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Vemurafenib-related photosensitivity

Bernadette Eberlein[1], Tilo Biedermann[1], Rüdiger Hein[1], Christian Posch[1,2]

(1) Department of Dermatology and Allergology, Biederstein, School of Medicine, Technical University, Munich, Germany
(2) Medical Faculty, Sigmund Freud Private University, Vienna, Austria

Summary

Increased photosensitivity is a common cutaneous adverse effect associated with the BRAF inhibitor vemurafenib. Clinically, it presents as an immediate sensation of heat and edematous erythema during sun exposure, as well as a sunburn reaction in terms of a late reaction. Phototesting has shown that the UVA range (320 nm to 400 nm), triggers both the immediate and the late reaction. In terms of pathogenesis, photochemical studies have suggested that exposure of vemurafenib to UVA radiation produces an UVA-absorbing photoproduct. In vitro studies on various cell models have also demonstrated that the phototoxic effects of vemurafenib are exclusively caused by UVA irradiation. This latter mechanism is probably responsible for the photosensitivity clinically observed in patients receiving vemurafenib.

In addition, vemurafenib is able to inhibit ferrochelatase. The resulting increase in protoporphyrin IX has also been observed in some human studies involving the drug. However, it is yet unproven whether porphyrins actually contribute to the immediate skin reactions seen in individuals on vemurafenib, even though the clinical presentation is similar to that found in erythropoietic protoporphyria with a comparable pathomechanism.

Other BRAF inhibitors, such as dabrafenib and encorafenib, are associated with significantly lower photosensitivity. It is essential that patients treated with vemurafenib are informed about immediate and delayed reactions potentially caused even by low doses of UVA. This includes counseling on photoprotective measures.

Introduction

By absorbing ultraviolet (UV) radiation, photosensitizing drugs can trigger chemical reactions, which either cause cellular damage (phototoxicity) or, less frequently, produce photoallergens (photoallergy). One such drug is vemurafenib. In the European Union, the agent has been approved for the treatment of patients with inoperable or metastatic BRAF V600-mutant melanoma since 2012. Vemurafenib inhibits the oncogene B-Raf, a serine-threonine kinase involved in regulating cell proliferation [1]. Animal models, in vitro tests and biochemical analyses have helped to further elucidate the pathomechanism resulting in increased photosensitivity in individuals on vemurafenib therapy. In vivo studies in humans have primarily used the minimal erythema dose (MED) as a measure of photosensitivity and for determining the action spectrum. MED is defined as the lowest dose of UV radiation that results in a well-defined erythema 24 ± 2 hours after irradiation.

Clinical characteristics of photosensitivity (Table 1)

Even in the first pivotal studies, it was noted that up to 52 % of patients experienced increased photosensitivity [2, 3]. Affected individuals reported severe, blistering sunburn reactions (Figure 1) as well as an immediate sensation of heat and solar urticaria-like erythema on exposure to sunlight; these reactions also occurred even behind car windows (transmission of UVA radiation, absorption of UVB radiation). Three individuals experienced the same kind of reactions after exposure to fluorescent lamps indoors [4]. Phototesting in five patients showed normal results in the UVB range (285 to 350 nm; peak at 310 to 315 nm) but an action spectrum in the UVA range (330 to 450 nm, peak at 390 to 410 nm). All patients showed a reaction already after ten minutes, as well as intense erythema with severe edema at the test site after 24 hours [5]. Monochromator phototesting in one patient confirmed an action spectrum in the UVA range at

Table 1 Phototesting during vemurafenib therapy (UVB: 280 nm–320 nm; UVA: 320 nm–400 nm; visible light: > 400 nm; abnormal findings are shown in italics).

Authors	Number (n)	UV source	Wavelengths	Immediate reaction (5 to 10 min)	Delayed reaction (24 h)	Minimal erythema dose (MED)
Dummer R et al. 2012	5	UVB	285 nm to 350 nm (peak 310 nm to 315 nm)	None	Normal	8 to 99 mJ/cm² (normal)
	5	UVA	330 nm to 450 nm (peak 390 nm to 410 nm)	*Yes (burning pain, erythema, edema)*	*Yes*	*Decreased after 10 min and after 24 h (10 to 49 J/cm²)*
Gelot P et al. 2013	18	Sunlight simulator	280 nm to 400 nm (with WG320 filter)	Not stated	Normal	1,613–4,427 mJ/cm² (normal)
	18	UVA	320 nm to 400 nm	*Yes (sensation of heat, solar urticaria-like erythema)*	*Yes (erythema, persisting for < 7 days)*	*Decreased after 5 min and after 24 h (5 to 20 J/cm²; median 12 J/cm²)*
Brugière C et al. 2014	12	Polychromatic light source	275 nm to 750 nm (with WG305 filter)	Not stated	Normal	Mean 115 mJ/cm² (normal)
	12	UVA	330 nm to 450 nm	*Yes*	*Yes*	*Decreased (10 to 22,5 J/cm²; mean 14,3 J/cm²)*
Gabeff R et al. 2015	34	UVA	320 nm to 400 nm	*Yes*	*Yes*	*Decreased (5 to 20 J/cm², median 12 J/cm²)*
	11	Visible light (halogen lamp)	Not measured	None	None	
Woods JA et al. 2015	1	Monochromator (UVB/UVA/visible light)	305 ± 5 nm; 335 ± 27 nm; 365 ± 27 nm; 400 ± 27 nm; 430 ± 27 nm; 460 ± 5 nm	None at any of the wavelengths tested	None at 305 ± 5 nm; 430 ± 27 nm; 460 ± 5 nm *Yes at 335 ± 27 nm; 365 ± 27 nm; 400 ± 27 nm*	Not stated

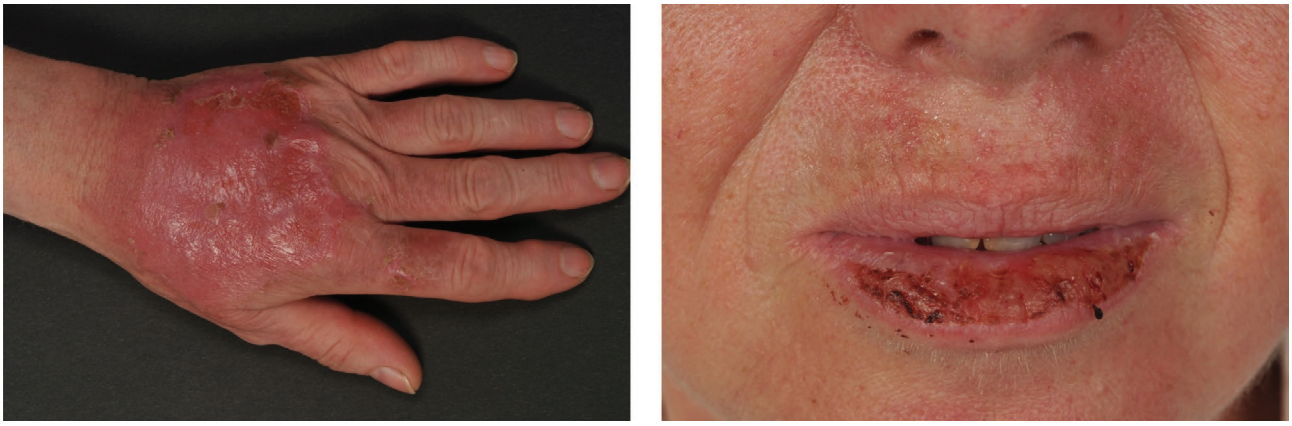

Figure 1 65-year-old female patient on vemurafenib therapy. Sunburn-like reaction two days after 30-minute sun exposure during lawn mowing. The skin lesions healed within four weeks.

335 ± 27 nm, 365 ± 27 nm and 400 ± 27 nm (no reaction to 305 ± 5 nm [UVB] and 430 ± 27 nm [blue light]) after one month of vemurafenib therapy. Immediate readings revealed no reaction [6].

A study that compared photosensitivity prior to and after two months of vemurafenib therapy showed a decrease in UVA MED (readings after 20 min) in 17 of 18 patients (94.4 %), with a median UVA MED of 12 J/cm^2 during vemurafenib treatment (MED < 20 J/cm^2 is considered pathological). The MED remained unchanged when using a sunlight simulator. In this particular study patients also developed vemurafenib-induced erythema (solar urticaria-like lesions without edema or pruritus) during UVA exposure. The associated burning sensation resolved quickly after UV exposure had been stopped, whereas the erythema persisted for a period of 24 hours and was no longer detectable after seven days. The study showed a significant increase in erythrocyte porphyrins (predominantly zinc protoporphyrin) and a decrease in vitamin B3 (niacinamide) levels after two months of vemurafenib therapy. These tests were performed based on the fact that the skin reactions clinically resembled erythropoietic protoporphyria (EPP) [7].

In another study, the one patient under investigation showed an increase in total erythrocyte protoporphyrin only after several months of vemurafenib treatment; here, abnormal phototest results did not correlate with higher-than-normal porphyrin levels [6].

Yet another study showed similar results: While eleven out of twelve patients saw a decrease in UVA MED (UVA light source with an emission spectrum of 330 nm to 450 nm), there were no changes in MED when using a polychromatic light source with UVB (305 nm to 750 nm) [8]. Other studies investigated whether photosensitivity might also be triggered by visible light, but phototesting (using a halogen lamp) before and after two months of vemurafenib treatment was negative. The immediate UVA-related photosensitivity disappeared within one to two weeks after discontinuation of the drug. Again, UVA MED was decreased in 30 of 34 patients (88 %), with a median of 12 J/cm^2 after two months of vemurafenib therapy in this study [9].

Studies in animal models

Using an established mouse model (oral UV-local lymph node assay, UV-LLNA), scientists studied the role of various factors in terms of the development of photosensitivity and established a pharmacokinetic profile. These factors included both the formulation and dose of vemurafenib, the duration of treatment as well as the timing of the readings following UV exposure.

The backs and ears of Balb/c mice were exposed to 10 J/cm^2 of UVA generated by a sunlight simulator with H1 filter (320 nm up to more than 590 nm). Exposure occurred on three consecutive days, two hours after oral administration of various doses of vemurafenib, either in a crystalline form or an amorphous form; alternatively, the mice were exposed once after three days of vemurafenib treatment. Biopsies from the apical portion of the ears were taken 24 hours after the last exposure, and the lymph nodes were characterized on a cellular level. In a further approach, the ears were examined 1, 2, 3, 4 and 6 hours after UV exposure.

Crystalline vemurafenib and amorphous vemurafenib (corresponding to the commercially available preparation) at a dose of 100 mg/kg did not elicit any phototoxicity. After oral administration of amorphous vemurafenib at doses of 350, 450 and 800 mg/kg, erythema was observed immediately after UV exposure on the last day of the three-day treatment period. As this effect faded within 15 hours,

examination of the ears and lymph nodes 24 hours after UV exposure revealed no abnormalities. However, six hours after exposure, there was a pronounced erythema and edema of the ears [10].

Biochemical analyses and in vitro tests

During the early development of the drug, it was already noted that vemurafenib exhibited phototoxic properties. This clinically relevant feature was shown to be due to a certain chemical structural element (benzophenone chromophore) and an absorption of UV radiation at wavelengths of up to 350 nm [10, 11]. Spectrofluorometric analyses found peaks at 210 nm, 260 nm (UVC spectrum) and 310 nm (UVB spectrum), both in lyophilized vemurafenib as well as in serum and feces of patients treated with the drug. Hence, it was concluded that vemurafenib-related UVA phototoxicity could not be explained by the absorption spectrum of the substance but possibly by the formation of newly generated metabolites [8]. Photochemical analyses suggest that UVA irradiation of vemurafenib produces singlet oxygen and free radicals and, under certain conditions, generates a UVA-absorbing photoproduct that might also be responsible for in vivo photosensitivity [12].

In vitro studies of murine fibroblast cell lines irradiated using a light source emitting predominantly UVA and visible light (320 nm up to > 700 nm) (in vitro 3T3 Neutral Red Uptake phototoxicity test) provided evidence of vemurafenib-induced phototoxicity as well [11]. It has also been shown that vemurafenib induces lipid peroxidation in erythrocytes and may thus lead to photohemolysis following UVA irradiation (300 nm up to 410 nm, $\lambda_{max.}$: 350 nm) [13]. In another study, cytotoxic effects in HaCaT keratinocytes incubated with vemurafenib occurred after exposure to UVA ($\lambda_{max.}$: 365 nm), but not when irradiated with visible (blue) light ($\lambda_{max.}$: 420 nm, no radiation < 400 nm), in contrast to the comparative assay using protoporphyrin IX (PPIX). No intracellular PPIX was detected in the presence of vemurafenib [6].

While vemurafenib did have UVA-induced phototoxic effects on other cell lines, too, these effects were less dependent on singlet oxygen compared to other known photosensitizers such as fluoroquinolones. Highly toxic combinations of vemurafenib and UVA caused less protein carbonylation but nevertheless had inhibitory effects on nucleotide excision repair and were associated with reduced protection against mutagenic and carcinogenic DNA damage [14]. The fact that no such changes in DNA repair have been observed with dabrafenib suggests that this effect may be specific to vemurafenib [15].

In addition, it has been shown that vemurafenib – unlike dabrafenib, but similar to other kinase inhibitors – inhibits the enzyme ferrochelatase by blocking the protoporphyrin binding site [16].

Discussion

Vemurafenib is a drug with specific photosensitizing properties, which may be attributed to various pathogenetic causes. While photosensitizing drugs usually (with some exceptions such as chlorpromazine) lead to an increased (delayed) sunburn reaction, vemurafenib additionally causes an immediate reaction during and directly after UV exposure, characterized by erythema, edema as well as a sensation of burning and heat. Clinically, this immediate reaction resembles EPP, a condition characterized by partial deficiency in the enzyme ferrochelatase, which results in an increase in protoporphyrin IX (PPIX) [17].

Similar to other phototoxic agents, the action spectrum for both the immediate and the delayed reaction during vemurafenib therapy seems to be strictly limited to wavelengths between 320 nm and 400 nm (UVA spectrum). Neither UVB-rich irradiation nor visible light have been shown to be able to elicit these reactions. Remarkably, only immediate-type reactions were reproducible in animal models. In vitro studies on cell lines and erythrocytes support the drug's UVA-induced phototoxic mechanism of action, which appears to be the primary cause, at least of the delayed reaction. The same studies also suggest inhibitory effects on DNA damage repair. However, the occurrence of squamous cell carcinoma (SCC), which is known to develop more frequently and rapidly in patients treated with BRAF inhibitors, is likely not associated with the phototoxic properties of these agents [18].

Apart from the direct phototoxic properties, some patients on long-term vemurafenib therapy have also been shown to have elevated protoporphyrin levels. On a biochemical level, it has been demonstrated that vemurafenib is associated with ferrochelatase inhibition by binding to the protoporphyrin site of the enzyme, which may explain the increase in PPIX and the EPP-like immediate reactions. However, the action spectrum for the clinical manifestations of EPP is in the visible light spectrum, especially in the Soret band (400 nm to 415 nm), and is therefore different from the action spectrum of vemurafenib-related phototoxicity (wavelengths ≤ 400 nm). Given that phototesting with visible light at higher doses is not standardized (use of slide projector lamps) and given that the monochromator study only included one patient, it is currently impossible to conclusively determine the actual significance of elevated porphyrin levels for photosensitivity in humans treated with Vemurafenib.

Other BRAF inhibitors such as dabrafenib and encorafenib are associated with significantly lower photosensitivity

(1–3 %) and a less pronounced decrease in UVA MED. These agents might therefore represent a treatment alternative [9, 19, 20].

It is essential that patients treated with vemurafenib are informed about the immediate and delayed reactions potentially triggered even by low doses of UVA [21]. Adequate counseling should be offered with respect to their behavior (UVA radiation even in the evening sun), wearing sun-protective clothing and the use of sunscreens with broad-spectrum UV filters (UVA protection attention to the UVA-label).

Correspondence to

Prof. Bernadette Eberlein, MD
Department of Dermatology and Allergology Biederstein
Technical University of Munich

Biedersteiner Straße 29
80802 Munich, Germany

E-mail: bernadette.eberlein@tum.de

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