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Letter to Editor

Prevention of Anti-BRAF-Induced Phototoxicity: not Just a Question of Photoprotector

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Targeted therapies changed the prognosis of metastatic melanoma. Flaherty & al. and the BRIM-II study found a response rate between 53-81% and a median progression-free survival of about seven months [1,2]. The BRIM-III study reported a median survival of 13.6 months and a 6-month survival rate of 84% with Vemurafenib versus 9.7 months and 64% with dacarbazine [3]. The UVA-phototoxicity induced by Vemurafenib through a decrease in minimal erythema dose [4,5], was found respectively in 16% (1), 52% (2) and 40% (3) of patients in these 3 studies. Although the benefit of sunscreen has been mentioned (4), to our knowledge, no efficacy study with an anti- UVA sunscreen has been conducted. This study assesses the benefit of therapeutic education associated with a photoprotector in a real-life setting. Patients with unresectable stage IIIC or IV BRAFV600E-mutated melanoma, treated with Vemurafenib 960mg twice daily, were included in the Dermatology department of Nantes University Hospital. Patients received 30mn training session performed by a nurse on the sunscreen during which they received free SPF50+ anti UVA (⩽3) photoprotector.

Regular follow-up was as well organized. After 12 weeks, patients were asked to self-asses: average daily application, application areas, tolerance to the treatment, by looking at redness level, burning sensation and/or pruritus sensation (classified in absent, mild, moderate or severe). The nurse assessed compliance at each follow-up. Patients were classified in group 1 with no or mild phototoxicity and in group 2 with moderate or severe phototoxicity. Only patients who applied photoprotector at least twice daily were considered compliant. Twenty-seven patients with a mean age of 56.2 years (32-89 years) were included. Fifteen patients were classified in group 1 and 12 in group 2 based on their self-reporting, including 6 patients with moderate phototoxicity and 6 patients with severe phototoxicity. Fourteen patients were considered compliant. Nurse questioning revealed that patients did not evaluate their observance correctly, and that only 2 patients of the group 2 were actually observant. The 10 other patients confessed regular omissions. Therefore in 25 out of the 27 patients, no significant phototoxicity on sun protected areas was observed.

A non-significant increase in phototoxicity (group 2) was observed in non-compliant patients (OR=2.04, 95%CI (0.35; 12.89), p=0.45). There was a non-significant difference in phototoxicity according to the age (OR=0.63, 95%CI (0.10; 3.7), p=0.70) or to the gender (OR=0.80, 95%CI (0.130; 5.23), p=1). Anti-BRAF, photosensitivity and sunscreen There was a non-significant trend toward a decreased phototoxicity in patients with skin phototype 3 (OR=0.2621, 95%CI (0.10; 3.7), p=0.70) and in women (OR=0.24, 95%CI (0.02; 1.76), p= 0.22). Despite a therapeutic education and a free photoprotector, only 55% of patients reported no or mild phototoxicity and 52% were observant Various factors could explain these results, including a possible over-reporting of phototoxicity; Indeed, the phototoxicity was self-assessed by patients themselves since the treatment was taken at home and in addition, a strict definition of phototoxicity was used. Sunscreen has to be applied several times a day and in a context of anti-cancer treatment, it could appear of secondary importance compared to anti-cancer treatment explaining the low observance. In addition, UVAs pass through clouds and windows [6].

Patients should understand that photoprotection is needed daily in any weather and in any place. The absence of refund could be an additional barrier. A sun protection kit with Vemurafenib could be interesting. Phototoxicity appeared only on under-treated areas, except in 2 patients of group 2. This emphasizes the link between efficacy and compliance with treatment and the importance of therapeutic education. Klaeger et al. [7] reported that Vemurafenib could inhibit ferro chelatase responsible for an accumulation of Protoporphyrin. In analogy to Erythropoietic Protoporphyrin, light absorption induces a production of Reactive oxygen species and inflammatory process with complement activation and mast cell degranulation explaining vasodilation and edema described in phototoxic reactions [8]. Alfamelanotide, an analog of alpha-

melanocyte-stimulating hormone approved in Erythropoietic Protoporphyrin, could theoretically be discussed in combination with Vemurafenib [9]. However, carcinogenic potential is unknown [10]. In conclusion, the systematic prescription of an anti-UVA/UVB photoprotector is insufficient to protect against Vemurafenib-induced phototoxicity. It should be accompanied by therapeutic education repeated during treatment. Cutaneous prevention is not a central concern for patients with metastatic melanoma. In this context, protective clothing remains essential.

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