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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-