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Voriconazole-Associated Cutaneous Malignancy: A Literature Review on Photocarcinogenesis in Organ Transplant Recipients

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This article synthesizes the current data regarding the implication of voriconazole in the development of skin cancer in organ transplant recipients (OTRs) and offers suggestions for additional research. According to Organ Procurement and Transplantation Network data, 28 051 solid organ transplants were performed in 2012. Due to advancements in immunosuppression and management of infectious diseases, survival of OTRs has substantially increased. Voriconazole is a widely prescribed antifungal medication used for prophylaxis and for treatment of invasive fungal infections in OTRs. Case reports describing skin cancer associated with voriconazole exposure emerged shortly after US Food and Drug Administration approval of the drug, and it is now established that voriconazole is an independent risk factor for the development of cutaneous malignancy in lung transplant recipients. The mechanism of voriconazole-induced skin cancer is still unknown and may involve its primary metabolite, voriconazole N-oxide. Here we discuss the current data and potential mechanisms of voriconazole-associated photosensitivity and carcinogenesis and identify areas that require further research.

Keywords. voriconazole; organ transplant; skin cancer; squamous cell carcinoma; photocarcinogenesis.

Skin cancer is the most common malignancy after solid organ transplantation [1]. Within the family of skin cancers, cutaneous squamous cell carcinoma (SCC) is the most common after transplantation, with a 65-fold increased incidence among organ transplant recipients (OTRs) as compared with the general population [1]. The risk of developing SCC increases steadily with time after transplantation [2]. OTRs have a higher incidence of multiple tumors and tumors with more aggressive behavior. Outcomes from SCC are thus significantly worse, with a 52-fold increased risk for disease-specific death compared with the general population [2, 3].

Several factors increase an OTR's risk for developing skin cancer (Table 1). The first group of risk factors comprises those related to patient demographics and include male sex and older age, likely due to greater cumulative sun exposure [4]. The second group includes factors that are associated with ultraviolet (UV) radiation exposure and include fair skin and Fitzpatrick skin type, which is a measure of the propensity to burn rather than tan under UV exposure. Patients with significant prior exposure to UV radiation have an increased risk for skin cancer [4–6]. Patients with a lower Fitzpatrick skin type are at increased risk for skin cancer development. The third group of risk factors includes those related to the patient's type of transplant, age at time of transplant, and posttransplant care. Duration of immunosuppression and more intense immunosuppression are related to degree of cancer risk [7, 8]. Specifically, heart and lung transplant recipients have a higher risk of SCC than kidney and liver transplant recipients due to older age at time of transplant and more intense immunosuppression [2, 9].

A new category of risk factors has recently emerged as studies have demonstrated an association between the antifungal medication voriconazole and the risk of

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Table 1. Risk Factors for Skin Cancer Development in Organ Transplant Recipients

Fitzpatrick skin type I to III
Increasing age at transplantation
Duration and level of immunosuppression
Type of organ transplant (heart/lung > kidney > liver)
Previous transplant
Squamous cell carcinoma before transplant
History of lymphoma pretransplant/posttransplant
Pretransplant end organ disease (eg, rheumatoid arthritis, systemic lupus erythematosus, or autoimmune hepatitis)
Liver transplant recipients with psoriasis on previous biological therapy/psoralen plus ultraviolet A light phototherapy

From Zwald FO and Brown M. J Am Acad Dermatol. 2011 Aug; 65(2):253–61; quiz 262. doi: 10.1016/j.jaad.2010.11.062.

cutaneous SCC in lung transplant recipients. Here we review the literature to date on the role of voriconazole in the development of photosensitivity, SCC, and melanoma in lung transplantation.

VORICONAZOLE AND PHOTOSENSITIVITY

Voriconazole is a broad-spectrum triazole antifungal medication that was first given marketing authorization in 2002. It is currently indicated for treatment of invasive aspergillosis, candidemia in nonneutropenic patients, severe invasive fluconazole-resistant *Candida* spp. infections, severe *Fusarium* spp. infection, and severe *Scedosporium* spp. infections.

Voriconazole is commonly administered to lung and bone hematopoietic cell transplant patients both prophylactically and as treatment for invasive fungal infection. Invasive aspergillosis contributes significantly to infection-related morbidity and mortality of solid organ transplant patients. It was shown in clinical trials for invasive aspergillosis that voriconazole was more efficacious than amphotericin B and it had decreased toxic effects [10, 11]. This relative effectiveness and its ease of administration have caused a growth in its popularity over the past several years. Although voriconazole has proven to be effective, the side effects seen with prolonged voriconazole exposure are cause for concern.

While voriconazole is the treatment of choice for invasive aspergillosis, there are important side effects and risks associated with its use. Adverse reactions include vision changes (20%), hepatic enzyme abnormalities (12%–20%), and photosensitivity [12]. Photosensitivity induced by voriconazole results in a sunburn-like erythema that is limited to sun-exposed sites [13]. Photosensitivity causing facial erythema and cheilitis has been reported in 8%–10% of patients using voriconazole [14–16]. This adverse reaction has been seen at much higher rates in some settings such as in cystic fibrosis patients [17]. However, most cystic fibrosis patients are fair northern Europeans and thus intrinsically more photosensitive; this may contribute to the increased rates of adverse skin reactions. In all reported cases, photosensitivity has been shown to resolve with discontinuation of voriconazole. Other dermatologically adverse reactions reported include pseudoporphyria, discoid lupus erythematosus, and accelerated photoaging [15].

VORICONAZOLE BIOLOGY

Voriconazole is administered by intravenous and oral routes. It provides antifungal activity by inhibiting enzymes necessary for the synthesis of ergosterol, a component of fungal membranes. It has a high volume of distribution, suggesting extensive penetration into the extracellular and intracellular compartments of peripheral tissues including the skin [18]. Ninety-eight percent of voriconazole is metabolized, with only 2% being excreted unchanged [2]. Voriconazole is metabolized primarily by cytochrome P450 enzymes in the liver, predominantly CYP2C19 and, to a much lesser extent, CYP2C9 and CYP3A4 [1]. Some studies have noted expression of these enzymes in human keratinocytes, suggesting the possibility of peripheral drug metabolism in the skin [19]. The primary metabolite of voriconazole metabolism is voriconazole N-oxide (VNO), which accounts for 72% of circulating metabolites in plasma [4]. VNO has been shown to offer minimal to no antifungal activity and has been implicated in the adverse skin reactions seen with voriconazole exposure [1, 2, 4].

The mechanism for voriconazole-induced carcinogenesis is unclear. Hypotheses proposed include potentiation of UV-mediated DNA damage or a reduction of DNA damage repair. Both voriconazole and VNO absorb UVA and UVB radiation, but VNO has no detectable emission after absorption of UVB. This suggests that the photoexcited states of this molecule decay by nonradiative mechanisms that might be associated with phototoxicity [20]. After exposure to UVB, VNO may decay largely or entirely by chemical reactivity, a process that could contribute to phototoxicity. However, neither voriconazole nor VNO appear to potentiate UVB-associated cell death. The role of VNO as the causal agent in adverse skin reactions still requires further investigation.

Several case reports and studies have established voriconazole as an independent risk factor for the development of skin cancer, particularly SCC. The dermatological effects of voriconazole have been described as a phototoxicity caused by absorption then reemission of light energy by a molecule present in the skin. This process creates free radicals and thermic lesions that alter the skin's DNA, making it prone to and inducing skin cancer. Voriconazole and its metabolite VNO have been implicated in this process [21].

Table 2. Summary of Main Epidemiological Studies

Author	Study Design	Population Studied	Outcome Measure	Results
Feist et al [24]	Retrospective cohort	120 lung transplant recipients: cases (n = 32), controls (n = 88)	Incidence of SCC	• SCC developed in 39.5% of patients who received voriconazole compared with 19.5% of patients who did not receive voriconazole ($P = .03$)· Older age at time of transplant, skin cancer pretransplant, and longer voriconazole therapy were independent risk factors for skin cancer development
Singer et al [26]	Retrospective cohort	327 lung transplant recipients: cases (n = 50), controls (n = 277)	Time to first SCC after transplantation	• Exposure to voriconazole was associated with a 2.6-fold increased hazard for SCC ($P = .014$) • Hazard of SCC increased by 5.6% with each 60-day exposure at a standard dose of 200 mg twice daily ($P = .006$) • Significant covariates include white race, older age at transplantation, skin cancer pretransplant, use of voriconazole therapy, voriconazole cumulative dose, and voriconazole duration of therapy
Vadnerkar et al [25]	Retrospective case control	68 lung transplant recipients selected from a cohort of 543 patients: cases (n = 17), controls (n = 51)	Incidence of SCC	• 3.1% of study population developed SCC during a 6-year period; patients received voriconazole for a significantly longer duration compared with controls ($P = .03$) • Duration of voriconazole use ($P = .04$) and residence in locations with high levels of sun exposure ($P = .0004$) were independent risk factors for SCC
Zwald et al [28]	Retrospective cohort	91 lung transplant recipients: cases (n = 28), controls (n = 63)	Number of nonmelanoma skin cancers after lung transplantation	• Number of months on voriconazole was found to be significantly associated with number of NMSC ($P = .007$) • Time since transplantation, age, skin type I or II, and months of exposure to voriconazole were found to be independent risk factors for number of skin cancers posttransplantation

Abbreviations: NMSC, nonmelanoma skin cancer; SCC, squamous cell carcinoma.

VORICONAZOLE AND SCC

The association of voriconazole and SCC began with several case reports describing this phenomenon in lung transplant recipients [2, 16, 22–26]. One case report described a patient who developed severe photosensitivity immediately following introduction to voriconazole, resulting in multifocal facial SCCs. The photosensitivity reaction quickly resolved after voriconazole was stopped [16]. Several of these case reports have demonstrated the increase in the aggressive nature of voriconazole-induced SCC [22, 27].

This was the case of a man who developed a rapidly expanding, poorly differentiated SCC with perineural invasion and lymph nodal metastases following prolonged exposure to voriconazole that later required radical surgery and radiotherapy [22]. Several other cases describe rapidly growing actinic keratoses followed by multifocal and aggressive SCCs appearing after the introduction of voriconazole, with dramatic regression of preneoplastic lesions after discontinuation of the drug [27].

The growing number of reported cases culminated in a multicenter case series that identified 51 cutaneous SCCs among 8 patients diagnosed with HIV, Wegener granulomatosis, and graft-versus-host disease. All patients had long-term voriconazole exposure; the short time to onset of SCC, short duration of immunosuppression before onset of SCC, and high numbers of SCCs suggest voriconazole induces SCC in immunocompromised patients [15].

These findings led to 4 epidemiological studies investigating the association of voriconazole and SCC (Table 2). A retrospective case-control study of lung transplant recipients showed that patients who developed skin cancer had received voriconazole for a significantly longer duration than the control population. Duration of voriconazole therapy was identified to be an independent risk factor for SCC development. In 17% of the cases, unusually aggressive treatment was required due to

extensive involvement and metastasis, demonstrating the aggressive nature of voriconazole-associated SCC. This study also demonstrated that geographic location was an independent risk factor for the development of SCC since location determined UV exposure. Patients who resided in areas with high levels of sun exposure were more likely to develop SCC compared with those who resided where there were low levels of exposure [25]. In a separate retrospective study, 120 lung transplant recipients with similar immunosuppression regimens were studied for the development of SCC by comparing those with and without voriconazole exposure. The investigators found that those with a history of voriconazole use were at an increased risk for developing SCC. Further, longer voriconazole therapy was shown to be an independent risk factor for development of SCC and was associated with more aggressive tumors. Voriconazole-associated SCC was also found to be potentially more aggressive in nature than nonvoriconazole-associated SCC because 4 patient deaths due to metastatic SCC were reported only among those with drug exposure [24]. These findings suggest a duration-dependent relationship.

A 20-year retrospective cohort study of 327 lung transplant recipients that evaluated cumulative exposure to voriconazole demonstrated that *any* exposure to voriconazole is associated with a 2.6-fold increased risk for SCC. Further, the risk for SCC increased by 5.6% for each 60-day exposure at 200 mg twice daily (a typical duration of treatment for invasive fungal infection), which supports the findings of Feist et al [24] of a duration-dependent relationship between voriconazole and risk of SCC development. It should be noted that the 20-year study measured cumulative dose in milligrams as a time-varying covariate, while Feist et al used univariate analysis and measured duration of therapy in years and cumulative dose in grams. Last, it was found that 5 years post lung transplant, 46% of patients ever exposed to voriconazole developed skin cancer in comparison with 18% of those never exposed, accounting for an absolute risk increase of 28% [26]. It should be noted that intensity of immunosuppression was not considered in the analysis. Furthermore, voriconazole is more likely to be administered both as a prophylaxis and as treatment to patients at a higher risk of invasive infection, which may correlate with intensity of immunosuppression.

While greater voriconazole exposure has been shown to confer an increased risk of SCC development, duration of voriconazole use has also been determined to be an independent risk factor for number of skin cancers after lung transplantation. A study of 91 lung transplant recipients showed that duration of voriconazole exposure correlates with number of nonmelanoma skin cancers [28].

Though the majority of research supports the association between voriconazole and SCC, a single study performed by investigators at Pfizer suggests the relationship may be due to confounding by indication [29]. Confounding factors reported included patient gender, history of chronic obstructive pulmonary disease (COPD), and history of immune disorder. Of note, Singer et al adjusted for gender and diagnostic category prior to transplant, which includes COPD [26]. Furthermore, the decision to conflate basal cell carcinoma (BCC) and SCC in the Pfizer study may have greatly diminished the likelihood of finding a signal between voriconazole exposure and SCC. The rate of BCC in the general population greatly exceeds that of SCC. Also, because the ratio of BCC and SCC in the studied population is unknown, it becomes increasingly difficult to assess SCC risk in this population. Additional studies will be needed to clarify this finding.

VORICONAZOLE AND MELANOMA

Solid OTRs have a 3- to 5-fold increased risk for developing melanoma compared with the general population [30]. While nonmelanoma skin cancer is most common, melanoma still accounts for 6.2% of posttransplantation skin cancers in adults and for 15% in children [31]. Risk factors for melanoma are similar for OTRs and the general population and include presence of multiple nevi and fair complexion [30, 32, 33]. Melanoma development posttransplantation arises in 3 clinical scenarios: as a recurrence of a pretransplantation melanoma (risk of recurrence is 20%), transmission of melanoma from organ donor, and as a de novo melanoma [31, 33].

The relationship between voriconazole and melanoma is not as well studied as SCC; however, cases of voriconazole-associated melanoma have been reported. One case report describes 2 patients who developed melanoma after long-term voriconazole therapy. Five melanoma in situ lesions were discovered in the setting of extreme voriconazole-associated photosensitivity in these patients. In both cases, patients experienced hyperpigmentation and lentigines of sun-exposed areas after being exposed to voriconazole. The melanomas were treated with Mohs micrographic surgery, and the patients discontinued voriconazole. Since discontinuing voriconazole, neither patient developed any new melanomas and 1 patient reported fading of the lentiginous pigmentation after voriconazole was stopped [32].

Although a definitive causative role of voriconazole in these developing melanomas cannot be determined, it can be hypothesized that voriconazole-associated photosensitivity led to accelerated photodamage, contributing to its development. Since the role of voriconazole in the development of melanoma is still unclear, further research, specifically multicenter studies, is required to investigate the mechanism by which voriconazole may be involved. In the meantime, diligent surveillance of skin reactions to voriconazole is important for prevention and early detection of melanoma.

DISCUSSION

Since its approval by the US Food and Drug Administration in 2002, voriconazole has been shown to be effective for the prophylaxis and treatment of invasive fungal infections, namely, invasive aspergillosis. Following its introduction, case reports emerged describing cutaneous SCCs developing in lung transplant recipients taking voriconazole. Current literature now supports the association between voriconazole exposure and SCC risk; however, the mechanisms have yet to be discovered. One proposed mechanism involves the primary metabolite of voriconazole, VNO, but further investigation is needed to establish its definitive role.

Invasive fungal infections contribute significantly to morbidity and mortality of solid OTRs. Specifically, invasive aspergillosis (IA) is the most common infection seen in lung transplant recipients and is associated with higher mortality compared with other fungal infections [11]. Voriconazole is an effective treatment for IA with ease of administration and more reliable absorption compared with other oral antifungal medications [18].

There is an anticipated increase in incidence of SCC in lung transplant recipients as average age at time of transplant is increasing. According to the Scientific Registry of Transplant Recipients, which captures data from the United Network on Organ Sharing/Organ Procurement and Transplantation Network, more than 25% of lung transplant recipients in 2012 were aged ≥65 years. This percentage has steadily increased over the past decade and is expected to rise as more transplants are performed for elderly patients with pulmonary fibrosis. Older age overall and older age at time of transplant both confer an increased risk for SCC development, suggesting the incidence of SCC is likely to increase [4, 6]. With our emerging understanding of voriconazole-associated SCC, the decision to administer voriconazole is becoming increasingly complex.

There is currently no universal guideline for voriconazole prophylactic dosing in lung transplant recipients, resulting in variable prophylactic strategies. Further investigation into the risk factors associated with voriconazole in lung transplant recipients is necessary for proper dosing to be determined. Since several studies have supported a duration-dependent risk associated with voriconazole and SCC, the next step is to determine dosing that will increase therapeutic benefits while minimizing risk. While voriconazole has been shown to be an effective prophylaxis and treatment, randomized controlled trials are needed to determine its relative effectiveness.

Due to the number of reported cases of skin cancer, product labeling of voriconazole was changed in June 2010 to recommend discontinuation of voriconazole if skin lesions consistent with SCC or melanoma develop. While the relationship between voriconazole and SCC has been supported by several research institutions, it is important to now investigate the mechanism by which voriconazole confers an increased risk in the development of skin cancer. To aid in solving this problem, investigation is required to determine the role of VNO in the development of skin cancer. Furthermore, since voriconazole is metabolized by CYP2C19, genetic variations in drug-metabolism rates would cause varying levels of circulating metabolite and may incur varying levels of skin cancer risk. Pharmacogenomic studies have shown that those with the poor metabolizer genotype had concentrations of voriconazole 3 to 4 times higher than those considered to be extensive metabolizers [34, 35]. Pharmacogenomic studies investigating risk of SCC and genotype will contribute to the understanding of VNO's role in the development of skin cancer. To date, 2 small studies of cystic fibrosis patients have been conducted to investigate the relationship between blood plasma levels of voriconazole and photosensitivity reactions. These studies showed that genetic variation of CYP2C19 enzymes had an effect on voriconazole serum levels but did not show any significant correlation between incidence of photosensitivity and voriconazole serum levels [36, 37]. These studies are limited by small size, short follow-up time, and potential confounding factors such as drug–drug interactions. Further studies are needed to investigate the role of CYP2C19 genotype and adverse cutaneous reactions.

Voriconazole is an important drug that effectively decreases morbidity and mortality of invasive fungal infections in OTRs. However, its association with accelerated SCC in susceptible individuals requires careful attention until further studies are able to identify population risk, pharmacogenomics data, and causal mechanisms.

Note

Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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