Case report

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BRAF V600E MUTATIONS IN METASTATIC MELANOMA - CASE REPORT

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The treatment of metastatic melanoma represents a challenge. Vemurafenib, a selective BRAF kinase inhibitor, is a new medicine against carcinoma. Recently, it has been shown that it raises the survival rate among patients with metastatic melanoma who have BRAFV600mutation. This work will discuss new approaches to the treatment of patients with metastatic melanoma, who have been proved to have BRAF V600 mutation and we will present the case of a female patient with whom the clinical study with Vemurafenib has been started. *Acta Medica Medianae 2014;53(3):39-41.*

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Introduction

The frequency of melanoma is rapidly increasing throughout the world (1). With about 13.000 death cases a year and the mean overall survival (OS) of between 8 and 18 months, metastatic melanoma is the most aggressive form of the skin carcinoma (2). Among the members of the white population the incidence is 10–100 times higher than among the members of the black race or Asians. A highly malignant tumor can appear at any age, rarely before the age of 15, but mainly between the ages of 40 and 55 (3).

In fact, melanoma is the eight most frequent malignity diagnosed in developed countries. Mortality is also on the rise, although an early diagnosis ensures cure in most cases.

Melanoma metastasis usually appears first in regional lymph nodes, with or without later development of distant metastases (most frequently in the skin, lungs, liver, central nervous system and bones). Metastases commonly become visible clinically or are detected during routine monitoring after the treatment of primary lesion (4).

The treatment of metastatic melanoma represents a challenge. In the past three years we have witnessed a unique development in the treatment of melanoma (5). Vemurafenib, a selective BRAFkinase inhibitor, is a new medicine against carcinoma. Recently, it has been shown that it raises the survival rate among patients with metastatic melanoma who have BRAFV600 mutation.

This article will discuss new approaches to the treatment of patients with metastatic melanoma, who have been proved to have BRAF V600 mutation and we will present the case of a female patient with whom the clinical study with Vemurafenib has been started.

Case report

The excision of the pigment change in the skin of the left calf was performed in a 62-year-old patient in 2002 in the Health Centre Valjevo. The result of the HP test was Melanoma invasivum nodular, Breslow III, Clark IV, p T3, without angioinvasion, with a clean resection margin. The stage of illness was M1a (AJCC).

She was operated on the second time in 2004, when dissection of the left inguinal region was performed. In April 2005 retroperitoneal dissection lgl was performed in IORS. Afterwards, in 2007, CT verified the relapse of illness (bilaterally in the adnexal region), and therefore the patient was operated on. Bilateral adnexectomy was performed with partial omentectomy, extirpation of retroperitoneal Tu, as well as the region of intestine with the HP verification of meta-melanoma.

Postoperative CT examination indicated the remaining lymph glands in the retroperitoneum, and the Council decided to begin the HT treatment according to the DTIC protocol of the IX cycle with the PR effect. After that, the patient had regular examinations.

In April 2010, MR examination of the abdomen was performed and on the left, in the bifurcation region of a.iliacacommunis, the 65x25mm change was seen, which corresponds to lgl, inguinal right lgl 30x20mm and inguinal left

subcutaneous, of the diameter 28x15mm (SD). Then the HT retreatment was started according to the DTIC protocol. After the IX cycle the progression of illness was registered – de novo lgl retroperitoneal, and in the further treatment sec. HT VLB-BLM-CDDP, VI cycle was started. CT screening verified the progression of lgl, the appearance of the conglomerate inguinal right.

Then, in November 2011 dissection of the right inguinal region was performed. At the regular control in June 2012 the examination of the control ultrasound of the abdomen and pelvis registered the progression of disease. The liver indicated multiple changes of sec. deposit type, the largest of which was 24mm parailiac left conglomerate lgl 53mm, inguinal left 23mm.

It was confirmed that the patient had the mutation on the BRAF gene and she was included in the clinical study in the illness stage M1c (AJCC). Subsequently, the therapy with Vemurafenib 960 mg was introduced twice a day, after which side effects were registered: rash gr. 2, arthralgia gr. 1 (pain in the hand joints) and the swelling of ankle joints gr. 1.

On the 9th of August, 2012, the excision de novo of the melanoma in the lumbar region on the left was performed. The patient continued with Vemurafenib therapy. At the latest examination in October, the control CT screening registered the regression of sec. deposit by 40%.

Discussion

When melanoma is detected early (stage I), there is 97% likelihood that in the course of five years patients will survive after the surgical removal of non-ulcerated thin (<1mm) primary melanoma (6).

On the other hand, patients with the advanced melanoma, with metastases in the regional lymph nodes or visceral organs, have a five-year survival rate less than 10% (6).

Until 2011 FDA had approved only two therapies in treating metastatic melanoma, Dacarbazin and high doses of Interleukin 2 (HD IL-2).

Dacarbazin is limited by the low response (10–15%) and the overall survival up to eight months. HD IL-2 is limited by the low response (6–10%) as well as serious toxicity and a minority of patients with the long-term and permanent response (7,8).

Recognizing the key molecular mutations leading to tumorogenesis in melanoma brought about the development of the promising agents which selectively target and inhibit these mutations and thus ensure the increase in the response rate with lower toxicity. Secondly, the progress in understanding tumor immunology and immune escape have led to the appearance of more recent immunology agents which are less toxic than HD IL-2, but they also ensure long-term benefits.

While these breakthroughs are encouraging, certain limitations remain. In case of Vemurafenib, the response lasts for a relatively short time. In case of Ipilimumab, the response rate is low (9). In 2011 FDA approved Ipilimumab and Vemurafenib in the treatment of advanced melanoma (10).

BRAF serin / treonin kinase is a member of RAF-kinase family involved in RAS / RAF / MEK / ERK kinase cascade regulating the cell differentiation and proliferation (11). BRAF protein kinase mutations are associated with a wide range of malignities, including up to 70% of melanoma, 40–70% of papillary carcinoma of anaplastic thyroid carcinoma and a small percentage of other types of cancer (11, 12).

As far as melanoma is concerned, BRAF mutation is most common among patients with skin tumors without any chronic damage caused by the sunlight, whereas BRAF mutations are rare in the mucosal or acral melanomas (13).

Identification of BRAF significance has led to the development of numerous new medicines against carcinoma. One of them is Vemurafenib (PLKS4032), a medicine inhibiting particularly BRAF V600 mutation. Stage 1 of studying this medicine showed a complete or partial tumor regression in 81% patients with V600 BRAF mutation, while the stage showed a relative reduction of death risk in 63% patients, as well as a relative reduction of tumor progression risk in 74% of patients in comparison to Dakarbazin (14, 15). The application of this medicine is accompanied by numerous side effects, the most frequent being arthralgia (21%), rash (18%) and fatigue (13%) (16). Effects on the skin are common, including itching, alopecia and hyperkeratosis, keratoacanthoma and planocellular carcinoma (15). Planocellular carcinoma was detected in 10–20% of patients (10).

However, it is also clear that most patients develop immunity to Vemurafenib. Manifested with the progression of illness and rapid recidives, once-established resistance may be rapid as an initial response to drugs. Apart from that, there is a small number of patients whose tumors indicate primary resistance to Vemurafenib (16). Still, patients who take Vemurafenib develop resistance to this medicine within seven months on average. Recent reports have indicated that several complex and context-dependent mechanisms cause resistance to BRAF inhibition (17). Understanding the biology of melanoma is crucial for an accurate selection of patients who will be more likely to benefit from Vemurafenib.

Conclusion

The development of Vemurafenib and the role of BRAF targeted therapy in the treatment of metastatic melanoma ensure a new basis for the clinical research.

In this case report, the treatment with Vemurafenib showed the regression of second deposit by 40%.Vemurafenib shows great therapeutical potential.

Further clinical studies will focus on complex molecular mechanisms underlying resistance and toxicity to Vemurafenib.

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BRAF V600E MUTACIJE KOD METASTATSKOG MELANOMA – PRIKAZ BOLESNIKA

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Lečenje metastatskog melanoma predstavlja izazov. Novi lek koji se koristi u lečenju karcinoma je Vemurafenib, selektivni BRAF kinaza inhibitor. Nedavno je dokazano da povećava stopu preživljavanja kod bolesnika sa metastatskim melanomom koji imaju BRAF V600 mutaciju. U ovom radu se opisuju novi pristupi u lečenju bolesnika sa metastatskim melanomom kod kojih je dokazana BRAF V600 mutacija. Biće prikazan slučaj bolesnice kod koje se sprovodi klinička studija saVemurafenibom. *Acta Medica Medianae 2014;53(3):39-41.*

Ključne reči: *metastatski melanom, BRAF V600 mutacija, lečenje*

