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High cumulative dose exposure to voriconazole is associated with cutaneous squamous cell carcinoma in lung transplant recipients

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BACKGROUND: Lung transplant recipients (LTR) have an increased risk of cutaneous squamous cell carcinoma (SCC) due to immunosuppressive therapy. Voriconazole, which is associated with phototoxic side effects in some patients, may be an additional risk factor for SCC in this population.

METHODS: To test whether voriconazole is a risk factor for developing SCC in LTR, we evaluated cumulative exposure to voriconazole in 327 adults who underwent lung transplantation at one center between 1991 and 2010. Voriconazole exposure was assessed as a time-varying covariate. We used survival analysis methods to assess the risk of developing SCC over time.

RESULTS: Exposure to voriconazole was associated with a 2.6-fold increased risk for SCC. This phenomenon was dose-dependent: the risk for SCC increased by 5.6% with each 60-day exposure at a standard dose of 200 mg twice daily. At 5 years after transplant, voriconazole conferred an absolute risk increase for SCC of 28%.

CONCLUSIONS: These results suggest that caution should be taken when using voriconazole in LTR because this drug increases the already high risk for SCC in this population.

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Skin cancer is the most common malignancy in organ transplant recipients (OTRs), and cutaneous squamous cell carcinoma (SCC) is the most frequently diagnosed.[1] Further, OTRs are at increased risk for recurrence, metastasis, and multiple primary tumors. Lung transplant (LT) recipients (LTR) have an increased risk of developing SCC compared with recipients of abdominal allografts,[1] likely due to older age at transplant and more intense immunosuppression used to prevent allograft rejection.

In addition to malignancies, OTRs are at high risk for invasive fungal infections. In 2002, the U.S. Food and Drug Administration (FDA) approved voriconazole for the treatment of serious fungal infections. It is a second-generation triazole broad-spectrum antifungal that inhibits P450-dependent ergosterol synthesis, disrupting cell membrane lipid formation.[2] Although its efficacy against many molds and ease of administration have led to widespread use in many, but not all, transplant centers, its use is off-label. Voriconazole is also associated with significant side effects, including vision changes, hallucinations, and hepatic enzyme abnormalities.[3–5] It can also cause photosensitivity, which can range from mild sunburn-like erythema to blistering pseudoporphyria.[6] Photosensitivity may be reversible after drug discontinuation or can progress to freckling and epithelial dysplasia.[7–14]

The association between voriconazole phototoxicity and SCC has been reported in conditions including chronic

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granulomatous disease, bone marrow transplantation, graft vs host disease, and HIV.[15–21] It has also been recognized in LTRs, which is of particular importance given its common use.[22,23] A recent a case–control study reported that voriconazole and geographic location were independent risk factors for SCC in LTRs.[24] Given these findings, we sought to investigate whether voriconazole is associated with an increased risk of developing SCC in LTRs. To do so, we performed a 20-year retrospective single-center cohort study of LTRs.

Methods

To investigate the effect of voriconazole exposure on post-transplant SCC, we performed a retrospective cohort study of all patients who underwent single, double, or heart-lung transplantation at the University of California at San Francisco (UCSF) from January 1, 1991, to December 31, 2010. Demographic data, including date of death, were acquired from the Organ Procurement and Transplantation Network (OPTN) registry (STAR File #020910–16). Medical records were reviewed to determine the details of skin cancer diagnoses and to obtain the dates and doses of voriconazole administration. This study was approved by the UCSF Committee on Human Research and was performed in compliance with the Declaration of Helsinki.

We collapsed pre-transplant listing diagnoses into the 4 groupings used in calculating the Lung Allocation Score (LAS).[25] The LAS is an urgency-based allocation system used in the United States to prioritize LT candidates on the waiting list. Medication records are maintained on a specific flowchart for each LTR. This allows for the straightforward identification of dates of administration and doses for each medication. For the purposes of this study, we standardized Post-operative Day 3 after LT as our index (start) date for voriconazole dosing. Dates and doses were abstracted until the time of SCC diagnosis, patient death, or last follow-up as of March 1, 2011. If the last follow-up date was within 1 month of death, censoring was defined as the date of death. Three patients transitioned their clinical care to other institutions before developing SCC. Therefore, their SCCs were reported to OPTN after their last follow-up at UCSF. We were unable to determine voriconazole administration dates and doses for these 3 patients after they left our center. We therefore right-censored their data at the date of their last follow-up at UCSF. One additional patient had SCC preceding LT and was excluded.

Our study period spanned 20 years. Temporal trends in the care of LTR during this period, including immunosuppression regimens, may have affected the risk of SCC development separate from the introduction of voriconazole. Given our modest sample size, to investigate the potential for an effect of temporal trends in LTR care, we created an era-effect variable dichotomizing patients who received allografts before or after January 1, 2004.

Voriconazole doses could not be confirmed for 52 LTRs due to incomplete or missing medical records, and they were excluded from the analysis. They did not differ from those included with respect to the predictor variables, follow-up time, or frequency of SCC.

Statistical analysis

Variables were analyzed with the 2-sided Fisher's exact test or 2-sample Wilcoxon rank sum test. We assessed correlations between predictors, including male sex, age at transplant, white vs non-white race, transplant type (single, bilateral, or heart-lung), LAS diagnostic category, body mass index (BMI), and ever/never voriconazole exposure. Correlation coefficients were $< \pm 0.3$ in all cases (-0.24 to 0.29), except for ever/never exposure to voriconazole and transplant type, which had a correlation coefficient of 0.48. We identified a preferential performance of bilateral LT after 2003. In addition, "ever use" of voriconazole was more frequent in patients who received allografts after 2003. These findings suggested that the correlation was due to temporal factors. Stratified by time, the correlation for these 2 variables was 0.28 before 2003 and 0.18 after 2003.

We used Cox proportional hazard models to assess the effect of voriconazole exposure on the risk of developing SCC. The mechanism by which voriconazole may affect the risk of developing SCC is unknown. We hypothesized that voriconazole could be related to the subsequent development of SCC in 2 ways: (1) any exposure to voriconazole could confer an increased risk or (2) the risk could be dose-dependent. We therefore developed 2 analytic approaches to assess these potential risks:

First, to assess the impact of "any" voriconazole exposure on SCC development, we created a dichotomous time-dependent variable: "ever or never exposed." To be considered "ever exposed," patients had to have received voriconazole *before* SCC development.

Second, to assess how the risk of SCC development varied with increasing exposure to voriconazole, we considered the cumulative dose of voriconazole as a continuous time-dependent covariate. The cumulative dose of voriconazole was calculated from the index date until LTRs developed SCC, died, or the study period ended. We treated the cumulative dose of voriconazole as a time-dependent covariate to align the timing of exposure and outcome, thereby eliminating the potential for immortal time bias.[26]

Sex and age were included in the Cox models a priori based on known associations with skin cancer after organ transplant.[1] We confirmed model robustness using likelihood ratio testing. Binary tests of interaction between all predictors revealed interactions between race and sex as well as between race and age. Further, we identified that 94% of SCC developed in white LTRs. Because of these interactions and the rarity of SCC development in non-white LTRs, models were stratified by race (white/non-white).

The proportionality of hazards assumption was tested and confirmed with the Schoenfeld test. The goodness of fit of the models was confirmed by comparing a plot of the Cox-Snell residuals with the Nelson-Aalen cumulative hazard function.

Kaplan-Meier methods for survival curves do not translate to the setting of competing risks.[27] Instead, we esti-

mated the proportion of patients in 4 possible states after transplant: they could develop SCC and remain alive, develop SCC and then die, die before developing SCC, or remain alive without developing SCC. To project these cumulative incidence probabilities,[28] we represented the cumulative incidence function in terms of the cause-specific hazards for SCC and death and used estimates from the Cox models for the cause specific hazards of death and SCC. We compared 2 scenarios: continuous voriconazole through the development of SCC or no voriconazole.

To investigate whether our findings were sensitive to the effect of transplant era, we repeated our analyses including the era-effect variable in the final multivariate models. These models were compared with the models without the era-effect variable by likelihood ratio testing.

Results

Of 327 LTRs included in the analysis, 50 (15%) had at least 1 SCC (cases), and the remaining 277 (85%) did not (controls; Table 1).[27] Comparing cases and controls, there were no differences in age (mean 53.2 ± 10.4 vs 51.2 ± 12.9 years, $p = 0.37$), male sex (60% vs 53%, $p = 0.44$), transplant type ($p = 0.65$), or listing diagnosis category ($p > 0.99$). Race did differ, however, between cases and controls: 94% of cases were white compared with 76% of controls ($p = 0.002$).

Overall, 242 LTRs (74%) were "ever exposed" to voriconazole and manifested a 2.6-fold increased risk of subsequent SCC development compared with those who were "never exposed" (hazard ratio [HR], 2.62; 95% confidence interval [CI], 1.21–5.65; $p = 0.014$; Table 2). Importantly, this risk was dose-dependent. For each additional 1 gram of voriconazole exposure, LTRs experienced a 0.2% increased risk of developing SCC (HR, 1.002; 95% CI, 1.001–1.004; $p = 0.006$). Most invasive fungal infections are treated clinically for 6 to 8 weeks. For each 60-day exposure to voriconazole at standard dosing of 200 mg twice daily (~8 weeks of treatment), LTRs manifested a 6% increased risk of developing SCC (HR, 1.06; 95% CI, 1.02–1.10; $p = 0.006$). Male sex and age ≥ 60 years demonstrated trends towards increased risk for developing SCC (Table 2).

The cumulative incidence of SCC in the overall cohort at 3, 5 and 10 years was 11.9%, 29.8%, and 45.5%, respectively. Figure 1 illustrates the extrapolated incidence of SCC in LTRs "ever exposed" to voriconazole accounting for death as a competing risk. In this model, SCC development was predicted at 5 years after transplant: 46% of LTRs ever exposed to voriconazole developed SCC compared with 18% of those never exposed, corresponding to an absolute risk increase of developing SCC of 28%.

Table 1 Demographics

Characteristic[a]	Cases ($n = 50$)	Controls ($n = 277$)	p-value
Age at transplant, years	53.2 ± 10.4	51.2 ± 12.9	0.37
Age < 60	35 (70)	199 (71.8)	0.86
Age ≥ 60	15 (30)	78 (28.2	
Make sex	30 (60)	146 (53.09)	0.44
Ethnicity			
White, non-Hispanic	47 (94.0)	210 (75.81)	0.002[b]
Hispanic	2 (4.0)	30 (10.83)	
Black/African American	0	19 (6.86)	
Asian	0	12 (4.33)	
Other/missing	1 (2.0)	6 (2.17)	
Body mass index, kg/m^2	24.8 ± 4.8	24.7 ± 5.0	0.98
Type of transplant			
Bilateral lung	37 (68.52)	235 (72.76)	0.65
Single lung	15 (27.78)	80 (24.77)	
Heart-lung	2 (3.70)	8 (2.48)	
LT indication by diagnostic category[c]			
Group A	17 (34.0)	88 (32.12)	>0.99
Group B	5 (10.00)	28 (10.22)	
Group C	5 (10.0)	24 (8.76)	
Group D	23 (46.0)	134 (48.91)	
Voriconazole, ever exposed[d]	40 (80.0)	202 (72.92)	

LT, lung transplant.

[a]Continuous data are presented as n mean ± standard deviation, and categoric data as number (%).

[b]White vs non-white.

[c]Diagnostic grouping used for calculation of the Lung Allocation Score.[27]

[d]Does not account for timing of exposure relative to squamous cell carcinoma development.

Table 2 Relative Risk of Developing Cutaneous Squamous Cell Carcinoma in Lung Transplant Recipients Exposed to Voriconazole

Exposure to voriconazole	HR[a] (95% CI)	*p*-value
Cumulative dose[b]	1.002 (1.001–1.004)	0.006
Male sex	1.57 (0.87–2.83)	0.138
Age ≥ 60 years	1.57 (0.84–2.94)	0.16
Any exposure[c]	2.62 (1.21–5.65)	0.014
Male sex	1.65 (0.91–2.98)	0.097
Age ≥ 60	1.43 (0.76–2.69)	0.27

CI, confidence interval; HR, hazard ratio.

[a]A hazard ratio of > 1.0 represents greater risk for developing squamous cell carcinoma for recipients who were exposed to voriconazole after transplant compared with those who were not. Models were stratified by race (white vs not-white).

[b]Cumulative voriconazole dose is the HR per 1-gram exposure to voriconazole.

[c]Any exposure to voriconazole is defined as any exposure before the development of squamous cell carcinoma.

In a sensitivity analysis, the era of LT before or after January 1, 2004, did not affect the effect sizes or statistical significance of our findings (likelihood ratio $p = 0.42$ for any exposure and $p = 0.87$ for cumulative dose).

Discussion

We found that voriconazole is associated with the development of cutaneous SCC after LT, that any exposure to voriconazole confers a 2.6-fold increased risk of SCC development, and that, importantly, this risk is dose-dependent. Indeed, each 8-week exposure to voriconazole at 200 mg, twice-daily dosing (a common duration of therapy for invasive fungal infections) increases the risk of developing SCC by 6%. Lastly, we found that 5-years after LT, 46% of patients ever exposed to voriconazole developed SCC compared with 18% of those never exposed, an absolute risk increase of 28%.

Overall, our cohort suffered from a high incidence of SCC, with a cumulative incidence of 30% at 5 years and 46% at 10 years. The median time to development of SCC was 3.6 years. The cumulative incidence reported here is markedly higher than that reported rate of 5% to 25% in renal transplant recipients at 10 years.[29–32] The difference in incidence of SCC in LTRs underscores the importance of identifying risk factors for the development of SCC in this population. Although LTRs are typically exposed to more intensive immunosuppression regimens than renal transplant recipients, it is unlikely that these differences can entirely be ascribed to levels of immunosuppression or sun exposure. Other important potential explanations may include voriconazole exposure, older age at transplant, and other, yet to be determined factors.

Our results build on a recent nested case-control study of LTR.[24] In 17 LTRs with SCC and 51 controls, Vadnerkar et al[24] demonstrated that duration of voriconazole exposure was associated with an increased risk of SCC. LTRs in that study had a shorter median time to SCC than is reported here (1.6 vs 3.6 years). The induction regimen may be a factor in explaining this difference. The authors postulated that the short time to the development of SCC might have been due to induction with alemtuzumab.[24] Our center typically uses basiliximab, a less immunosuppressive agent. In part, due to this more intense induction, Varderkar et al reports using 6 months of voriconazole prophylaxis whereas UCSF uses 3 months. On the basis of our findings, the higher cumulative exposure to voriconazole could be an alternative explanation for our differences in time to SCC development. Another potential explanation is that the median age at transplant in their cases was 63 years vs 53 years in our cohort.

Our study has notable strengths. Our detailed medication records and analytic approach allowed us to consider voriconazole exposure that occurred only *before* SCC development. In doing so, we accounted for both competing risks and the risk of immortal time bias. Our methods and findings confirm the work of Vadnerkar et al[24] as well as provide clinically relevant evidence that the risk of SCC from voriconazole exposure is dose-dependent. Indeed, there does not appear to be a threshold below which voriconazole is without risk. In addition, our findings are derived from a 20-year retrospective cohort study of 327 LTRs and represent an analysis of voriconazole as a risk factor for development of SCC in a large number of LTRs. Finally, we selected biologically known risk factors for SCC and used statistically rigorous methods for selecting covariates for inclusions in multivariate models.

Our study also faces some limitations. First, we were unable to retrospectively ascertain the Fitzpatrick skin type or prior sun exposure history, or to determine whether photosensitivity preceded dysplasia in those LTRs who developed SCC. Prospective studies using a combination of survey-based sun exposure and physical assessment methods could address these limitations.

Second, although our study represents a large cohort study of SCC in LTR, it is a single-center study with a relatively modest sample size. Thus, it may have been

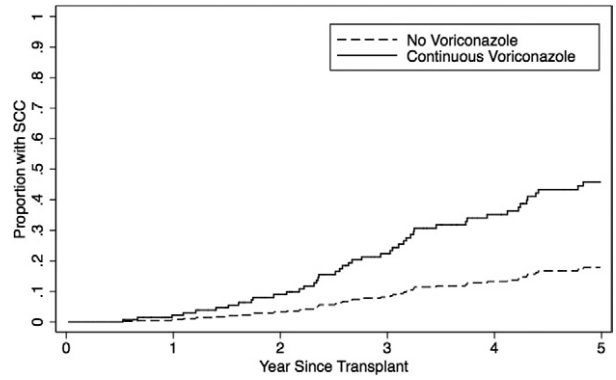

Figure 1 Cumulative incidence model of squamous cell carcinoma (SCC) in lung transplant recipients exposed to voriconazole. Model is based on continuous exposure to voriconazole.

underpowered to identify associations between SCC and male sex or age.

Third, this study did not account for the types and intensity of immunosuppression. Although it likely plays a role in SCC development, a single effective and accepted measure of overall immunosuppression intensity is lacking. Given that immunosuppressive agents are generally weaned over time (with occasional increases in the setting of acute allograft rejection), a comprehensive consideration of immunosuppression intensity would have treated each agent as its own time-varying covariate. Despite this limitation, we suspect voriconazole does confer an increased risk for SCC development. In this study, cases and controls were generally treated similarly according to established treatment protocols. A sensitivity analysis of transplant era did not have a substantive or significant effect on our findings. Nevertheless, accounting for immunosuppression intensity in future prospective studies of this question will be important.

Although single-center studies in LT are often limited by modest sample sizes, in general, investigators benefit from access to more detailed patient-level data. This allows for more accurate cancer assessment than registry-based studies. This is particularly important for studies of non-melanoma skin cancer, which are not captured in standard cancer registries and share a single International Classification of Diseases (9th Edition) code with several other cancer diagnoses, among them SCC, basal cell carcinoma, and adnexal carcinomas. Notably in our study, 18 of 50 SCC cases were identified by internal medical record review that had not been reported to the OPTN. This suggests that future studies on this subject should not rely solely on UNOS or other registry data for ascertainment of non-melanoma skin cancer.

Since the FDA approved voriconazole, the approach at UCSF has been to use this drug as standard anti-fungal prophylaxis for the first 3 months after LT. Voriconazole is discontinued thereafter if voriconazole-sensitive fungus is not identified on surveillance bronchioalveolar lavage and/or computed tomography scans of the chest do not reveal findings consistent with an invasive fungal infection. Voriconazole is reinstituted for the treatment of invasive fungal infections or if increased immunosuppression is required for acute allograft rejection. Because other transplant centers may use different protocols, tracking cumulative dose exposure may allow physicians to identify patients at increased risk for SCC.

Our center does not routinely check serum voriconazole trough levels. Levels are checked if there are concerns about drug absorption in the setting of gastroparesis or if patients are not improving radiographically on standard therapy. Given our findings, it could be hypothesized that higher serum levels are a biomarker for SCC risk. This assay, however, cannot be recommended for SCC risk assessment until studies investigate its clinical utility.

In summary, voriconazole is an independent risk factor for the development of cutaneous SCC in LTRs. Its efficacy and ease of administration makes voriconazole an extremely attractive and important therapeutic agent to combat invasive fungal infections. It is important, however, to be aware of the increased risk of SCC associated with this agent. The risks and benefits of using voriconazole as prophylaxis and treatment compared with alternative anti-fungal medications should be weighed carefully. When voriconazole is used, we recommend heightened attention to risk factors for photosensitivity and/or SCC, as well as skin cancer screening. This is especially important in patients with other known non-modifiable risk factors for SCC such as fair skin, male sex, and older age.

Disclosure statement

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