Vandetanib Photoinduced Cutaneous Toxicities

Hung Q. Doan, MD, PhD; Mimi I. Hu, MD; Jennifer Goldstein, MD; Sarina A. Piha-Paul, MD; Vivek Subbiah, MD; Anisha B. Patel, MD

PRACTICE **POINTS**

- Vandetanib is a US Food and Drug Administration–approved once-daily oral multikinase inhibitor for patients with progressive medullary thyroid cancer with a high incidence of cutaneous toxicities including phototoxicity. Early recognition of such cutaneous toxicities leads to early intervention and may allow greater compliance with treatment.
- The most common toxicity is phototoxicity. Diligent interventions include photoprotection such as sunscreen, sun-protective clothing, and avoiding peak hours of sun exposure.
- Topical steroids as well as bland emollients are the mainstay of therapy for symptomatic lesions.
- Extensive cutaneous involvement may include blistering, pain, and pruritus and necessitate dose reduction or even drug cessation.

Vandetanib is a once-daily oral multikinase inhibitor that targets the rearranged during transfection (RET) tyrosine kinase, vascular endothelial growth factor receptor, and epidermal growth factor receptor. Among its observed toxicity profile is QT prolongation, diarrhea, and rash, including photosensitivity. This article presents 3 patients with photoinduced cutaneous side effects of vandetanib, including both photoallergic and phototoxic reactions. We review the spectrum of cutaneous photosensitivity reactions and the necessity of histopathologic evaluation to distinguish photoallergic and phototoxic reactions. Given its high prevalence of specifically photoinduced side effects and the variety of the histologic and clinical presentations, reinforcing attentive sun protection could potentially prevent dose reduction or drug cessation in patients treated with vandetanib.
Cutis. 2019;103:E24-E29.

Vandetanib is a once-daily oral multikinase inhibitor that targets the rearranged during transfection (RET) tyrosine kinase, vascular endothelial growth factor receptor, and epidermal growth factor receptor. It has shown efficacy at doses of 300 mg daily in the treatment of progressive medullary thyroid cancer and has shown promise in non–small cell lung cancer and breast cancer. Vandetanib's toxicity profile includes QT prolongation, diarrhea, and rash.[1-3] Cutaneous involvement has been described in the literature as a photodistributed drug reaction with both erythema multiforme (EM) and Stevens-Johnson syndrome (SJS)–like eruptions, phototoxicity, and photoallergy (Table).[4-12] Photoinduction is the common thread, but various mechanisms have been proposed, including drug deposition within the dermis and direct toxicity to keratinocytes; however, an understanding of the varied presentation is lacking.

We present 3 cases of vandetanib photoinduced cutaneous toxicities and review the literature on this novel kinase inhibitor. This discussion highlights the spectrum of photosensitivity reactions to vandetanib among patients with varying histologic and clinical presentations.

Case Reports

Patient 1—A 74-year-old woman with a history of recurrent metastatic squamous cell carcinoma of the cervix and Fitzpatrick skin type III presented with erythematous, well-demarcated, photodistributed, eczematous papules that were coalescing into plaques on the scalp, hands, and face. The rash appeared sharply demarcated at the wrists bilaterally and principally involved the dorsal sun-exposed areas of her hands (Figure 1). The rash also involved the face and the V of the neck with sharp demarcation.

From the University of Texas MD Anderson Cancer Center, Houston. Drs. Doan and Patel are from the Department of Dermatology, Division of Internal Medicine; Dr. Hu is from the Department of Endocrine Neoplasia and Hormonal Disorders, Division of Internal Medicine; Dr. Goldstein is from the Hematology and Medical Oncology Fellowship Program, Division of Cancer Medicine; and Drs. Piha-Paul and Subbiah are from the Department of Investigational Cancer Therapeutics, Division of Cancer Medicine. Drs. Doan and Patel also are from the Department of Dermatology, University of Texas Medical School, Houston.
The authors report no conflict of interest.
Correspondence: Anisha B. Patel, MD, 1515 Holcombe Blvd, Unit 1452, Houston, TX 77030 (APatel11@mdanderson.org).

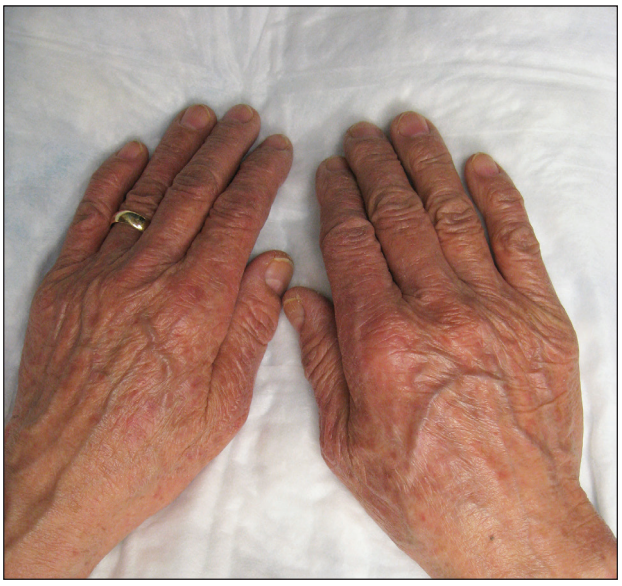

FIGURE 1. Erythematous and eczematous papules that were coalescing into plaques on the bilateral dorsal hands in a photodistributed pattern with sparing of the forearms in a patient taking vandetanib for recurrent metastatic squamous cell carcinoma of the cervix (patient 1).

Two weeks prior to onset, she initiated a phase 1 trial of oral vandetanib 100 mg twice daily and oral everolimus 5 mg daily. She did not recall practicing sun protection or experiencing increased sun exposure after starting that trial. The patient demonstrated symptom improvement with desonide cream, hydrocortisone cream 2.5%, and over-the-counter analgesic cream while continuing with the study drugs. However, she developed new, warm, painful papules on the hands and face. Phototesting and biopsy were not performed, and the etiology of the photosensitivity was unknown.

The patient was counseled about regular sun protection and was prescribed triamcinolone cream 0.1% for the arms and hydrocortisone cream 2.5% for the affected facial areas. Therapy with vandetanib and everolimus was continued without dose reduction or further cutaneous eruptions.

Patient 2—A 54-year-old man with a history of progressive medullary thyroid carcinoma and Fitzpatrick skin type II presented with erythematous, well-demarcated, photodistributed, edematous plaques and bullae of the head and neck, bilateral dorsal hands, and bilateral palms of 2 weeks' duration. The rash spared the upper back and chest with a well-demarcated border (Figure 2A). There were ulcerations and erosions at the base of the neck and the dorsal hands (Figure 2B). He also had conjunctivitis but uninvolved oral and genital mucosae.

Two weeks before the rash appeared, oral vandetanib 300 mg daily was initiated. The patient initially noted some dry skin, which progressed to an eruption involving the face and neck and later the hands with palmar blistering and desquamation. Medication cessation for 1 month led to moderate improvement of the rash on the face and neck. He had not been practicing sun protection but did wear a baseball cap when outside. The patient did not recall an incidence of increased sun exposure. He underwent a skin biopsy of the right dorsal hand, which revealed interface dermatitis with dyskeratosis and subepidermal and intraepidermal bullae (Figure 3). The biopsy findings were most consistent with a phototoxic eruption. Phototesting was not performed.

The patient then initiated sun-protective measures, a prednisone taper, and high-potency steroid ointments. As he tapered his prednisone, he noted continued improvement in the rash. His disease progressed, however, and he did not restart vandetanib.

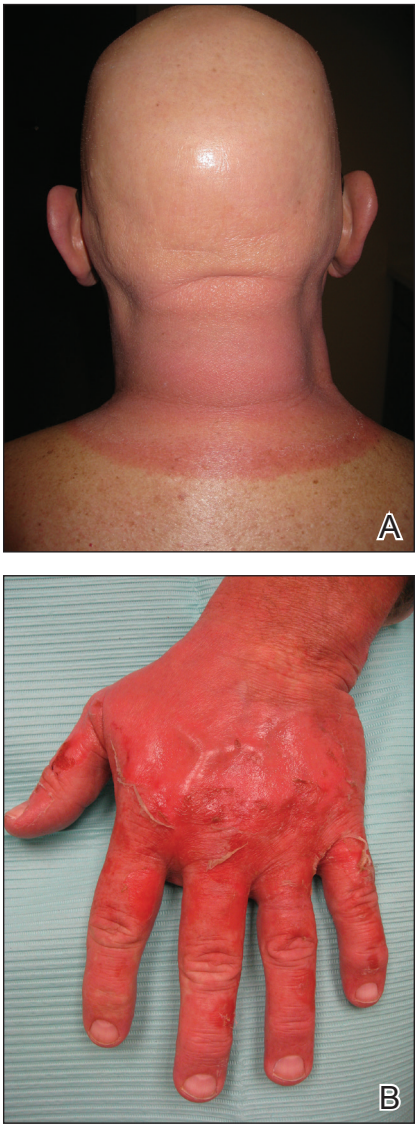

FIGURE 2. A, Erythematous, well-demarcated plaques on the neck in a photodistributed pattern with sparing of the upper back in a patient taking vandetanib for progressive medullary thyroid carcinoma (patient 2). B, There were ulcerations on the dorsal hand.

Patient 3—A 73-year-old man with a history of metastatic lung carcinoma and Fitzpatrick skin type II presented with a rash on the scalp, face, and arms of 2.5 weeks' duration. There was sharp demarcation at the edges of sun-exposed skin, and no bullae were noted (Figure 4). Prior to presentation, the patient started a 4-week phase 1 trial with vandetanib 300 mg daily and everolimus 10 mg daily. He did not recall any episodes of increased sun exposure. A punch biopsy of the arm showed an interface dermatitis suggestive of a phototoxic reaction. Phototesting was not performed to further clarify if there was a diminished minimal erythema dose with UVA or UVB radiation. Both drugs were discontinued, strict photoprotection was practiced, and triamcinolone cream 0.1% was initiated with resolution of rash. Vandetanib and everolimus were resumed at initial doses with strict photoprotection, and the rash has not recurred.

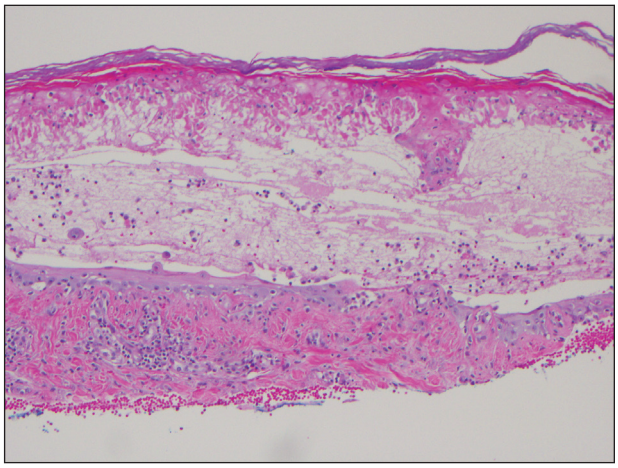

FIGURE 3. Histopathology demonstrated an interface dermatitis with dyskeratosis and a subepidermal vesicle (H&E, original magnification ×200).

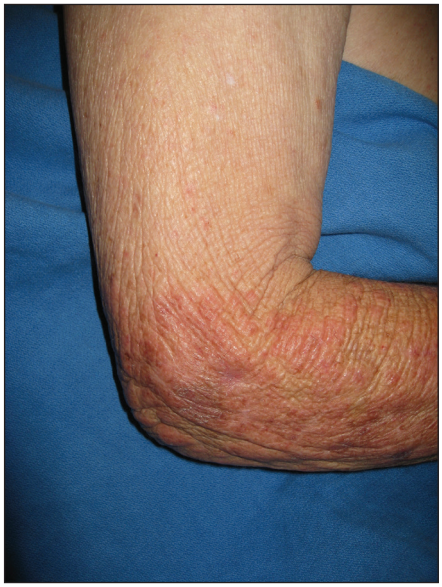

FIGURE 4. Erythematous indurated plaques on the arm with sharp photodemarcation in a patient taking vandetanib for metastatic lung carcinoma (patient 3).

Comment

Adverse Events Associated With Vandetanib—Vandetanib is a novel multikinase inhibitor that targets RET tyrosine kinase, vascular endothelial growth factor receptor, and epidermal growth factor receptor.[1,2] It currently is approved by the US Food and Drug Administration for the treatment of progressive medullary thyroid cancer and is being used in clinical trials for non–small cell lung cancer, glioma, advanced biliary tract cancer, breast cancer, and other advanced solid malignancies. Frequently reported adverse events (AEs) include QT prolongation, diarrhea, and rash.[1-3] In a large phase 3 trial, 45% of patients had a rash; of these, 4% were grade 3 and above.[3] The most common reasons for dose decrease or cessation were diarrhea and rash (1% and 1.3%, respectively).[13] Outside of a trial setting, 75% (45/60) of patients in one French study reported a cutaneous AE, with photosensitivity noted in 22% (13/60). Thus, cutaneous reactions tend to be a common occurrence for patients on this drug, requiring diligent dermatologic examinations.[14] In one meta-analysis comprising 9 studies with a total of 2961 patients, the incidence of all-grade rash was 46.1% (95% CI, 40.6%-51.8%), and it was concluded that vandetanib has the highest association of all-grade rash among the anti–vascular endothelial growth factor tyrosine kinase inhibitors. In this meta-analysis, the specific diagnosis of AEs was not further classified.[15] In another cohort of vandetanib-treated patients, as many as 37% (28/63) of patients had photosensitivity, with no clarification of the etiology.[16]

Photoallergic vs Phototoxic Reactions—Photosensitivity reactions are cutaneous reactions that occur from UV light exposure, typically in conjunction with a photosensitizing agent. Photosensitivity reactions can be further classified into phototoxic and photoallergic reactions, which can be distinguished by histopathologic evaluation and history. Although phototoxic reactions will cause keratinocyte necrosis similar to a sunburn, photoallergic reactions will cause epidermal spongiosis similar to allergic contact dermatitis or eczema. Also, phototoxic reactions appear within 1 to 2 days of UV exposure and often are painful, whereas photoallergic reactions can be delayed for 2 to 3 weeks and usually are pruritic. Photosensitivity reactions related to vandetanib have been reported and are summarized in the Table.[4-12]

Although reported cutaneous reactions to vandetanib thus far in the literature were reported as photoinduced reactions, there have been isolated case reports of other eruptions including cutaneous pigmentation[5] and one case of SJS.[9] According to a PubMed search of articles indexed for MEDLINE using the terms *vandetanib* and *rash*, we found that there are a variety of clinical findings, but most

Reports of Photoinduced Skin Reactions to Vandetanib Therapy

Reference (Year)	Age, y (Sex/ Race)	Type of Reaction	Vandetanib Dose	Time to Reaction	Clinical Presentation	Histology	Therapy	Outcome	Notes
Chang et al[4] (2009)	60 (M/A)	Phototoxic	300 mg	3 wk	Photodistributed erythema with bullae	Lichenoid and interface dermatitis, dyskeratosis, melanophages	Mid-potency topical steroid, oral antihistamines, drug cessation	Resolution	
Kong et al[5] (2009)	49 (M/W)	Pigment disorder	Not reported	2 mo; reconsultation at 6 mo for new-onset eruption	Eczematous dermatitis; reconsultation: photodistributed brown and blue-gray pigmentation	Reconsultation: elanophages in brown and blue-gray areas, hemosiderin in blue-gray areas	Bland emollients; reconsultation: low-potency steroid, retinoid, hydroquinone, and photoprotection	Resolution; reconsultation: brown areas faded with sun protection alone, blue-gray areas resistant to treatment	Subsequent report showed pigmentary changes in another patient on vandetanib successfully treated with Q-switched 755-nm alexandrite laser[6]
	59 (F/W)		Not reported	10 mo	Blue-gray pigmentation of face, anterior tibial scars, and sclerae; eczematous dermatitis	Melanophages and hemosiderin in blue-gray areas	Photoprotection, fluocinolone acetonide cream 0.025%	Eczematous dermatitis improved with topical steroids, pigmentation persisted	
Fava et al[7] (2010)	80 (F/W)	Photoallergic	300 mg	2 mo	Erythema and edema with erosions	Lichenoid dermatitis with mild spongiosis, eosinophils, and melanophages	Topical steroids, drug cessation	Improvement with PIH	
Son et al[8] (2011)	67 (M/A)	Phototoxic	300 mg	1 mo	Photodistributed erythematous patches and plaques	Interface dermatitis, dyskeratosis, melanophages with superficial edema	Oral steroids, mid-potency topical steroids, oral antihistamines, drug cessation	Resolution	Recurred with docetaxel only
	51 (M/A)	Phototoxic	300 mg	Within days	Photodistributed erythematous papules and patches	Hyperkeratosis, interface dermatitis, dyskeratosis, melanophages	Oral steroids, mid-potency topical steroids, oral antihistamines, drug cessation	Resolution	Recurred with docetaxel only

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Reference (Year)	Age, y (Sex/ Race)	Type of Reaction	Vandetanib Dose	Time to Reaction	Clinical Presentation	Histology	Therapy	Outcome	Notes
Yoon et al[9] (2011)	71 (M/A)	SJS	300 mg	3 wk	Bullae of face and neck, targetoid lesions on face and palms, oral erosions; 15% BSA	Epidermal necrosis, eosinophils and dense perivascular lymphocytic infiltrate	Oral antihistamines, topical steroid wet wraps, drug cessation	Resolution	Fever, leukocytosis, and abnormal liver function results
Caro-Gutierrez et al[10] (2014)	66 (M/W)	Photoinduced EM	300 mg	3 wk	Photodistributed eczematous dermatitis, targetoid lesions on hands involving palms	Interface dermatitis with dyskeratosis and eosinophils	Photoprotection, topical steroids	Resolution	Reduced MED on patch phototesting to UVA1
Bota et al[11] (2015)	61 (M/B)	Lichenoid phototoxic	300 mg	5 mo	Photodistributed papules, vesicles, erosions	Lichenoid and interface dermatitis with dyskeratosis and melanophages	Topical steroids, oral antihistamine, strict photoprotection	Symptomatic relief	Possibly a delayed cell-mediated photosensitivity reaction
Goldstein et al[12] (2015)	51 (F/W)	Photoallergic	300 mg	2 wk	Photodistributed erythematous eczematous plaques with progression to vesicles focally	Spongiotic dermatitis with eosinophils	Oral steroid taper, mid-potency topical steroid, photoprotection, drug cessation	Resolution	No recurrence with reintroduction of vandetanib with photoprotection
Current report									
Patient 1	74 (F/A)	Photoallergic	100 mg	2 wk	Photodistributed erythematous eczematous plaque	Not performed	Topical low- and mid-potency steroids, strict photoprotection	Resolution	Rash controlled without stopping vandetanib
Patient 2	54 (M/W)	Phototoxic	300 mg	2 wk	Photodistributed edematous plaques and bullae	Interface dermatitis with dyskeratosis and subepidermal and intraepidermal bullae	Oral steroid taper, high-potency topical steroid, photoprotection, drug cessation	Resolution	Vandetanib discontinued due to progression of cancer
Patient 3	73 (M/W)	Phototoxic	300 mg	2.5 wk	Photodistributed edematous plaques involving scalp, face, and arms	Interface dermatitis	Mid-potency topical steroid, photoprotection, drug cessation	Resolution	No recurrence with reintroduction of vandetanib with photoprotection

Abbreviations: M, male; A, Asian; W, white; F, female; PIH, postinflammatory hyperpigmentation; SJS, Stevens-Johnson syndrome; BSA, body surface area; EM, erythema multiforme; MED, minimal erythema dose; B, black.

of the reported photosensitivity cases were phototoxic. Fava et al[7] and Goldstein et al[12] both reported 1 photoallergic reaction each, plus patient 1 in our case series was noted to have a photoallergic reaction. Phototoxic reactions were reported in 4 patients (including our patient 2) who had dyskeratotic keratinocytes and vacuolar degeneration of the basal layer on histopathology.[4,8] Fava et al[7] described a lichenoid infiltrate with spongiosis consistent with a photoallergic reaction, but Chang et al[4] and Bota et al[11] described a lichenoid infiltrate with dyskeratotic cells. Also, Giacchero et al[16] described a photosensitivity reaction in 28 of 63 patients. Although only 6 patients had biopsies performed, the range of photosensitivity reactions was demonstrated with lichenoid, dyskeratotic, and spongiotic reactions. However, the cases were not further defined as photoallergic or phototoxic.[16] Vandetanib also has been associated with cutaneous blue pigmentation after likely phototoxic reactions. Pigment changes occurred after photosensitivity, but the clinical presentation of photosensitivity was not further characterized.[5,16]

Classic Drug Eruptions—Two patients were described as having classic drug eruptions—EM[10] and SJS[9]—in photodistributed locations. Histologically, these entities are identical to phototoxic reactions, resulting in epidermal necrosis and an interface dermatitis, but the presence of targetoid lesions on the palms prompted the diagnosis of photodistributed EM and SJS in both cases.[9,10] Unique to the SJS case was oral involvement.[9]

Distinguishing between a phototoxic reaction and photodistributed EM or SJS may be inconsequential if both can be prevented with photoprotection. Rechallenging patients with vandetanib while practicing photoprotection would help to clarify the mechanism, though this course is not always practical.

Mechanism of Action—As seen in our case series, cutaneous reactions occurred only on sun-exposed surfaces, and patients presented with sharp cutoff points that spared non–sun-exposed areas. Although clinically organized as a subtype of photosensitivity, the phototoxicity mechanism of action is considered a direct toxic effect on keratinocytes, which explains the histopathologic finding of dyskeratotic cells and the clinical spectrum of sunburn reaction, phototoxic EM, and SJS. UVA1 induces 2 photoproducts of vandetanib via a UVA1-mediated debromination process,[17] but these photoproducts are not responsible for epidermal dyskeratosis.[18] It was subsequently demonstrated that keratinocyte death was induced by apoptosis through photoinduced DNA cleavage and the formation of an aryl radical, which can induce further DNA damage.[18] Caro-Gutierrez et al[10] demonstrated a lowered minimal erythema dose in their patient with vandetanib-induced phototoxic EM.

Conversely, photoallergic reactions are considered immune-mediated delayed-type hypersensitivity reactions.[4,7,11] Although the mechanism of a photoallergic reaction remains unclear, it is possible that vandetanib or a metabolite (in susceptible patients) induces an immune-mediated delayed-type hypersensitivity reaction with repeated exposure to the compound, which may explain the varied timing of photoallergic onset, including the events featured in the Bota et al[11] case that occurred several months after drug initiation.

Conclusion

Considering the high prevalence of cutaneous AEs, especially varied photosensitivity reactions, these cases emphasize the importance of sun protection to help prevent dose reduction or drug cessation among patients taking vandetanib therapy.

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