ULTRAVIOLET A AND PHOTOSENSITIVITY DURING VEMURAFENIB THERAPY

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TO THE EDITOR: Vemurafenib (PLX4032, Zelboraf) is a selective inhibitor of V600E BRAF.[1] In phase 1, 2, and 3 clinical trials involving patients with tumors that have V600E BRAF mutations, vemurafenib was associated with consistent efficacy and improved survival.[2,3] These data led to approval of vemurafenib for use in the United States and Switzerland.

OBSERVATION

Common toxic effects observed with vemurafenib include arthralgia, rash, fatigue, and photosensitivity.[4] In our experience, some patients have had a severe sunburn reaction consisting of painful blistering. This reaction has affected their daily activities, including driving; such patients experience photosensitivity through glass while driving a car.

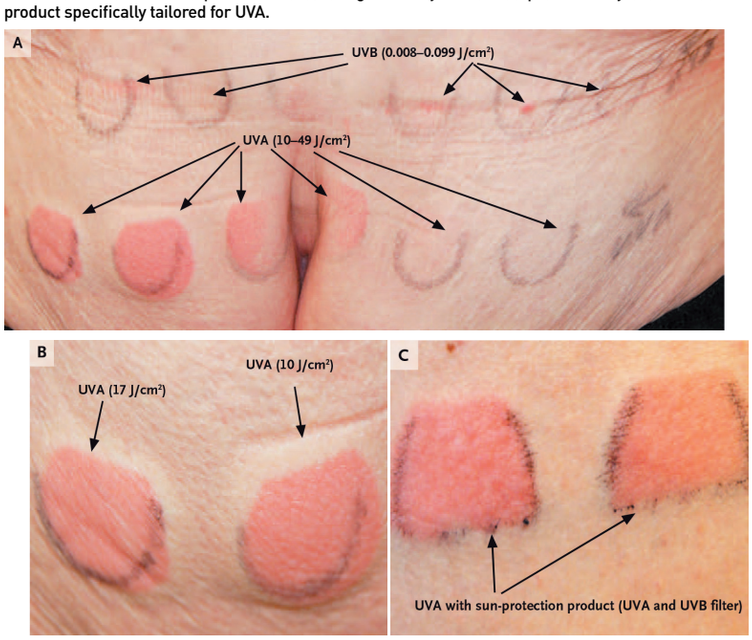
DISCUSSION

To advise patients about the most appropriate photoprotection measures, it is essential to identify the responsible ultraviolet spectrum. Therefore, we determined the minimal erythema dose (i.e., the lowest dose that results in visible erythema on depigmented skin) using ultraviolet irradiation devices (Waldmann Lichttechnik). For ultraviolet B (UVB), the emission spectrum included wavelengths from 285 to 350 nm (peak, 310 to 315), and for ultraviolet A (UVA), the emission spectrum was 330 to 450 nm (peak, 390 to 410) at 10 minutes and at 24 hours after irradiation in five patients during vemurafenib treatment. None of the patients had a history of photosensitive diseases.

The minimal erythema dose of UVB was normal (range, 0.008 to 0.099 J per square centimeter) in all patients. The minimal erythema dose of UVA (range, 10 to 49 J per square centimeter) was already strikingly reduced in all patients after 10 minutes and after 24 hours (Fig. 1A). Three patients reported a burning, painful sensation during UVA exposure. The ultraviolet-irradiated fields showed intense erythema associated with pronounced edema (Fig. 1B).

In one patient , we performed minimal erythema dose testing for UVA after the application of a UVA-tailored sun-protection product (the UVB filter was octocrylene, and the UVA filters were ecamsule, drometrizole trisiloxane, avobenzone, and titanium dioxide), resulting in a complete normalization (Fig. 1C).

Figure 1: **Photosensitivity during Vemurafenib Therapy.**
Panel A shows the minimal erythema dose of ultraviolet B (UVB) (upper row of fields) and ultraviolet A (UVA) (lower row of fields). The fields irradiated with UVA showed increasing erythema 24 hours after irradiation. The UVB-irradiated fields did not show any erythema or pigmentation. Panel B shows UVA-induced reddening and swelling 24 hours after irradiation. Panel C shows the UVA minimal erythema dose. Prior to irradiation, the irradiation field for UVA was divided into two parts with a covering film. Erythema was prevented by a sunscreen product specifically tailored for UVA.



CONCLUSION

On the basis of the nature and the evolution of the skin lesions, we conclude that vemurafenib causes UVA-dependent phototoxicity. The UVA dependency is also compatible with reports of sunburns after ultraviolet exposure through glass while driving a car. In contrast to UVB, UVA penetrates glass.[5] This information and other UVA-specific properties such as constant intensity regardless of daylight and season should be communicated to patients who are beginning to receive therapy with vemurafenib. In our experience, broad-spectrum sunscreens were effective in eliminating UVA-induced phototoxicity, and we now routinely recommend the use of UVA-tailored sunscreens and ultraviolet-dense clothing to patients receiving vemurafenib.[5] An ultraviolet-protection schedule that takes into account UVA-dependent phototoxicity should largely prevent vemurafenib photosensitivity.

REFERENCES

Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.

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