

# Chronic phototoxicity and aggressive squamous cell carcinoma of the skin in children and adults during treatment with voriconazole

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**Background:** Voriconazole is a broad-spectrum antifungal agent associated with photosensitivity and accelerated photoaging. A possible link with aggressive squamous cell carcinoma (SCC) has also been reported.

**Objective:** We sought to determine the incidence and frequency of cutaneous SCC among patients undergoing long-term treatment with voriconazole who also manifest features of chronic phototoxicity.

**Methods:** We conducted a retrospective review of patients who developed one or more squamous cell neoplasms during long-term treatment with voriconazole at 3 academic dermatology centers.

**Results:** A total of 51 cutaneous SCC were identified in 8 patients (median age 34.5 years, range 9-54) treated with chronic voriconazole (median duration 46.5 months, range 13-60). Underlying diagnoses included graft-versus-host disease, HIV, and Wegener granulomatosis. Signs of chronic phototoxicity and accelerated photoaging included erythema, actinic keratoses, and lentigo formation.

**Limitations:** The retrospective nature of the study cannot determine the true population risk of SCC associated with voriconazole therapy. A prospective cohort study is needed.

**Conclusion:** A high index of suspicion for photosensitivity and SCC may be warranted with chronic voriconazole use when used in the setting of concurrent immunosuppression. (J Am Acad Dermatol 2010;62:31-7.)

**Key words:** fungal infection; immunosuppression; photoaging; photosensitivity; phototoxicity; squamous cell carcinoma; voriconazole.

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Voriconazole (Vfend, Pfizer, New York, NY) is a second-generation triazole antifungal approved by the Food and Drug Administration in 2002 for the treatment of invasive aspergillosis, candidemia in nonneutropenic patients, esophageal candidiasis and disseminated candidal infections, and infections caused by *Scedosporium apiospermum* and *Fusarium* species. Its antifungal spectrum, oral bioavailability, and generally well-tolerated side effect profile has led to the drug's widespread use in the treatment of invasive aspergillosis<sup>1</sup> and off-label use as long-term prophylactic therapy after allogeneic hematopoietic cell transplantation (HCT).<sup>2,3</sup>

Frequently reported adverse reactions during voriconazole therapy are vision abnormalities (21%), hepatic transaminase elevation (15.6%), and skin rash (7%), including photosensitivity.<sup>4</sup> Phototoxicity from the drug results in prominent sunburnlike erythema that is limited to the exposed

surfaces of the skin, particularly the head and neck, back of hands, and forearms.<sup>2,5</sup> Vesicle and bullae formation on sun-exposed areas resembling porphyria cutanea tarda (drug-induced pseudoporphyria) may occur.<sup>6-8</sup> Although the long-term effects of drug-induced phototoxicity are not well described, 3 reports of single patients from Australia, France, and Belgium depict aggressive and multifocal squamous cell carcinoma (SCC) of the skin in immunocompromised patients undergoing chronic treatment with voriconazole.<sup>9-11</sup> In this report, we describe, to our knowledge, the first series of 8 US patients, including two children and two young adults, who developed SCC during chronic treatment with voriconazole. One patient died from metastasis of his SCC. All patients had concurrent signs of chronic photodamage, suggesting that in the setting of immune compromise, chronic voriconazole-associated photosensitivity may accelerate ultraviolet (UV) radiation-induced skin damage and promote the development of skin cancer.

## METHODS

In this analysis, 8 patients with a history of voriconazole-associated phototoxicity who developed cutaneous SCC were identified at the National Institutes of Health (NIH), University of California-San Francisco Medical Center, and the Duke University Dermatology Units between April 2005 and January 2009. Medical records, clinical photography, and histologic specimens were reviewed. Solid organ allograft recipients and patients with a history of azathioprine exposure were excluded because of the expected high rate of SCC in these settings. Patients with a history of SCC before voriconazole exposure were also excluded.

## RESULTS AND REPRESENTATIVE CASES

Eight patients, including two children and two young adults, with features of voriconazole-related phototoxicity who developed one or more cutaneous SCC were identified (Fig 1 and Table I). Manifestations of phototoxicity and chronic photodamage included erythema of photoexposed

surfaces, actinic keratosis (AK) (Fig 1, A and B), and numerous lentigines, including dark brown lentigines resembling xeroderma pigmentosum in one patient (Fig 1, E and F). The median age at time of first SCC diagnosis was 34.5 years (range 9-54). A total of 51 SCC were diagnosed. Patients were treated with voriconazole at 50 mg daily to 350 mg twice a day (median 200 mg twice a day) for a median duration of 46.5 months (range 13-60) at the time of diagnosis of the first SCC. Six patients had a history of hematopoietic stem cell transplantation, one was infected with HIV, and one had long-standing Wegener granulomatosis. The median duration of immunosuppression (excluding the patient with HIV) was 51 months (range 13-122).

### Accelerated photodamage and AK/SCC in a pediatric patient after long-term voriconazole therapy

A 9-year-old Caucasian boy (Table I [patient 1]) was evaluated for a 3-year history of skin eruption on the face, back of hands, and front of neck. Three years and 10 months before evaluation the patient received an unrelated cord blood HCT for Philadelphia chromosome-positive acute lymphocytic leukemia. At the time of transplantation, he began voriconazole (150 mg twice a day) that had been discontinued 6 months before his current evaluation. The patient had a history of acute skin graft-versus-host disease (GVHD) that responded to cyclosporine and methylprednisone. Approximately 4 months after transplantation, erythema of his forearms, cheeks, and lower extremities was noted, and was attributed to mild GVHD. The eruption did not respond to topical tacrolimus, oral corticosteroids, daclizumab, cyclosporine, thalidomide, and tacrolimus. His medications at the time of evaluation were acyclovir, amlodipine, trimethoprim/sulfamethoxazole, prednisone (2.5 mg on alternating days), and thalidomide (100 mg daily).

On examination, multiple erythematous papules were present on the front of chest with erosions on the face, distal arms, and back of neck. Ephelides, lentigines, and erythema were limited to the photoexposed surfaces of the body (Fig 1, A and B). Hyperkeratotic papules were noted on the hands

## CAPSULE SUMMARY

- Voriconazole is an oral broad-spectrum antifungal frequently used for the long-term management of chronically immunosuppressed patients. It has been associated with photosensitivity, accelerated photoaging, and aggressive squamous cell carcinoma.
- In this series, 51 cutaneous squamous cell carcinomas were identified in 8 patients treated with chronic voriconazole in the setting of graft-versus-host disease, HIV, and Wegener granulomatosis.
- A high index of suspicion for photosensitivity and squamous cell carcinoma may be warranted with voriconazole use in the setting of concurrent immunosuppression.

*Abbreviations used:*

AK:	actinic keratosis
GVHD:	graft-versus-host disease
HCT:	hematopoietic cell transplantation
NIH:	National Institutes of Health
SCC:	squamous cell carcinoma
UV:	ultraviolet

and back of neck. A skin biopsy specimen from the back of neck demonstrated AK, but superficially invasive SCC could not be ruled out (Fig 1, C). Oral acitretin, topical 5-fluorouracil, and aggressive photodynamic therapy were instituted; however, the child subsequently developed two additional high-risk invasive SCC of the right conchal bowl and the lower lip.

**Adult patient with multiple aggressive SCC after long-term voriconazole treatment**

A 46-year-old man (Table I [patient 5]) with a 10-year history of Wegener granulomatosis on chronic therapy with prednisone and methotrexate developed pulmonary aspergillosis. Treatment with amphotericin was complicated by renal toxicity, and voriconazole (200 mg twice daily) was initiated and maintained for long-term prophylaxis. After 3 years of treatment, he developed photosensitivity, photodamage, and multiple AK on the face, arms, and back of hands. During the next 2 years he developed 10 SCC, predominantly on the scalp and cheeks. These included acantholytic and desmoplastic subtypes, with recurrent tumor foci on the left preauricular area (Fig 1, F). Multiple tumors recurred after Mohs micrographic surgery, and cetuximab was initiated for multiple inoperable SCC, followed by the addition of carboplatin when cetuximab failed to halt the progressive enlargement of tumors on the forehead and left preauricular area (Fig 1, G). Radiation therapy was initiated for involvement of the left parotid, followed by total parotidectomy. Four months later a focal mass lesion was demonstrated by magnetic resonance imaging in the right parietal lobe and was confirmed to be metastatic disease by biopsy. The patient died from complications of metastatic disease.

**DISCUSSION**

Voriconazole-induced photosensitivity most commonly presents as a sunburn response on sun-exposed surfaces of the body; it may also present as cheilitis, exfoliative dermatitis, pseudoporphyria cutanea tarda, or lesions resembling discoid lupus erythematosus.<sup>5,6,8,12</sup> In general, these reactions are reversible on discontinuation of the drug. Recent

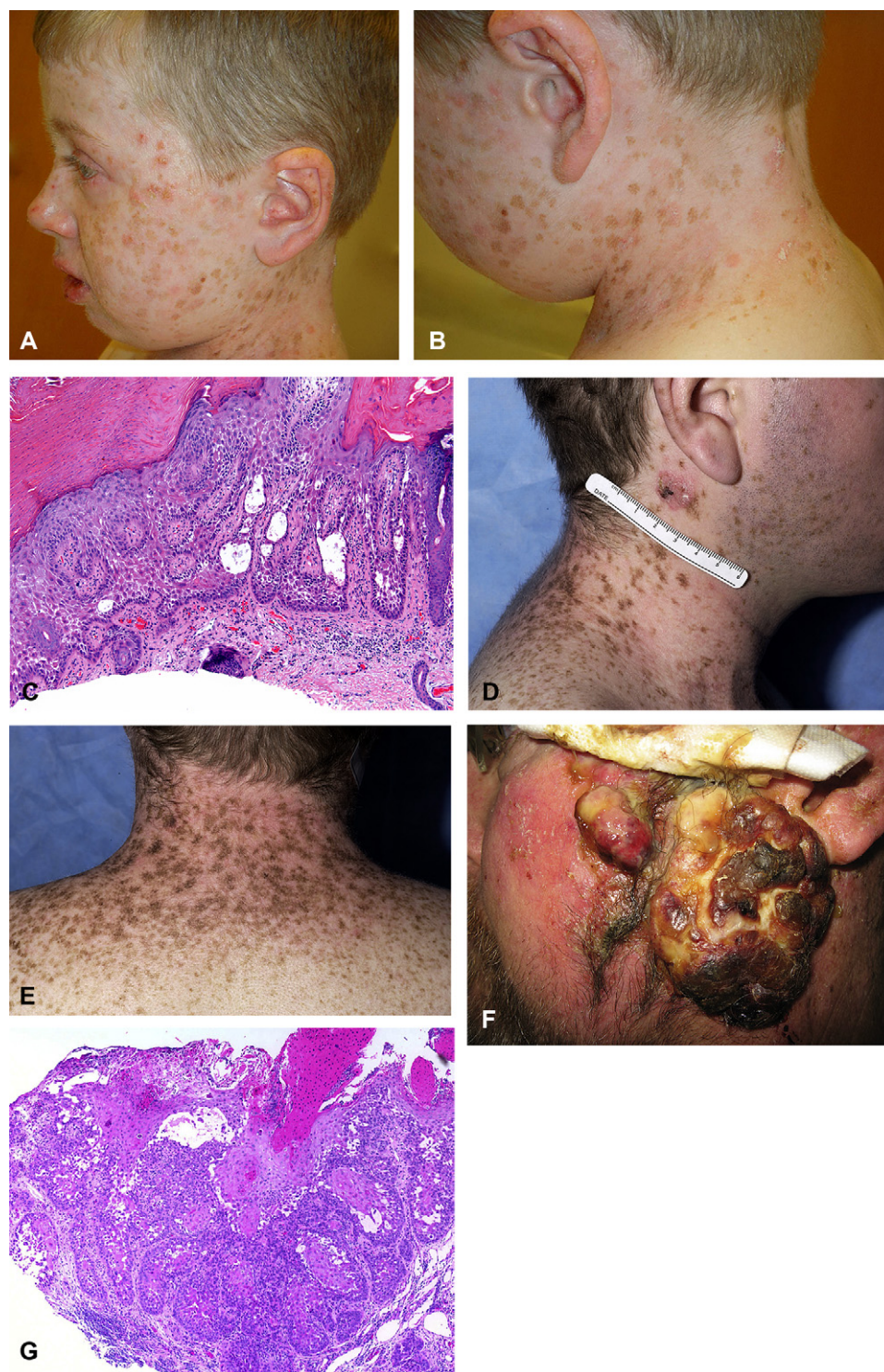
reports have also described pigmentary changes limited to the photoexposed surfaces of the skin in voriconazole-treated pediatric patients, suggestive of accelerated photoaging and chronic photodamage.<sup>2,13</sup> Of greatest concern are 3 single international case reports of aggressive and multifocal cutaneous SCC with voriconazole use in the immunocompromised setting (renal allograft recipient, HIV infection, and chronic granulomatous disease).<sup>9-11</sup> In addition, preliminary abstract data suggest that patients with lung transplantation taking voriconazole antifungal prophylaxis may be at increased risk of nonmelanoma skin cancer.<sup>14</sup>

Chronic immunosuppression is a well-recognized risk factor for the development of nonmelanoma skin cancer. SCC in particular is a significant long-term complication for many renal allograft recipients.<sup>15</sup> However, the short duration of immunosuppression preceding the development of SCC, the unusually high number of SCC tumors after stem cell transplantation, and the young age at onset of SCC observed in this series suggest that voriconazole-associated phototoxicity accelerates the risk of SCC formation in the immunocompromised setting.

The mechanism of voriconazole-induced photosensitivity is not clearly understood, but may result from a metabolite of the drug, rather than the drug itself. Although voriconazole does not absorb in the UVA or UVB spectrum, its major metabolite, voriconazole N-oxide, absorbs in the UVB and UVA ranges,<sup>16</sup> and may therefore act as the requisite chromophore for phototoxicity. Voriconazole is extensively metabolized by the cytochrome P450 enzymes CYP2C19, CYP2C9, and CYP3A4, and less than 2% of the drug is excreted unchanged.<sup>17</sup> Polymorphisms in CYP2C19 significantly influence voriconazole metabolism.<sup>17</sup> Homozygous poor metabolism polymorphisms in CYP2C19 result in plasma voriconazole concentrations 3 to 5 times that found in extensive metabolizers. The prevalence of homozygous poor metabolizer CYP2C19 polymorphisms in the population is 20% to 30% in Asians and 2% to 3% in Caucasians.<sup>17</sup> To our knowledge, a relationship between voriconazole metabolism and phototoxicity has not been reported, and further investigation is needed to determine the variability in photosensitivity observed between individual patients.

All of the patients in this series demonstrated one or more cutaneous signs of phototoxicity, implicating UV radiation—induced DNA damage in promoting cutaneous malignancy. In addition to direct UVA-induced DNA damage, there is evidence that UV-induced alteration of the microenvironment (cell-cell interactions, cytokine release, cell-extracellular



**Fig 1.** (Continued)

matrix interactions, inflammation, and loss of T-regulatory cells) may also promote the development of cutaneous malignancy.<sup>18</sup> The extensive lentigo formation seen in this series is reminiscent of a similar phenomenon noted in patients undergoing

phototherapy with psoralen (a photosensitizer) and UVA. Patients receiving high cumulative doses of psoralen plus UVA are at greatly increased risk of SCC formation, an effect that persists even after discontinuation of the treatment.<sup>19</sup>

There is also experimental evidence that phototoxic drug exposure is associated with an elevated risk of cutaneous malignancy. Photocarcinogenesis studies using fluoroquinolones have demonstrated accelerated skin tumor formation in mice, even when subphototoxic doses of UVA radiation were administered chronically.<sup>20</sup> A correlation between photosensitizing drug exposure and nonmelanoma skin cancer was also identified in two recent population-based case-control studies.<sup>21,22</sup> Although we cannot completely discount the potential contribution of other potential photosensitizing agents (trimethoprim/sulfamethoxazole, dapsone) administered concurrently with voriconazole in 4 patients in this series, it should be noted that other signs of premature photoaging (lentiginoses, AK) and SCC are not typically encountered with the use of these agents.

Although prolonged immunosuppressive therapy and severity of GVHD are known risk factors for the development of SCC in the HCT setting,<sup>23</sup> in our 5-year experience systematically evaluating approximately 150 treatment-refractory patients with chronic GVHD at the NIH, cutaneous SCC is uncommon, despite chronic immunosuppression used in nearly all patients. In contrast to the organ transplantation setting, the cumulative incidence of oral and cutaneous SCC in a cohort of 24,011 HCT recipients was only 1.1% at 20 years (95% confidence interval: 0.7-1.7).<sup>23</sup> Similarly, a 20-year follow-up of 4810 allogeneic HCT recipients at the Fred Hutchinson Cancer Research Center (Seattle, WA) yielded a cumulative SCC incidence estimate of only 3.4%.<sup>24</sup>

Both the early age of onset (median 34.5 years, range 9-54) and short duration of immunosuppression (median 51 months, range 13-122) before the development of skin cancer in our series are also highly unusual in comparison with established data on SCC incidence after immunosuppression in the renal allograft and HCT settings. The latency between renal transplantation and first skin cancer formation is approximately 3 years in allograft

recipients older than 60 years, but increases to 8 years in patients younger than 40 years.<sup>15</sup> In the bone marrow registry review of 24,011 patients with HCT by Curtis et al,<sup>23</sup> the median interval between HCT and SCC diagnosis was 7 years. Similarly, at Fred Hutchinson Cancer Research Center (Seattle, WA), SCC developed a median 6.3 years after HCT in a somewhat older population (median age 48.9 years).<sup>24</sup> In comparison, the median duration to first SCC among the 6 HCT recipients in this series was only 4.1 years, despite a younger age (median 34.5 years, range 9-54) at time of transplantation.

Even with the apparent link between photosensitizing drugs and cancer risk suggested by both this study and preliminary population-based data, a complete understanding of the role of phototoxic drugs in SCC development in individual patients, particularly those who are immunosuppressed, is unclear. Most phototoxic drugs, including trimethoprim/sulfamethoxazole and fluoroquinolones, are typically prescribed for a limited time period, and alternative regimens are readily available if severe photosensitivity is detected. By contrast, voriconazole is often used as chronic therapy for ambulatory, immunocompromised patients for whom oral alternatives with similar broad-spectrum antifungal activity were not available until recently. Thus, SCC development may require chronic phototoxicity and a high-risk immunocompromised population in a manner analogous to the increased risk of SCC after long-term psoralen plus UVA phototherapy in patients who also receive cyclosporine.<sup>25</sup>

We believe a high index of suspicion for photosensitivity is warranted when using voriconazole, particularly in light of the potential for misdiagnosis of this reaction as GVHD in the post-HCT setting.<sup>2</sup> Until the role of voriconazole in the development of SCC in the immunocompromised setting is more clearly understood, we recommend strict photoprotective measures be used. Careful reappraisal of the need for long-term voriconazole prophylaxis may be of value, particularly in patients who

**Fig 1.** Cutaneous manifestations of long-term treatment with voriconazole. **A**, Patient 1, 9-year-old boy with extensive lentigo formation and multiple actinic keratoses on head and neck after 3 years of treatment with voriconazole. **B**, Patient 1, Hyperkeratotic lesion with erythema on left side neck. **C**, Patient 1, Histology of lesion on left side of neck (**B**) identified acanthotic solar keratosis with acantholysis. Lesion bordered on superficially invasive SCC. **D**, Patient 3, 22-year-old man with long-standing HIV infection with SCC on left side of neck after 15 months of voriconazole therapy. Chronic phototoxicity with erythema and dark brown lentiginous pigmentation is present on head and side of neck. **E**, Patient 3, similar erythema and pigmentation resembling xeroderma pigmentosum is present on photoexposed surfaces of back of neck and upper extremities. **F**, Patient 5, 46-year-old man after 4 years of treatment with voriconazole with recurrent SCC on left preauricular aspect of cheek. Patient subsequently died of metastatic disease. **G**, Patient 5, histology of SCC from right cheek reveals deeply invasive SCC with keratinocyte pleomorphism, representative of multiple SCC that developed in this patient. (**B** and **G**, Hematoxylin-eosin stain; original magnifications: **B**,  $\times 100$ ; **G**,  $\times 40$ .)

**Table I.** Characteristics of patients with squamous cell carcinoma after chronic treatment with voriconazole

Patient No.	Age, y/sex	Ethnicity	Medical history/ duration of immunosuppression	Voriconazole dose/duration	History of immunosuppressant use	Other photosensitizing drugs	Phototoxicity/photodamage	Neoplasia
1	9/M	Caucasian	ALL/46 mo s/p CBHCT	150 mg twice daily/ 39 mo*	Cyclosporine, daclizumab, prednisone, <sup>†</sup> thalidomide, <sup>†</sup> topical tacrolimus	TMP/SMX	Erythema, cheilitis, lentigo formation on face, neck, back of forearms, hands	AK/superficially invasive SCC SCC (2)
2	11/M	Caucasian	ALL, ITP/54 mo s/p CBHCT	50 mg daily/54 mo	Azathioprine, <sup>†</sup> cyclosporine, daclizumab, sirolimus, prednisone, <sup>†</sup> thalidomide <sup>†</sup>	None	Faint erythema, mild lentigo formation on side of neck, back of hands	AK (2) SCCis (2) SCC (2)
3	22/M	Caucasian	HIV (age 2 y)	250 mg twice daily/ 15 mo	None	TMP/SMX	Extensive erythema and lentigo formation on back of hands, head/neck, forearms, upper aspect of back	SCC
4	41/M	Caucasian	Non-Hodgkin lymphoma/48 mo s/p allo-HCT	250 mg twice daily/ 48 mo	Etanercept, methylprednisolone, <sup>†</sup> rituximab, tacrolimus <sup>†</sup>	None	Faint erythema/extensive lentigo formation on side, back of neck	SCC (4)
5	46/M	Caucasian	Wegener granulomatosis/ 122 mo	200 mg twice daily/ 45 mo	Prednisone, methotrexate	None	Telangiectasias	SCC (10)
6	43/M	Caucasian	ALL/51 mo s/p allo-HCT	200 mg twice daily/ 51 mo	Cyclosporine, prednisone, mycophenolate mofetil, <sup>†</sup> sirolimus <sup>†</sup>	TMP/SMX	Erythema, telangiectasias, advanced photodamage	SCC (25)
7	28/M	Caucasian	CML/84 mo s/p allo-HCT	200 mg twice daily/ 60 mo	Tacrolimus, <sup>†</sup> mycophenolate mofetil, prednisone, <sup>†</sup> sirolimus <sup>†</sup>	Dapsone	Erythema, dermatoheliosis	SCC (2), inflamed AK
8	54/M	Caucasian	CLL/SLL/13 mo s/p allo-HCT	350 mg twice daily/ 13 mo	Prednisone, tacrolimus	None	Erythema, AK	SCC (2), AK (5)

AK, Actinic keratosis; ALL, acute lymphoblastic leukemia; Allo-HCT, allogeneic hematopoietic cell transplantation; CBHCT, cord blood hematopoietic cell transplantation; CLL, chronic lymphocytic leukemia; CML, chronic myelogenous leukemia; ITP, idiopathic thrombocytopenic purpura; M, male; SCC, squamous cell carcinoma; SCCis, squamous cell carcinoma in situ; SLL, small lymphocytic leukemia; s/p, status post; TMP/SMX, trimethoprim/sulfamethoxazole.

\*Drug discontinued 6 mo before evaluation.

<sup>†</sup>Current immunosuppressant therapy at time of evaluation.

manifest signs of chronic photodamage or have a history of skin cancer.

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