

Skin toxicity in BRAF(V600) mutated metastatic cutaneous melanoma patients treated with vemurafenib

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Abstract

Introduction: The use of orally available BRAF kinase inhibitor – vemurafenib is associated with numerous adverse skin reactions.

Aim: To assess the safety and early side effects of vemurafenib treatment in the unselected group of patients treated at the outpatient clinic, in particular the assessment of the incidence of skin cancer.

Material and methods: We carried out a systematic study of patients (pts) treated with vemurafenib. Skin toxicity during vemurafenib therapy was analyzed. Toxicity was determined on the basis of the toxicity scale CTCAE, version 4.0.

Results: The most common cutaneous side effects were hyperkeratotic perifollicular rash (69%) and photosensitivity (15%). Skin rash developed more frequently in the first month of treatment. Squamous cell carcinoma occurred in 38% of patients. Patients with skin cancer development during vemurafenib therapy had non-significantly longer overall survival (OS) than patients without skin cancer, $p = 0.4$. Skin cancer developed more often in women than in men (60% vs. 25%), $p = 0.249$. It was detected only in patients with normal weight compared to overweight patients (55% vs. 0), $p = 0.09$. The median OS was 26 months and median OS from the time of distant metastases diagnosis was 9.8 months. In patients with a low body mass index, shorter OS was observed, $p = 0.09$.

Conclusions: The incidence of squamous cell carcinoma was high (38%). This study has many limitations mostly due to a small group of patients. That is why the results should be taken into consideration with caution. The proper symptomatic treatment in cooperation with dermatologists allows to continue the vemurafenib therapy.

Key words: cutaneous melanoma, BRAF inhibitor, vemurafenib, skin toxicity.

Introduction

Treatment of metastatic cutaneous melanoma (CM) patients is still a challenge for medicine due to poor prognosis. Median overall survival time (OS) for patients with metastatic CM is 6–15 months after diagnosis [1]. Dacarbazine and interferon, which have been available so far, did not give a high percentage of survival improvement. The response rate is 7–15% with a median duration of response of 4 months [2]. Multidrug chemotherapy did not significantly prolong OS.

The incidence of CM diagnosis increases. In 2011, in Poland 1259 deaths from CM were reported [3].

The introduction to melanoma treatment molecular targeted therapy during the last year increased the hopes of patients and physicians to improve treatment results. Ipilimumab is a monoclonal antibody against CTLA-4 lym-

phocyte receptor. Its mechanism of action interferes with the process of antigen presentation. The final results of this action are increased immune activation, allowing the immune system to recognize, home to, and attack malignant cells. Ipilimumab significantly prolongs overall survival of 3.5 months [4, 5]. Other drugs like dabrafenib or trametenib also showed activity in some patients with malignant melanoma [6].

Activating BRAF kinase mutations occur in 7% of malignancies and approximately 40–60% of cutaneous melanoma carry the mutation in BRAF. Vemurafenib demonstrated an unprecedented 60% antitumor response rate among the patients with BRAF V600 mutated CM. In Poland, until now, only vemurafenib is available to patients with the presence of a mutation in the BRAF V600 gene. The first refunding possibility has been available since

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July 2013. Due to the short time of patients recruitment, diseases rareness and unusual side effects of this kind of treatment we collected a group of patients treated in two oncology centers.

Vemurafenib treatment is associated with significant and sometimes severe and intriguing treatment-related dermatological toxicity. The most common adverse skin reactions include photosensitivity, induced malignant lesions of the skin such as keratoacanthoma, squamous cell carcinoma and new primary melanomas, as well as keratinocyte proliferation and differentiation dysfunctions that can manifest as skin papillomas, hand-foot skin reaction, keratosis pilaris-like rash, acantholytic dyskeratosis and cysts of the milia type [7–10].

Aim

The aim of this study was to assess the safety and early side effects of vemurafenib treatment in the unselected group of patients treated at the outpatient clinic, in particular the assessment of the incidence of skin cancer.

Material and methods

This retrospective analysis was performed at the Clinical and Experimental Oncology Department, Maria Skłodowska-Curie Memorial Cancer Center and Institute of Oncology in Gliwice, Poland (COI). The analysis of patients' medical records was performed according to national laws. The data including the age at onset, disease stage, surgical procedures, and histology were gathered from hospital records and pathology reports. All patients with metastatic or inoperable CM were diagnosed, treated and followed up in COI and in the Oncological Ward of the Independent Public Health Care Unit, Voivodeship Specialized Hospital in Rybnik. All of the patients were treated with the same inclusion criteria including age above 18 years, metastatic or inoperable skin melanoma with a BRAF V600 mutation. All mutations were diagnosed with the same test in the same laboratory. All patients underwent physical, including dermatological, examination and electrocardiography. All patients had a good performance status (ZUBROD 0-1). All patients were evaluated with RECIST 1.1 criteria using computed tomography or magnetic resonance of the brain, chest, abdomen and pelvis. Toxicity was determined on the basis of the toxicity scale CTCAE, version 4.0. All of patients were examined at the outpatient clinic every week. This enabled early toxicity diagnosis and its therapy.

Thirteen consecutive patients were included to the vemurafenib therapy (5 females and 8 males) according to inclusion criteria set by the Polish Ministry of Health. Patients received oral vemurafenib 960mg twice a day until progression, intolerable adverse effects or withdrawal of consent. Continuation the vemurafenib therapy

after disease progression was not allowed. Development of skin carcinoma and its surgical treatment did not require any dose modification or discontinuation of drug.

Statistical analysis

Statistical analysis was performed using Statistica 8 program. The impact of variables such as patients' gender, previous treatment, response to vemurafenib therapy and toxicity were analyzed by χ^2 test with Yates' correction. Differences were considered as significant if the p -value was ≤ 0.05 . Survival evaluation was performed using the Kaplan-Meier estimate with a log rank test.

Results

Median age at the time of CM diagnosis was 54 years (range: 42–70). Nine patients underwent radical surgery and 4 of them received adjuvant radiotherapy. Four (31%) patients had initial metastatic disease. At the time of inclusion to vemurafenib therapy, all of patients had distant inoperable metastases. The most frequent metastatic sites were mediastinal lymph nodes (in 10 patients – 77%), then lungs or liver as well as brain or skin, 39% and 31% of patients respectively. Brain metastases were stable and did not require any therapy during vemurafenib intake. Vemurafenib was used in the first- and second-line treatment in 11 (85%) and 2 (15%) patients, respectively. Median treatment time was 4.5 months. In some patients we noticed surprisingly quick tumor regressions. The median time of best response was 7 weeks. Disease response (complete response + partial response) was observed in 10 (77%) patients and disease stagnation (SD) was reached 1 (7%) patient. During the observation time, 5 patients died. Three of them had disease dissemination to the brain.

During the vemurafenib therapy, all patients developed skin toxicity. In the studied group the most common skin side effects were a diffuse hyperkeratotic perifollicular rash (69%), photosensitivity (15%) (Figure 1) and keratoacanthoma (Figure 2). Skin rash developed more



Figure 1. Photosensitivity

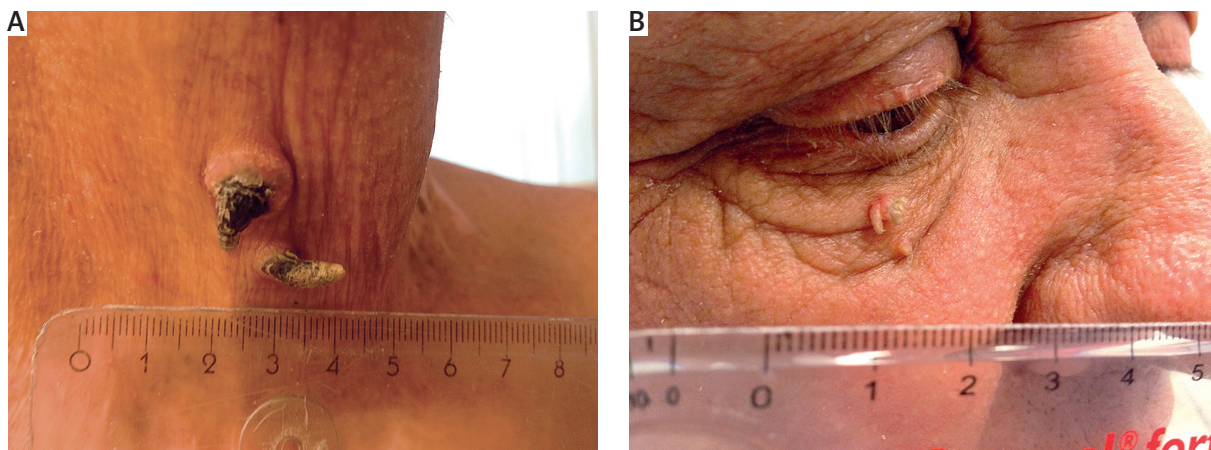


Figure 2. Keratoacanthoma

frequently during the first month of treatment. After symptomatic dermatological treatment (ointments with steroids, antibiotics), lesions have been reduced. Squamous cell carcinoma (SCC) requiring surgery occurred in 38% of patients. In all patients, skin cancer was located on the face. Surgery did not have any influence on systemic therapy administration. Median time to skin cancer development was 8 weeks.

Skin cancer developed more often in women than in men (60% vs. 25%), $p = 0.249$. It was detected only in patients with normal weight compared to overweight patients (55% vs. 0%), $p = 0.09$. Patients with skin cancer developed during vemurafenib therapy had non-significantly longer OS than patients without skin cancer (11.8 vs. 9.4 months), $p = 0.4$. Other common toxic effects were severe musculoskeletal pain (in 8 patients) and high fever (in 5 patients).

Median body mass index (BMI) was 26.6 (range: 22–39) kg/m². Two patients had normal weight, and 7 were overweight and 4 were obese. Body mass index had no influence on the skin toxicity incidence. Patients with low BMI had non-significantly shorter OS. Ten (77%) patients

had comorbid conditions such as hypertension, cardiovascular diseases and other in history.

Treatment response was observed more frequently in men than in women. The differences were not significant ($p = 0.128$). The better response was detected in patients who received vemurafenib in the first line of treatment ($p = 0.294$). Vemurafenib toxicity and treatment response are summarized in Table 1.

The median overall survival (OS) was 26 months and median OS from the time of distant metastases diagnosis was 9.8 months. Patient overall survival is summarized in Table 2.

Discussion

This retrospective study of early vemurafenib toxicity showed that all patients developed side effects related to vemurafenib therapy. Skin lesions occurred in the first month of treatment. The most common skin side effects were a diffuse hyperkeratotic perifollicular rash (69%) and photosensitivity (15%). The management and evolution of the skin symptoms were described by Bous-

Table 1. Vemurafenib toxicity and treatment response

Parameter	Percentage of patients	Statistical significance, <i>p</i>
Skin cancer development during treatment:		
Women	60	0.249
Men	25	
Skin cancer development during treatment:		
Overweight patients	55	0.09
Patients with normal weight	0	
Treatment response:		
Women	40	0.128
Men	95	

Table 2. Patients overall survival

Parameter	Time [months]	Statistical significance, <i>p</i>
Median overall survival:		
Women	13.7	0.3
Men	36.0	
Median overall survival for patients:		
With skin cancer development	11.8	0.4
Without skin cancer development	9.4	

semart *et al.* [11]. In this study most common cutaneous toxicity was verrucous papillomas (79%), perifollicular rash (55%), photosensitivity (52%) and alopecia (45%). Keratoacanthoma (KA) occurred in 14% and squamous cell carcinoma (SCC) in 26% of the patients [12]. The adverse events were consistent with toxicity reported in the BRIM-2 and BRIM-3 registration trials [10–12]. In BRIM-3 trial, the most frequent grade 3–4 events were cutaneous squamous-cell carcinoma (19% of patients) and keratoacanthoma (10%), rash (9%), and abnormal liver function tests (11%) in the vemurafenib group [12]. In the analyzed group, SCC occurred in 38% of patients. The incidence of cutaneous squamous cell carcinoma was higher than that reported in BRIM-2 and BRIM-3 (26% and 19%, respectively). The mechanism of skin cancer development during vemurafenib therapy is still under investigation. Neoplasms originating from keratocytes were observed during therapy with other BRAF inhibitor – dabrafenib and multikinase inhibitor – sorafenib.

Authors have attempted to find the influence of clinicopathological factors on skin toxicity and skin cancer development during vemurafenib therapy. Skin cancer developed slightly more often in women than in men ($p = 0.249$) and in patients with normal weight compared to overweight patients ($p = 0.09$). Authors did not find any data on this point in the literature and do not have any explanation for this. There was no association between patients' age, comorbid conditions and skin toxicity of vemurafenib. In an open label, multicentre trial described by Larkin *et al.*, there was an increased incidence of grade 3 and grade 4 adverse events, and adverse events leading to discontinuation in patients aged 75 years and older [9]. Other side effects was QTc prolongation. In this trial, cardiac comorbidity was a risk factor for QTc prolongation and long-term sun damage to the skin for the skin cancers [9]. We did not observe QTc prolongation in the studied group.

Vemurafenib produced improved rates of overall and progression-free survival in patients with previously untreated melanoma with the BRAF V600E mutation [12]. Median PFS and overall survival were 5.6 months and 12.0 months, respectively [6]. Similar overall survival was noted in the pivotal phase 2 and 3 trials [13, 14]. In the analyzed group, the median overall survival (OS) was

26 months and median OS from the time of distant metastases diagnosis was 9.8 months. In patients with lower BMI shorter OS was observed.

Conclusions

All of the patients developed skin toxicity. The incidence of squamous cell carcinoma was high (38%). The results of this study has many limitations mostly due to a small group of patients. That is why the results should be taken into consideration with caution. The proper symptomatic treatment in cooperation with dermatologists allows to continue the vemurafenib therapy.

Conflict of interest

The authors declare no conflict of interest.

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