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Long-Term Voriconazole and Skin Cancer: Is There Cause for Concern?

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Abstract Skin toxicity due to voriconazole is well recognized. Recently, several series have reported skin cancer, particularly cutaneous squamous cell carcinoma (C-SCC), following photosensitivity reactions among patients receiving long-term voriconazole (>12 months). Almost all patients were immunosuppressed, including stem cell and solid organ transplant recipients. A case-control study of lung transplant recipients identified long-term voriconazole (median cumulative dose: 76 grams) and residence in areas of strong sun exposure as independent risk factors for C-SCC. The mechanism(s) by which voriconazole may predispose to skin cancer is not clear. Moreover, the relative contribution of voriconazole and other factors such as immunosuppression, ultraviolet exposure, advanced age and skin type is unknown. Until further data are available, voriconazole should be used carefully for durations >6–9 months, particularly among patients with risk factors for skin cancer. In patients requiring prolonged voriconazole, diligent skin examinations, avoidance of excess sunlight, and liberal use of UV protectants are advisable.

Keywords Voriconazole · Skin cancer · Squamous cell · Toxicity

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Introduction

Voriconazole is a triazole antifungal agent that inhibits cytochrome P450–dependent ergosterol synthesis. Ergosterol is a key component of the fungal cell membrane, and voriconazole exerts broad-spectrum fungicidal activity. The drug has been shown to be effective in the treatment of serious mold infections, including those caused by Aspergillus and Fusarium species [1–4], mucosal and systemic candidiasis [2], endemic mycoses like histoplasmosis and coccidioidomycosis [5], and as empiric treatment of patients with febrile neutropenia [6]. Given the chronic nature of many invasive fungal infections, voriconazole therapy is often required for extended periods of months or longer. In particular, patients with ongoing immune system dysfunction such as solid organ transplant (SOT) recipients and those with chronic granulomatous disease are commonly treated with prolonged regimens [7••]. Voriconazole's antifungal spectrum, oral bioavailability, and well tolerated side effect profile also has led to its widespread, off-label use as long-term prophylaxis against invasive fungal infections after allogeneic hematopoietic stem cell transplantation (HSCT) and SOT [7••, 8].

The most common adverse events attributed to voriconazole include vision abnormalities, transaminase elevations, gastrointestinal complaints such as nausea, vomiting and diarrhea, central nervous system abnormalities, and skin lesions [9]. Voriconazole-associated photosensitivity has been described in 1% to 2% of patients receiving >12 weeks of therapy [10•]. It manifests most frequently as sunburn-like erythema on exposed skin surfaces [11]. Other dermatologic complications include exfoliative dermatitis, pseudoporphyria [12, 13], photoaging with multiple lentigines and premature dermatohe-

liosis [14]. In general, these reactions are reversible upon discontinuation of the drug. More recently, several reports of skin cancer among patients receiving long-term voriconazole therapy, in particular cutaneous squamous cell carcinoma (C-SCC), have been published. In this article, we will review the proposed mechanisms by which voriconazole may lead to skin cancer and the literature linking voriconazole use with the disease. In conclusion, we will attempt to determine if the long-term use of voriconazole is a cause for concern.

Potential Mechanisms for the Pathogenesis of Voriconazole-Associated Skin Lesions

The mechanisms by which voriconazole leads to the development of phototoxicity are not clearly understood. As one possibility, it has been proposed that skin lesions stem from the accumulation of phototoxic retinoid compounds due to the drug's inhibition of all-*trans* retinol (vitamin A) metabolism [11, 15–17]. Indeed, retinoids cause photosensitivity, erythema, xerosis and cheilitis [10•]. Arguing against this indirect association, however, is the fact that systemic retinoid treatment does not lead to lentigo formation, and, in fact, has protective effects in patients with xeroderma pigmentosum (XP) and SOT recipients who are at high risk for malignancies[18, 19]. Alternatively, voriconazole's principal metabolite (voriconazole N-oxide) has been proposed as an etiologic agent [20•, 21, 22]. The action spectrum for most phototoxic reactions is ultraviolet A (UVA) wavelengths (320 to 400 nm) [10•]. Unlike voriconazole, voriconazole N-oxide absorbs in the UVA and UVB spectrum [21], suggesting that it may act as a chromophore for phototoxicity.

Experimental data suggest that UV radiation is a keratinocyte mutagen, acting like a tumor initiator and promoter [23]. In addition to direct DNA damage, UV-induced alterations of cell-cell interactions, cytokine release, cell-extracellular matrix interactions, inflammation, and T-regulatory cell function may also promote the development of skin cancers [20•, 24]. In this regard, voriconazole-induced phototoxicity may be linked to the subsequent development of skin cancer. As detailed below, the case reports of C-SCC and melanoma among patients receiving voriconazole have all described antecedent phototoxicity reactions, which would support an association in the pathogenic process. In the setting of immune compromise, therefore, chronic voriconazole-associated photosensitivity may accelerate UV radiation-induced skin damage and promote the development of skin cancer. Even if voriconazole-related skin reactions ultimately are proven to be linked to the subsequent development of skin cancer, it will be as part of a complex, multi-step pathogenic process [7••].

In addition to identifying the molecular mechanisms of pathogenesis, future research into the role, if any, of voriconazole exposure in the development of skin cancer will need to define factors that determine why particular patients are at risk. Along these lines, photosensitivity skin reactions due to voriconazole have been described as idiosyncratic [2, 25•, 26•]. To date, a relationship between voriconazole metabolism and phototoxicity has not been demonstrated [20•]. Elevated voriconazole serum trough concentrations, however, have been linked to increased risk of other drug toxicities, including transaminase and central nervous system abnormalities [27]. Voriconazole drug exposure is marked by significant inter-patient variability, which reflects the drug's non-linear pharmacokinetics, drug-drug interactions, physiologic conditions associated with underlying diseases, and variation in cytochrome P450 activity [27]. Voriconazole is metabolized by cytochrome P450 enzymes CYP2C19, CYP2C9, and CYP3A4, and less than 2% of the drug is excreted unchanged. Persons with homozygous CYP2C19 poor metabolism polymorphisms have serum voriconazole concentrations that are several-fold higher than extensive metabolizers [28]. The prevalence of homozygous poor metabolizers ranges from 2% to 3% in Caucasians to 20% to 30% in Asians [28]. It is possible, therefore, that voriconazole pharmacokinetics and host genetic factors will be shown to be important considerations in assessing the risk of skin cancer.

Review of the Clinical Literature

Case Reports and Case Series

To date, there have been eight papers describing skin cancers among patients receiving voriconazole [7••, 10•, 20•, 25•, 26•, 29•, 30•, 31•]. A total of seven papers were case reports or series of patients with C-SCC ($n=17$) and melanoma ($n=2$) (Tables 1 and 2). Patients were seen at centers in the United States (San Francisco, North Carolina, and Washington, DC), Europe (Nimes and Grenoble, France, and Leuven, Belgium), and Australia (Queensland). All patients were white, 68% (13/19) were men, and they ranged in age from 9 to 71 years of age. Additionally, 95% (18/19) were immunosuppressed, most commonly following HSCT (32%, 6/19), lung (26%, 5/19), or renal transplantation (5%, 1/19). Other predisposing conditions included connective tissue/rheumatologic diseases treated with immunosuppressive agents (16%, 3/19), HIV infection, and chronic granulomatous disease (11% each, 2/19), and lung cancer treated with chemotherapy (5%, 1/19). Overall, 84% (16/19) of patients were receiving immuno-

Table 1 Published reports of patients who developed skin cancer while receiving voriconazole: Demographics and baseline characteristics

Ref	Skin CA	Type of study; locale	Underlying disease (n)	N	Median age (range)	Race	Sex	Immunosuppressive drugs	Median voriconazole (range)	Median time to diagnosis (range)
[7••]	SCC	Case-control; Pitt	Lung transplant (17)	17	63 yrs (42–75)	100% white	88% male	Alemtuzumab induction (94%), then CNI, MMF, prednisone (88%)	9.5 months (2–49)	19 months post-Tx (11–82)
[30•]	SCC	Case reports; San Fran	Heart-lung and lung transplant	2	55 yrs (54, 56)	White (1); N/S	Female	CNI, azathioprine, prednisone. Transition to FK, MMF-containing regimens.	60 months Not clear in 2nd case.	12 and 2 yrs post-Tx
[29•]	SCC	Case reports; Grenoble	Lung transplant (3); lung CA and RA	4	46 yrs (30–59)	White	50% male	CNI, MMF, steroids (1); N/S (3)	33 months (24–42)	6 yrs post-Tx or chemo (4–8)
[20•]	SCC	Multi-center case series; DC, San Fran, NC	HSCT (6); Wegeners (1); HIV (1)	8	34.5 yrs (9–54)	100% white	100% male	*Steroids (100%); FK/sirolimus (86%); cyclosporine (43%); MMF, daclizumab (29%).	46.5 months (13–60)	Non-HIV: 51 months (13–122) HIV: 20 yrs
[31•]	SCC	Case report; Nimes	HIV/AIDS; Kaposi sarcoma	1	62 yrs	White	Male	Doxorubicin	27 months	13 yrs
[26•]	SCC	Case report; Leuven	Polyarteritis nodosa, then renal transplant	1	71 yrs	White	Male	Cyclophosphamide, steroids for polyarteritis nodosa. Basiliximab, steroids, MMF induction for renal transplant, then FK and steroids	19 months	19 months post-Tx
[25•]	SCC	Case report; Queens-land	CGD	1	32 yrs	White	Female	None	48 months	26 yrs after CGD diagnosis
[10•]	Mel	Case reports; San Fran	Coccidio meningitis and CGD	2	30 yrs (21, 39)	White	Male and female	None	45 months (35 and 55)	35 months (CM) and N/S (CGD)

*Excludes HIV-infected patient, who was not receiving immunosuppressive drugs

CA cancer; *Coccidio* coccidiomycosis; *CGD* chronic granulomatous disease; *CM* coccidiomycosis meningitis; *CNI* calcineurin inhibitor; *DC* Washington, DC; *FK* tacrolimus; *HSCT* hematopoietic stem cell transplant; *Mel* melanoma; *MMF* mycophenolate; *N* number; *NC* North Carolina; *N/S* not specified; *Pitt* Pittsburgh; *RA* Rheumatoid arthritis; *Ref* reference; *SCC* squamous cell carcinoma; *San Fran* San Francisco; *Tx* transplant; *Yrs* years

Table 2 Published reports of patients who developed skin cancer while receiving voriconazole: Treatment and outcomes

Ref	Voriconazole-associated skin lesions prior to CA	Clinical details of skin cancer	Treatment	Outcome	Comments
[7••]	N/S	Head and neck (94%). Multiple lesions (53%). Subsequent lesions (47%). Metastases (12%).	Moh's (88%). Parotidectomy and craniectomy/radical neck (6% each). Adjunctive XRT (24%).	100% alive (36 months)	Patients followed median of 36 months post-Tx. Excluded patients with cancer prior to transplant/voriconazole. All patients received trimeth-sulfa.
[30•]	Both had skin CA prior to voriconazole, and photodamage, actinic keratoses and lentigines on voriconazole.	Sun-exposed areas. Multiple recurrences and metastases.	Excision, Moh's, XRT. Chemotherapy deferred.	Both died	
[29•]	Photodamage, actinic keratitis.	Sun-exposed areas. Multiple lesions. Metastases (1).	Surgical excisions, XRT, chemotherapy. Lymph node resection (1).	Alive (4–9 months)	Regression of lesions after voriconazole discontinuation (received posa- and itraconazole).
[20•]	Photodamage, including actinic keratoses, lentigenes, erythema, telangiectasias.	Total of 51 SCC diagnosed on sun-exposed areas.	Incomplete data, but 2 case reports describe chemotherapy, photodynamic therapy, Mohs and repeated surgical resections, total parotidectomy, XRT	Unclear, but at least one death due to metastases	Excluded patients with SCC prior to voriconazole and patients receiving azathioprine. 50% of patients received trimeth-sulfa (3) or dapsone (1).
[31•]	Photodamage.	Multifocal: scalp, ear, nose	None. Died prior to treatment.	Died due to systemic CMV.	Prior photodamage resolved on posaconazole.
[26•]	Photodamage, erythema, actinic keratoses	Multifocal, perineural and lymph node metastases	Radical surgery. XRT.	Alive, no recurrence (6 months)	Invasive pulmonary aspergillosis prior to transplant.
[25•]	Photodamage, erythema.	SCC on lip, progressing to multifocal disease of nose, septum and cheek	Radical surgery. XRT.	Alive, no recurrence (10 months)	Disseminated aspergillosis. Photosensitivity resolved, and no recurrence of SCC on posaconazole.
[10•]	Photodamage, erythema, lentigines	Multifocal melanoma	Repeated Moh's in 1st case; not stated in 2nd case.	Alive	1st patient had no evidence of IS. Both patients had extensive sun exposure. 2nd patient also received trimeth/sulfa, and he had fading of lesions after discontinuing voriconazole in favor of posaconazole.

CA cancer; *IS* immunosuppression; *N/S* not specified; *Ref* Reference; *SCC* squamous cell carcinoma; *trimeth-sulfa*—trimethoprim-sulfamethoxazole; *Tx* transplant; *XRT* radiation therapy

suppressive drugs, most commonly in regimens that included corticosteroids and agents such as calcineurin inhibitors, azathioprine and mycophenolate. One putatively immunocompetent patient was receiving voriconazole as maintenance therapy for chronic meningitis due to coccidiomycosis. Patients received voriconazole for 13 to 60 months. The time to diagnosis of skin cancer ranged from 13 months to 12 years following HSCT or SOT. Skin cancer was detected 13–26 years after the diagnosis of HIV infection or chronic granulomatous disease.

In each case, skin cancers were multi-focal and occurred on sun-exposed areas. Moreover, cancers were preceded by voriconazole-related skin lesions, including photodamage, actinic keratoses and lentigenes. In at least 26% (5/19) of patients, metastatic disease was diagnosed. Overall, 95% (18/19) of patients were treated for their cancer; one patient with AIDS died due to cytomegalovirus disease prior to treatment for C-SCC. Surgical interventions ranged from Moh's micrographic surgery through radical resections, generally in conjunction with radiation and/or chemotherapy. In several cases of both C-SCC and melanoma, regression of lesions was described after voriconazole was discontinued in favor of posaconazole or itraconazole. Despite aggressive multi-modality therapy, 16% (3/19) of patients died due to metastatic disease.

Case-Control Study

The case reports and series suggested a possible association between long-term voriconazole use, accelerated photodamage, and the development of skin cancer among patients with underlying immunosuppression. Of course, the reports did not conclusively establish a causal relationship between voriconazole exposure and skin cancer. To determine if prolonged voriconazole exposure was an independent risk factor for C-SCC, we conducted a retrospective, case-control study among patients who underwent lung transplantation at the University of Pittsburgh Medical Center (UPMC) between 2003 and 2008 (Tables 1 and 2).

In many ways, our lung transplantation program was well suited for a study of this sort. We performed 543 lung transplants during the study period, which afforded a large pool of at-risk patients. Voriconazole was recommended as universal anti-fungal prophylaxis for at least 6 months following lung transplantation, and alemtuzumab, a potent anti-CD52 monoclonal antibody, was employed as standard immunosuppressive induction therapy. Compared to HSCT recipients and other immunosuppressed hosts, SOT recipients are at particular risk for skin cancer because they receive long courses of intensive immunosuppressive therapy. Indeed, C-SCC is the most common malignancy after SOT [32–34], and SOT recipients have up to a 200-fold increased risk compared to the general population [35]. After kidney and heart transplantation, the incidence of non-melanoma skin cancer increases steadily from 5% at 2 years to 10% to 27% and 40% to 60% at 10 and 20 years, respectively [36–39]. The prevalence of skin cancer among adult lung transplant recipients surviving 1 and 5 years is 0.7% and 6.5%, respectively [40]. The rate of C-SCC among SOT recipients is fourfold greater than basal cell carcinoma [32, 41, 42], a ratio that is also observed in our lung transplantation program.

In our study, patients who developed C-SCC were identified from the UPMC Cardiothoracic Transplant database. Controls were defined as lung transplant recipients who did not develop C-SCC. Three controls were randomly identified for each case. Controls were matched by month and year of transplant, and survival time post-transplant. Voriconazole was given intravenously at 6 mg/kg per dose for two doses immediately after transplant, followed by oral voriconazole 200 mg twice daily. The duration of voriconazole was at the discretion of providers, guided by program recommendations, microbiologic data, and clinical events. In addition to voriconazole, standard antimicrobial prophylaxis included valganciclovir and trimethoprim-sulfamethoxazole.

Overall, 3.1% (17/543) of patients developed C-SCC at median follow-up of 36 months [7••]. In most regards, the demographics and clinical details of our patients with C-SCC were similar to those in the case reports and series (Tables 1 and 2). Notable differences among our patients included their receipt of induction immunosuppression (alemtuzumab, 94% [16/17], or thymoglobulin, 6% [1/17]), a shorter duration of voriconazole therapy (median: 9.5 months) and more rapid onset of skin cancer (median: 19 months post-transplant). As in other reports, C-SCC was encountered on sun-exposed areas in white patients, predominantly men, of a range of ages. Disease was multi-focal in 53% (9/17) of patients, and associated with recurrences and metastases in 47% (8/17) and 12% (2/17), respectively. Approaches to treatment were the same as in the case reports and series. Our outcomes were good, with 100% survival at median 36 months follow-up. Due to our study design, we were unable to determine if episodes of phototoxcity or other dermatologic lesions occurred in patients prior to C-SCC.

Comparing our cases with controls, significant risk factors for C-SCC by univariate analysis were older age at transplant (P=0.02), male gender (P=0.02), residence in a geographic area with high levels of sun exposure (specifically, Florida or South Carolina; P=0.0001), single-lung transplant (P=0.03), and duration and cumulative dose of voriconazole (P=0.03 each). By multivariate analysis, duration of voriconazole (hazard ratio (HR): 2.1; P=0.04) and residence in areas with high-levels of sun exposure

(HR: 3.8; P=0.0004) were independent risk factors for C-SCC. Cases received voriconazole for median 284 days (range: 68–1458 days), resulting in median cumulative dose of 76 grams (range: 28–295 grams). Controls received median 161 days (range: 19–1263 days), resulting in median cumulative dose of 53 grams (range: 7–470 grams). Voriconazole prophylaxis was extended beyond 6 months for 76% (13/17) and 45% (23/51) of cases and controls, respectively. Of note, longer durations of voriconazole prophylaxis were not associated with increased rates of rejection or augmented immunosuppression. Moreover, cases and controls did not differ in percentages of patients with rejection or requiring augmented immunosuppression, agents used to treat rejection, or number of bronchiolitis obliterans episodes.

Critical Assessment of the Literature

For a preliminary investigation of the epidemiology and potential risk factors for C-SCC, our case-control study offered advantages in time, labor and cost over alternative study designs. The strengths of the study included our ability to conduct highly-detailed reviews of voriconazole, immunosuppressive and other drug exposures, clinical events and the movement between different parts of the country on a patient-by-patient basis. At the same time, there were important limitations to the study. Its retrospective nature precluded assessments of skin type, prior photosensitivity reactions or activities associated with increased sun exposure. It reported a single-center experience, which may not be applicable to other centers or transplant populations. The study also was subject to limitations common to case-control studies. In particular, voriconazole exposure may be a surrogate for unrecognized confounding effects, rather than a risk in its own right.

Along these lines, our analysis was impacted by our program's use of universal voriconazole prophylaxis and alemtuzumab induction therapy. Since all lung transplant recipients at our center received voriconazole and alemtuzumab, we could not study the independent contributions of these agents. Our recommended duration of voriconazole prophylaxis post-lung transplantation is 6 months, and the agent is generally restarted for 1 to 3 months at the time of acute cellular rejection requiring augmented immune suppression. In addition, the duration of voriconazole is often extended at the discretion of clinicians, which may reflect concerns about a patient being at increased risk for fungal infection. The underlying reasons for longer durations of voriconazole were not clear in our study, and we cannot exclude that prolonged prophylaxis was a response to signs of depressed immune function, infections or other factors that also may have impacted the risk of C-SCC. We excluded an obvious confounder by demonstrating that longer durations of voriconazole prophylaxis were not associated with increased rates of rejection or augmented immunosuppressive drug regimens. Nevertheless, other data such as history of opportunistic infections, T cell counts, and results of functional immune assays were not consistently available.

Alemtuzumab induction reduces rejection and allows lower dose maintenance immunosuppression, but raises the risk of opportunistic infections and malignancies. Organ transplant recipients have reduced immune responsiveness, which may be intensified with transplant induction therapy. Moreover, patients also have heterogeneous health and immune phenotypes, ranging from the very frail to the highly functioning. Prospectively characterizing the immune fingerprints of patients will be necessary to advance our understanding of the relative contributions of immune function and voriconazole use to the development of C-SCC.

In order to demonstrate conclusively that voriconazole plays a causative role in the development of C-SCC, a multi-center, prospective study that includes careful patient follow-up over multiple years will be necessary. Such a study will need to assess numerous risk factors for skin cancer, catalogue voriconazole, immunosuppressive and other drug exposures, and systemically incorporate investigations of pharmacokinetics, host genetics and immune function. Clearly, this will be a complex undertaking, particularly given the heterogeneity of patients and immunosuppressed patient populations that are at risk. In many regards, lung transplant recipients are ideally suited for a study of this sort, for the reasons alluded to earlier. At the same time, narrowing such a study to a particular population may limit the general applicability of the findings.

Conclusions: Is the Long-Term Use of Voriconazole a Cause for Concern?

At present, it is impossible to definitively determine if the long-term use of voriconazole is a cause for concern in the absence of data that define the relationships between immune function, exposure to voriconazole, immunomodulatory drugs, and other agents that may manifest dermatologic effects, host genetic profiles, UV exposure, and other risk factors. Nevertheless, the experience to date suggests that voriconazole should be used carefully for durations greater than 6 to 9 months, particularly among older patients, persons with fair skin, and those residing in areas of high-sun exposure who have underlying conditions associated with particularly profound immunosuppression. In patients requiring prolonged voriconazole therapy,

diligent skin examinations, avoidance of excess sunlight, and liberal use of UV protectants is advisable.

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- • Of importance
- •• Of major importance

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