

SKIN TOXICITY OF TARGETED THERAPY: VEMURAFENIB, FIRST EXPERIENCES FROM MONTENEGRO

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Abstract: Introduction: Data on melanoma incidence and mortality in Montenegro is only partially complete. GLOBOCAN and EUCAN reports estimate melanoma incidence in Montenegro to be between 4.6–7.3 cases/100 000.

At least 50% of all metastatic melanoma cell lines carry an activating mutation in the BRAF oncogene. The treatment of advanced melanoma with the selective BRAF inhibitors, such as vemurafenib demonstrated improvement in progression free interval and overall survival when compared to conventional chemotherapy treatment. Up to 95% of patients treated with vemurafenib experience skin toxicity.

Material and methods: Five patients with metastatic melanoma have been treated with vemurafenib at the Clinic for Oncology and Radiotherapy Podgorica, Montenegro, during the period 2013–2014. They were treated with standard dose (960 mg twice a day, per os). Data about the occurrence and management of skin side-effects in these patients were retrospectively collected from medical charts. Severity of side-effects was graded using the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.0.

Results: In 2013, 41 new cases of melanoma were registered in Montenegro, 20 (48.7%) male and 21 (51.3%) female. In 2014, 49 new cases of melanoma were registered, 27 (55.1%) male and 22 (44.9%) female. Two out of five (40%) vemurafenib treated patients experienced photosensitivity, three (60%) had rash eruptions, four (80%) developed alopecia, and two (40%) had dry skin problems. Alteration in nevus color and size occurred in one (20%) patient, and two (40%) patients developed new pigmented lesions.

Conclusion: Skin side effects associated with vemurafenib are plentiful, but generally manageable with supportive care measures. In our experience, majority of described side-effects were of grade 1 or 2, and none required dose modifications, or discontinuation of the

therapy. Our experience suggests that patients taking BRAF inhibitors should have regular full body skin assessments, both prior to the beginning of the therapy and periodically after its onset. Clinicians should be aware of the skin related toxicities, in order to minimize their impact on treatment efficacy and patients' quality of life.

Key words: Melanoma, vemurafenib, skin side effects.

INTRODUCTION

Melanoma accounts for less than 2% of all skin malignancies, but it is responsible for majority of skin-malignancy related deaths (1). Epidemiologic studies demonstrate that both the incidence and the prevalence of melanoma have increased steadily during last 30 years (1).

Data related to incidence and mortality of melanoma in Montenegro are still incomplete. GLOBOCAN (2) and EUCAN (3) reports estimate the melanoma incidence in Montenegro to be between 4.6–7.3 cases/100 000. According to the register data at the Clinic for Oncology and Radiotherapy Podgorica in 2013, 41 new cases of melanoma were registered in Montenegro, 20 (48.7%) males and 21 (51.3%) females. In nine (21.9%) patients, disease was initially metastatic. In 2014, 49 new cases of melanoma were registered, 27 (55.1%) males and 22 (44.9%) females. In 7 (14.3%) patients disease was initially metastatic.

Activating mutation of BRAF oncogene is found in more than 50% of all metastatic melanoma cell lines (4, 5). Treatment of advanced melanoma with activating BRAF mutation with selective BRAF inhibitors, such as vemurafenib, proved to be effective both in terms of progression-free survival and overall survival, when compared to conventional chemotherapy treatment with dacarbazine (6, 7, 8).

Although the superior efficacy when compared to conventional chemotherapy, treatment with vemurafenib is often associated with numerous adverse effects (6, 9, 10). Most common side effects of selective BRAF inhibitors are skin side effects that occur in 92–95% of all patients (9, 10, 11). Vemurafenib causes rash and erythema eruptions, photosensitivity, hand foot syndrome, squamous cell skin carcinoma, keratoacanthoma, and some less common adverse effects such as erythema nodosum and toxic epidermal necrolysis (9, 10, 11). Although these side effects do not lead to the abruption of treatment, they can cause its discontinuation, or require doses reduction. In addition, quality of life in these patients can be decreased due to side effects. Literature shows that dose modifications or treatment discontinuation were required in less than 10% of all vemurafenib treated patients (12). Better understanding of skin related toxicities helps to minimize their impact on treatment efficacy and patients' quality of life.

AIM

Aim of this study is to analyze profile of vemurafenib treatment induced skin toxicity in patients with BRAF mutation positive metastatic melanoma at the Clinic for Oncology and Radiotherapy, Clinical Center of Montenegro, during the period of 2013 and 2014.

MATERIALS AND METHODS

For each patient with metastatic melanoma, whose performance status was 0-1, BRAF mutation analysis was suggested by the Clinic for Oncology and Radiotherapy Board for Skin Malignant Diseases. Analyses were performed at Institute of Pathology, University of Ljubljana, Slovenia. Patients with negative BRAF mutation status were not eligible for vemurafenib treatment. Medical documentation of all the patients with confirmed BRAF V600E mutation was reexamined by the Board of Health Insurance of Montenegro, whose confirmation was required to initiate the treatment.

Total of five (BRAF mutation positive) metastatic melanoma patients were treated with vemurafenib in 2013 and 2014. All of them were given standard dose (960 mg twice a day, orally). All patients were examined by an oncologist (full body skin exam included) prior to the onset of the BRAF inhibitor treatment, followed by reevaluations conducted every four weeks. We gathered data related to the occurrence and management of skin side-effects in these patients. Severity of side-effects was graded using the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.0 (13). Skin lesions with suspected

malignant potential were excised and submitted to pathologist for examination. Treatment was interrupted in patients with grade 3 or higher adverse effects. Vemurafenib treatment was resumed after improvement of toxicity to grade 1. For patients who experienced same side effects more than once during the course of treatment the highest recorded grade of toxicity was selected for this review.

RESULTS

Total of five metastatic melanoma patients were treated with vemurafenib in 2013 and 2014 at the Clinic for Oncology and Radiotherapy, Clinical Center of Montenegro. Two of them were male and three female, average age 39.6 years. Treatment with vemurafenib was recommended by the Board for Skin Malignancies.

Two (40%) patients experienced photosensitivity. In one case, photosensitivity was mild (grade 1); it required no treatment discontinuation. Symptomatic therapy was not administered. Another patient experienced grade 3 photosensitivity, painful, burning sensation after being exposed to UVA rays (patient did not apply protective sun-screen). The reaction was accompanied by face swelling. Vemurafenib had to be discontinued for a period of seven days, with adequate symptomatic treatment based on corticosteroids and non-steroid anti-inflammatory drugs. After full resolution of symptoms, vemurafenib was continued in full dose. A stricter UVA protection regime was conducted.

In three (60%) of our patients, we have noticed rash and erythema eruptions, all appearing within the first three months after the treatment onset. All of the rash eruptions were of grade 1 and grade 2. These required neither treatment interruption, nor doses modification, only a symptomatic treatment was prescribed by dermatologist.

Four patients (80%) acquired grade 1 and grade 2 alopecia. Two (40%) reported dry skin problems, which were treated with topical agents.

Alteration in nevus color and size occurred in one (20%) patient. Lesion proved to be a dysplastic nevus in pathological examination. In two (40%) patients, new pigmented lesions appeared on healthy looking skin, both compound nevi by the report of pathologist.

We have encountered neither keratoacanthoma, nor squamous cell carcinoma, although literature suggests they appear in more than 20% of all the patients treated with vemurafenib, which makes them most common *de novo* skin malignancies in these patients.

Results are summarized in Table 1.

Table 1: *Vemurafenib associated skin toxicities graded using the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.0.*

	M45yo	F28yo	F49yo	F37yo	M39yo
Photosensitivity	Grade 3	–	–	–	Grade 1
Rash	Grade 2	Grade 1	Grade 1	–	–
Erythema	–	Grade 2	Grade 2	–	–
Alopecia	Grade 2	Grade 1	Grade 2	–	Grade 1
Dry skin	–	–	Grade 1	–	Grade 1

- New melanocytic lesions were found in one patient (female, 37 years old).
- In two patients (both male, 45 and 39 years old) alteration of existing nevi occurred
- Other skin toxicities associated with vemurafenib treatment (keratoacantoma, squamous cell skin carcinoma, basal cell skin carcinoma, erythema nodosum, toxic epidermolysis and Stevens Jonson syndrome) did not occur in our five patients.

DISCUSSION

Rash and erythema

Rash and erythema occur in nearly three quarters of all vemurafenib treated patients, which makes them the most common side effects of this therapy (8, 11, 12). There is no known correlation of vemurafenib induced rash severity with treatment efficacy; this is unlike the acneiform skin eruptions seen in EGFR inhibitor treated patients that correlate positively with the treatment outcome (14). For example, in BRIM-2 (8) and BRIM-3 (11) trials, incidence of rash was similarly distributed between the responders and the non-responders. Development of grade 3 rash was slightly higher in the group of responders. This was, however without statistical significance. Rash (that is pruritic and maculopapular) is most likely caused by hypersensitivity reaction (12). Literature shows that in most cases rash and erythema are of grade 1 and 2. Therefore, there is no need for dose reduction or treatment discontinuation (12). We have observed rash eruptions in three of five patients treated at the Clinic for Oncology and Radiotherapy, Clinical Center of Montenegro. In all of the cases rash was of grade 1 or grade 2. Patients were referred to a dermatologist, who prescribed symptomatic treatment. In none of the patients dose reduction or treatment abruption were required. Our experience is similar to the findings of previous investigators, suggesting that although a cautious approach is needed, majority of rash outbursts are of lower to moderate severity and are usually well tolerated by patients.

Photosensitivity

Photosensitivity is a frequent side effect in vemurafenib treated patients (12). In BRIM studies 35–63%

of patients experienced photosensitivity, in majority of cases of mild severity. Other studies on side effects of BRAF inhibitors treatment report similar findings (15). Taking into consideration the nature and evolution of skin lesions, it can be concluded that BRAF inhibition treatment is associated with UVA dependent photosensitivity (16). Patients should therefore strictly follow protection schedule and stay away from direct sun exposure as much as possible. Broad spectrum sunscreens, ultraviolet dense clothes and protective sunglasses are highly recommended. It has been demonstrated that these measures could largely help to prevent vemurafenib induced photosensitivity (17).

In our series of cases, two patients had photosensitivity reaction. One patient experienced grade 1 photo-toxicity. In this case, there was no need for symptomatic treatment and protection schedule was reintroduced. Other patient experienced grade 3 photosensitivity, burning sensations and pain, followed by face swelling (he did not apply sunscreen). Vemurafenib treatment was paused until the resolution of symptoms and corticosteroids and non-steroid anti-inflammatory drugs were introduced. Seven days after the event, following another full body exam, vemurafenib treatment (full doses) was continued and denser reexaminations schedule and follow up was introduced. Vemurafenib induced photosensitivity in one male patient was the only grade 3 event we have encountered. No reduction of doses was needed and our experience was comparable to the results of previous studies.

Keratoacantoma and squamous cell skin carcinoma

Potential of BRAF inhibitors to cause secondary malignancies is concerning. Literature data suggests

that up to one third of patients treated with vemurafenib develop de novo skin malignancy, keratoacanthomas and squamous cell skin carcinoma in majority of cases (6–8, 18). Squamous cell skin carcinoma was observed in 79 patients (23.5%) in BRIM 3 trial (11) and in 25.8% in BRIM 2 trial (8). These lesions usually appeared between the eight and the twelfth week after the therapy onset.

Keratoacanthoma is a common skin lesion of low malignant potential, which usually appears on sun-exposed parts of the skin (19). It is considered to be a precursor lesion of squamous cell skin carcinoma, which develops in about 10% of all the cases (20).

Genetic and histological analysis of keratoacanthomas and squamous cell skin carcinomas suggest they are more aggressive in BRAF inhibitor treated patients when compared to spontaneously developed lesions (6). Numerous genetic alterations are deemed to be associated with appearance of skin malignancies, including p53 mutation (21) that was found in about 50% of all secondary squamous cell skin carcinomas in patients treated with vemurafenib (22). Furthermore, RAS protooncogen mutation was identified in about 40% of lesions (23). Other drugs that lead to the inhibition of RAF signaling pathway, such as sorafenib or dabrafenib, can also cause squamous cell skin carcinoma in up to 10% of all treated patients (24, 25). Therefore it has been suggested that RAF inhibition has a direct role in secondary malignancy development in these patients. There is no significant change in risk factors for primary squamous cell skin malignancies and vemurafenib-induced malignant lesions; chronic sun exposure is believed to be the most important risk factor (12). We believe that lack of chronic sun exposure could explain lack of secondary malignancies in patients treated at the Clinic of Oncology and Radiotherapy in Podgorica. Namely, average age of our patients was just above 39, compared to 54 in BRIM studies (8, 11), so preexisting sun induced skin toxicity was most probably of a lesser grade. Taking into consideration that de novo malignancies appear in the first three months of treatment (12), it is possible that already developed precursor lesions are of greater significance, while BRAF inhibition plays the role of a trigger. Numerous studies also show that BRAF inhibition leads to pathologic activation of MAPK signaling pathway in cells without BRAF mutation (26–28), which leads to assumption that MAPK pathway is also of importance in development of secondary skin malignancies during vemurafenib treatment.

Suggested therapeutic approach for keratoacanthomas is cryotherapy and surgical excision for squamous cell carcinomas. Secondary skin malignancies are not considered a reason for dose reduction of vemurafenib.

Alopecia, dry skin, hyperkeratosis and pruritus

Up to 45% of vemurafenib treated patients develop grade 1 or grade 2 alopecia (8, 11). Four out of five patients treated at our Clinic developed alopecia, two of them grade 2 (complete alopecia). Other common skin side effects associated with BRAF inhibition are pruritus (10–32% of cases), hyperkeratosis (23–30%) and dry skin (8, 11). Two out of five of our patients experienced problems with dry skin. Following recommendation of dermatologist, symptomatic treatment with topical agents was administered. In our experience, none of the mentioned adverse effects influenced vemurafenib treatment to any degree. Experiences of other researchers also show that melanoma treatment is not influenced in major degree by these side effects (11, 12, 15). Consultation of a dermatologist was needed in selected cases.

Less common side effects associated with BRAF inhibition such as basal cell skin carcinoma, hand foot syndrome, erythema nodosum were not observed in any of our patients.

Melanocytic lesions

De novo melanoma and benign melanocytic lesions were observed in a number of patients treated with vemurafenib in BRIM-2 and BRIM-3 trials. Recommended approach was a surgical removal and histological assessment. Secondary malignant melanomas were not considered as a progression of a disease; modification of specific BRAF inhibition treatment was not required. In our case series, we have detected changes in size and color of melanocytic nevi in a single patient, which were further evaluated by a pathologist after surgical excision and demonstrated to be dysplastic nevi. In two patients, de novo benign pigmentations appeared on the healthy looking skin. Pathological examination in these two patients verified compound nevi. No secondary melanomas were observed.

CONCLUSION

Skin side effects associated with vemurafenib treatment are plentiful, but generally manageable with supportive care measures. In our experience, majority of described side-effects were of grade 1 or 2 and none required dose modifications or abruption of the treatment. Our experience suggests that patients taking BRAF inhibitors such as vemurafenib should have regular full body skin assessments, both prior to the beginning of the therapy and periodically after its onset. Clinicians should be aware of the skin related toxicities, in

order to minimize their impact on treatment efficacy and patients' quality of life.

Abbreviations

GLOBOCAN — Global Burden Of Cancer Study

EUCAN — European Union Cancer Database

UVA — Ultraviolet A

EGFR — Epidermal Growth Factor Receptor

BRIM — BRAF Inhibitor In Melanoma

RAS — Rat Sarcoma

RAF — Rapidly Accelerated Fibrosarcoma

MAPK — Mitogen-Activated Protein Kinase

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

Sažetak

DERMATOLOŠKA TOKSIČNOST CILJANE TERAPIJE: VEMURAFENIB, PRVA ISKUSTVA IZ CRNE GORE

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Uvod: Još uvek nema sveobuhvatnih podataka o incidenci i mortalitetu melanoma u Crnoj Gori. Izveštaji GLOBOCAN-a i EUCAN-a procenjuju incidencu melanoma u Crnoj Gori na 4.6–7.3 na 100 000.

Aktivirajuća mutacija BRAF onkogeno postoji u preko 50% ćelijskih linija metastatskog melanoma. Lečenjem BRAF pozitivnog, neresektabilnog melanoma selektivnim BRAF inhibitorima (poput vemurafeniba) postiže se duže ukupno preživljavanje u poređenju sa konvencionalnim hemoterapijskim režimom. Tretman vemurafenibom je praćen brojnim neželjenim efektima, najčešće dermatološkim, koji se javljaju u skoro 95% obolelih.

Materijal i metode: Petoro obolelih od metastatskog melanoma su lečeni Vemurafenibom na Klinici za onkologiju Kliničkog centra Crne Gore 2013. i 2014. godine, po shemi: 960 mg dva puta dnevno, per os. Podaci o neželjenim efektima su retrospektivno sakupljeni iz medicinske dokumentacije. Za gradiranje neželjenih efekata su korišćeni kriterijumi National Cancer Institute's - Common Terminology Criteria for Adverse Events.

Rezultati: Prema podacima intrahospitalnog registra Klinike za onkologiju i radioterapiju Kliničkog

centra Crne Gore, u 2013. godini registrovan je 41 novooboleli, 20 (48.7%) muškaraca i 21 (51.3%) žena. U 2014. godini registrovano je 49 novoobolelih, 27 muškaraca (55.1%) i 22 žene (44.9%). Kod 2/5 (40%) pacijenata lečenih vemurafenibom su se javile fotosenzitivne reakcije, kod 3/5 (60%) su se javile erupcije osipa, kod 4/5 (80%) alopecija, a kod 2/5 (40%) suvoća kože. Promene veličine i boje postojećih nevusa su uočene kod jednog (20%) pacijenta, dok su se kod 2/5 (40%) javile de novo pigmentne promene.

Zaključak: Kožni neželjeni efekti povezani sa lečenjem vemurafenibom su brojni, ali se u najvećem broju slučajeva mogu kupirati simptomatskom terapijom. Kod obolelih tretiranih na Klinici za onkologiju Kliničkog centra Crne Gore, najveći broj neželjenih efekata je bio gradusa 1 i 2, bez potrebe za prekidom terapije ili za smanjivanjem doze leka. Oboleli na terapiji BRAF inhibitorom bi trebalo da prođu kroz redovne preglede kože, kako pre započinjanja terapije, tako i periodično u toku iste. Dobro poznavanje neželjenih efekata omogućava da se u praksi u što većoj meri ograniči njihov uticaj na uspešnost lečenja i na kvalitet života obolelih.

Cljučne reči: Melanom, vemurafenib, neželjeni efekti na koži.

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