indexed in Pubmed: 23020132.
6. Ackerman A, Klein O, McDermott DF, et al. Outcomes of patients with metastatic melanoma treated with immunotherapy prior to or after BRAF inhibitors. Cancer. 2014; 120(11): 1695–1701, doi: 10.1002/cncr.28620, indexed in Pubmed: 24577748.
7. Long GV, Weber JS, Infante JR, et al. Overall Survival and Durable Responses in Patients With BRAF V600-Mutant Metastatic Melanoma Receiving Dabrafenib Combined With Trametinib. J Clin Oncol. 2016; 34(8): 871–878, doi: 10.1200/JCO.2015.62.9345, indexed in Pubmed: 26811525.