Posaconazole and risk of cutaneous squamous cell carcinoma after lung transplantation: a single institution, retrospective cohort study

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Abstract

The antifungal voriconazole is often used to reduce the risk of invasive fungal infection after lung transplantation but is associated with an increased risk of cutaneous squamous cell carcinoma (SCC) in this population. The risk of post-transplant SCC related to posaconazole remains incompletely understood. To evaluate the post-transplant risk of SCC related to posaconazole, we created cohorts of lung transplant recipients were created post-transplant antifungal protocol including universal posaconazole prophylaxis (UAP-P), universal voriconazole prophylaxis (UAP-V), and targeted prophylaxis (TAP) with overall low antifungal use. Cumulative incidence of SCC in the UAP-V cohort was higher than either the TAP or UAP-P cohorts but did not differ between the UAP-P and TAP cohorts. In multivariate analysis, the hazard ratio for SCC was not statistically significantly different between the UAP-P and TAP cohorts (hazard ratio = 0.86, p = 0.6294), but was twice as high for the UAP-V cohort compared to the TAP cohort (hazard ratio = 2.06, p = 0.0111). Posaconazole does not appear to be associated with increased risk of SCC after lung transplantation.

Introduction

Lung transplantation is a treatment option for a variety of end-stage pulmonary diseases. Among transplant recipients, fungal infections are a common cause of morbidity and mortality (1), and invasive infection has been identified as an independent risk factor for death (2). To decrease the occurrence of this high-risk postoperative complication, routine antifungal prophylaxis has become increasingly common, although there remains no consensus on the optimal medication and duration of use.

Voriconazole is a triazole antifungal effective against a broad array of yeasts and molds and is commonly used for antifungal prophylaxis in the post-transplant setting. Voriconazole prophylaxis has been associated with favorable outcomes such as decreased incidence of fungal colonization and invasive infection (3). Associated toxicities include hepatitis, periostitis, and cutaneous reactions including photosensitivity, pseudoporphyia, lentigines, and an increased risk of cutaneous squamous cell carcinoma (SCC). The risk of SCC in relation to voriconazole is of particular concern due to an already high burden of SCC among transplant recipients, which may be accelerated by voriconazole and lead to a propensity for more aggressive features including perineural invasion (4, 5). Posaconazole is a more recently available broad-spectrum antifungal and represents a potential alternative to voriconazole for antifungal prophylaxis. Anecdotal evidence and case reports suggest a reduction in the number post-transplant SCCs related to posaconazole compared to voriconazole (6), but large-scale studies are lacking.

In this retrospective cohort study at a single academic medical center, we sought to better define the risk of SCC after lung transplantation in a recent cohort who received routine posaconazole prophylaxis compared to historical cohorts receiving universal or targeted voriconazole prophylaxis.

Methods

Study Population

Detailed methodology of similarly designed cohort studies after lung transplantation have been previously described (7, 8). Briefly, all consecutive lung transplants performed at UCLA are routinely documented with demographic and clinical information including patient date of birth, sex, date of transplant, type of transplant, and primary diagnosis for transplant. With approval of the UCLA Institutional Review Board, additional data were extracted from the medical record including race, induction regimen (anti-thymocyte globulin (ATG), basiliximab, or other), pre-transplant diagnosis of KC, post-transplant discharge antifungal, dates of antifungal use, incident post-transplant keratinocyte cancer (KC), and last follow up date (defined as last progress note by either a dermatologist or a pulmonologist), and date of death, if applicable.

Study Cohorts

Patients were grouped into three cohorts by date of transplant and the corresponding institutional antifungal prophylaxis practice at the time: targeted antifungal prophylaxis (TAP), universal antifungal prophylaxis with voriconazole (UAP-V), or universal antifungal prophylaxis with posaconazole (UAP-P). Both TAP and UAP-V cohorts were given voriconazole 200mg twice daily for 6 months, either to high-risk transplant recipients only (TAP) or to all transplant recipients (UAP-V). The protocol switched from targeted to universal prophylaxis on 7/1/2009. High risk patients were defined as those with a history of fungal infection prior to transplant, those with fungal infection identified in explant pathology, and those with cystic fibrosis. The TAP cohort included transplant dates from 7/1/2005 through 6/2/2009. The UAP-V cohort included transplants from 7/1/2009 through 12/31/2012. Both cohorts were followed through 12/31/2013.

The UAP-P cohort was created similarly by collecting consecutive patients with transplant dates from 1/1/2017 though 12/31/2021. The UAP-P cohort was given posaconazole 300mg twice daily delayed release tablets for at least 3 months. Data were collected through 1/31/2022. For all cohorts, antifungal treatment could be adjusted at the discretion of the treating physician. Alternative antifungals included fluconazole, itraconazole, posaconazole suspension (TAP and UAP-V cohorts only), and isavuconazole.

For the purposes of this study, patients with an unclear prophylactic antifungal regimen, those who received multiple transplants, or those who died prior to discharge from transplant hospitalization were excluded.

Skin Cancers

Incident post-transplant KC, SCC only for the TAP and UAP-V cohorts, and both SCC and basal cell carcinoma (BCC) for the UAP-P cohort, were identified through patient chart review and confirmed for histology in UCLA Medical Center pathology records. SCC included invasive disease, SCC in situ, or “at least SCC in situ”. Other atypical squamous proliferations were not included. For the UAP-P cohort, additional data on anatomic location was collected.

Statistical Analysis

We conducted all statistical analyses using SAS 9.4 (SAS Institute, Cary NC). We compared demographic and clinical characteristics across the UAP-P, UAP-V, and TAP cohorts using chi-square tests for categorical variables and Kruskal-Wallis for continuous variables. We calculated time to first SCC for all three cohorts as the years between date of transplant and date of incident SCC.

Among the UAP-P cohort, we further explored KC (including both SCC and BCC) and antifungal exposure data including all exposure events to posaconazole, voriconazole, and isavuconazole. We calculated the relative risk of any KC and SCC for patients on posaconazole only compared to posaconazole and voriconazole, and posaconazole only compared to posaconazole and isavuconazole, and examined associations using chi-square tests.

We examined the associations between each cohort and SCC in two ways. First, we calculated product-limit survival estimates and used the log-rank test to assess equality over all three cohorts, as well as conduct pairwise comparisons between cohorts, using SAS Proc LIFETEST. We calculated unadjusted and Sidak-adjusted p-values. Secondly, we performed similar analyses to a prior study to replicate and expand on their two-cohort design (7). We computed cumulative incidence curves using nonparametric estimators (9) using the SAS macro %CIF (10). We conducted an overall comparison of all three curves, as well as pairwise comparisons, using Gray's test.

Lastly, we examined the risk of SCC relative to cohort as well as other possible risk factors for SCC including sex, race, age at transplant, primary diagnosis for transplant, induction type, and pre-transplant diagnosis of keratinocyte cancer in a multivariable proportional hazards regression model. We assessed the proportionality assumption using plots of Schoenfeld residuals against time, as well as a method utilizing the empirical score process built into SAS Proc PHREG.

Results

A total of 752 patients were included in this study: 396 in the UAP-P cohort, 176 in the UAP-V cohort, and 180 in the TAP cohort. Descriptive statistics by cohort can be found in Table 1. The average age at transplant was similar across all cohorts. Male sex and white race were more common, though the proportion of white race was lower in the UAP-P cohort. Restrictive parenchymal lung disease was the most common primary diagnosis pre-transplant. As expected by design, 67.8% of the TAP cohort received no post-transplant discharge antifungal, while 92.1% of the UAP-V cohort was discharged on voriconazole, and 90.4% of the UAP-P cohort was discharged on posaconazole. Median follow up time was longer for the TAP cohort (3.9 years, IQR 1.7 years) compared to the UAP-V cohort (1.7 years, IQR, 1.9 years) and UAP-P cohort (1.4 years, IQR 2.1 years). Pre-transplant KC different between cohorts and was most common in the UAP-P cohort. However, post-transplant SCC was less prevalent in the UAP-P cohort (28 patients, 7.1%) with a median time to first SCC of 1.6 years (IQR = 1.7), compared to 29 (16.5%)

patients with a median time of 1.4 years (IQR = 0.9) in the UAP-V and 34 (18.9%) patients with a median time of 2.8 years (IQR = 1.7) in the TAP cohorts.

Additional data on KC and antifungal use were collected for the UAP-P cohort (Table 2). Among patients with post-transplant KC, SCC occurred more commonly (28 patients, 96.6%) than BCC (12 patients, 41.3%). Additionally, the risk of SCC grew over time compared to BCC, accounting for a higher proportion of the total number of incident KCs (Fig. 1). KC arose more often on sun exposed sites (30 on the head/neck or forearms/hands compared to 8 on all other sites). When examining all post-transplant antifungal exposure in this cohort, posaconazole remained the most common agent with 393 patients (99.2%) being exposed, followed by isavuconazole (99 patients, 25.0%), and voriconazole (55 patients, 13.9%). Posaconazole trended toward a lower relative risk (RR) compared to voriconazole for KC overall (RR = 0.45, p = 0.0965) and for SCC (RR = 0.44, p = 0.0774), but there was no difference in RR compared to isavuconazole.

Comparisons of the cumulative incidence of first SCC between cohorts (Figs. 2) suggested significant differences between groups (X^2 = 11.2; p = 0.0037). Similarly, pairwise comparisons suggested a significant difference in cumulative incidence of first SCC between the TAP and UAP-V cohorts (X^2 = 6.2; p = 0.0125), with UAP-V demonstrating an overall shorter time to first SCC relative to TAP. A comparison of the UAP-P and UAP-V cohorts also suggested a significant difference (X^2 = 10.0; p = 0.0016), with UAP-V likewise demonstrating an overall shorter time to first SCC relative to UAP-P. There was no significant difference between the UAP-P and TAP cohorts (X^2 = 0.2; p = 0.6274). To address the possibility of bias due to differences in follow up time across cohorts, a sensitivity analysis was performed censoring all patients who developed SCC ≥ 4 years post-transplant and the results were unchanged (supplemental Fig. 1).

In a multivariable proportional hazards model (Table 3), we identified other known risk factors for SCC. Assessments of the proportional hazards assumption suggested a possible time-dependent trend in age, thus we categorized age using the 25th, 50th, and 75th percentiles, resulting in four total age categories. In this multivariable model, additional risk factors for SCC included white race (HR = 7.1; p < .0001), age between 55 and 62 years (HR = 2.3; p < 0.0196), and a history of KC (HR = 3.2; p = 0.0002), further controlling for sex, restrictive parenchymal lung disease, and ATG induction, which were not significantly associated with rate of SCC. Patients in the UAP-V continued to have a higher rate of SCC compared to the TAP cohort (HR = 2.1; p = 0.0111), while patients in the UAP-P cohort do not have a significantly different rate of SCC compared to the TAP cohort (HR = 0.9; p = 0.6294).

Discussion

In this study we explore the risk of post-transplant keratinocyte cancer after lung transplantation and its relationship to antifungal prophylaxis with posaconazole. We found that patients receiving posaconazole had a similar risk of incident post-transplant SCC to those from a historical cohort who received targeted antifungal prophylaxis (TAP). Given the low overall antifungal exposure in the TAP cohort, this group

approximates the baseline post-transplant SCC risk and our results show that frequent use of posaconazole does not significantly change this risk. In contrast, the universal antifungal prophylaxis with voriconazole cohort (UAP-V) was significantly more likely to develop SCC compared to either the TAP or UAP-P cohorts, with an associated risk over twice that of the TAP cohort in multivariate analysis, as expected based on the known association between voriconazole and SCC shown across multiple populations (7, 11).

Other known risk factors for SCC were also identified in our study including White race, age at transplant, and pre-transplant diagnosis of KC, providing further evidence for the validity of our conclusions. Interestingly only the second quartile age range showed a statistically significant increased risk of SCC relative to the lowest quartile, although higher ages trended toward significance. This could be due to older patients being less likely to be observed developing SCC due to competing risks, selection bias against SCC in older patients accepted for transplant, or other risk factors more common in the second quartile age group such as increased exposure to ultraviolet light. Regardless of age, the median time to first SCC was between 1.4 and 3 years across cohorts, and the incidence of new SCC appeared to decrease after 3 years. Therefore, it may be most prudent to perform regular SCC surveillance early after transplantation and to perform a detailed risk assessment for all patients including consideration of age and other factors.

Our lung transplant population had a higher incidence of SCC than BCC, consistent with the established link between immunosuppression and SCC, but not BCC. In a prior population-based study from a lung transplant registry, exposure to either posaconazole or itraconazole was found to be associated with BCC (12). This may have been due to selection bias with high-risk patients preferentially being given an alternative to voriconazole. In fact, itraconazole is thought to have some antitumoral activity against BCC (13). Although we did not investigate the relationship between BCC and posaconazole due to low numbers of BCC, a potential association deserves additional study.

Unlike voriconazole, posaconazole does not appear to be photosensitizing, which may partially explain its lack of association with SCC. Both photosensitivity and eruptive SCCs have been noted among some patients receiving voriconazole and demonstrated regression with cessation of the medication, including after transition to posaconazole (5, 6). Prior studies in non-transplant patients have shown a modest increase in the risk of KC with photosensitizing agents, however, the risk appears to be stronger for BCC than SCC (14) and studies among transplant recipients are limited. Other hypotheses include both ultraviolet radiation dependent and independent DNA damage by the metabolite voriconazole-N-oxide as well as inhibition of DNA repair mechanisms (15). Posaconazole likely has different metabolic intermediates from voriconazole, which may contribute to its differing relationship to SCC, though further research is needed to clarify these mechanisms.

As a retrospective study from a single academic medical center, this study has several limitations. First, it cannot demonstrate a definitive lack of association between posaconazole and SCC. In one prior case report, a patient who transitioned from voriconazole to posaconazole continued to develop numerous

SCCs resulting in metastatic disease (16). Importantly though, this patient had been on prolonged voriconazole therapy and increasingly longer courses have stronger associations with SCC (7). It does suggest, however, that earlier transition to posaconazole or preferential initial selection of posaconazole may be prudent. Second, we did not evaluate a duration-dependent association between posaconazole and SCC, though a prior study did not find such an association (12). As a tertiary medical center, it is difficult to reliably determine the exact duration of medication use for patients that regularly follow up with outside physicians. Third, our follow up time in the UAP-P cohort was limited and observation time may not have been long enough to detect an increase in SCC, if present. Our sensitivity analysis censoring SCCs developed ≥ 4 years post-transplant across all cohorts did not change our results, but future studies should include longer observation periods and larger cohort sizes to confirm our findings. Fourth, we did not evaluate clinical outcomes of fungal infections in patients treated with voriconazole compared to posaconazole. A study of voriconazole in lung transplant recipients showed an increase in SCC but a reduction in all-cause mortality (17). Further studies should include similar clinically important outcomes for posaconazole. Finally, isavuconazole is increasingly being used in clinical practice. While we did not detect a difference in relative risk of SCC for posaconazole compared to isavuconazole, the small number of patients given isavuconazole in our cohorts limits the interpretation. Nonetheless, transplant clinicians and dermatologists should be aware of posaconazole as an effective alternative prophylactic antifungal agent with a potentially reduced risk for SCC compared to voriconazole, particularly for patients considered to be at high risk for SCC or those who develop cutaneous reactions to voriconazole.

Declarations

IRB Approval Status: Approved by UCLA IRB, #11-003042

Conflicts of interest: None declared

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Data availability: Data used for this study will be made available upon reasonable request.

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Tables

Table 1
Characteristics of UCLA Lung Transplant Recipients by Cohort

	Cohort			
	UAP-P (N = 396)	UAP-V (N = 176)	TAP (N = 180)	p-value[1]
Age at Transplant, mean (sd)	58.9 (11.4)	59.4 (10.2)	58.2 (12.6)	0.6684
Sex, N (%)				0.4641
Female	169 (42.7)	73 (41.5)	67 (37.2)	
Male	227 (57.3)	103 (58.5)	113 (62.8)	
Race, N (%)				< .0001
Asian	25 (6.3)	6 (3.4)	7 (3.9)	
Black	26 (6.6)	9 (5.1)	12 (6.7)	
Hispanic	119 (30.0)	23 (13.1)	22 (12.2)	
Other	19 (4.8)	6 (3.4)	5 (2.8)	
White	207 (52.3)	132 (75.0)	132 (73.3)	
Missing	—	—	2 (1.1)	
Primary Diagnosis				< .0001
Restrictive Parenchymal Lung Disease	294 (74.2)	118 (67.1)	107 (59.4)	
Obstructive Lung Disease	41 (10.4)	40 (22.7)	49 (27.2)	
Cystic Fibrosis/bronchiectasis	24 (6.1)	6 (3.4)	13 (7.2)	
Pulmonary Vascular Disease	26 (6.6)	2 (1.1)	5 (2.8)	
Other	10 (2.5)	9 (5.1)	3 (1.7)	
Missing	1 (0.2)	1 (0.6)	3 (1.7)	
Induction Type, N (%)				< .0001
Anti-thymocyte Globulin	43 (10.9)	51 (29.0)	91 (50.5)	
Basiliximab	353 (89.1)	121 (68.7)	86 (47.8)	
Other/none	—	3 (1.7)	—	
Missing	—	1 (0.6)	3 (1.7)	
Discharge Antifungal, N (%)				< .0001

	Cohort			
	UAP-P (N = 396)	UAP-V (N = 176)	TAP (N = 180)	p-value[1]
Voriconazole	4 (1.0)	162 (92.1)	40 (22.2)	
Posaconazole	358 (90.4)	9 (5.1)	2 (1.1)	
Isavuconazole	30 (7.6)	—	—	
Other[2]	—	5 (2.8)	16 (8.9)	
None	4 (1.0)	—	122 (67.8)	
Pre-transplant KC, N (%)				0.0316
Yes	31 (7.8)	8 (4.5)	5 (2.8)	
No	354 (89.4)	168 (95.5)	175 (97.2)	
Missing/Unavailable	11 (2.8)	—	—	
Post-transplant SCC, N (%)	28 (7.1)	29 (16.5)	34 (18.9)	< .0001
Time to First SCC (years), median (IQR)	1.6 (1.7)	1.4 (0.9)	2.8 (1.7)	< .0001
Total follow-up time (years), median (IQR)	1.4 (2.1)	1.7 (1.9)	3.9 (4.1)	< .0001

SD, standard deviation; KC, keratinocyte cancer; BCC, basal cell carcinoma; SCC, squamous cell carcinoma; RR, relative risk; IQR, interquartile range

[1]p⁻values from chi-square tests for independence (Fisher's exact when appropriate) for categorical variables, Kruskal-Wallis test for continuous variables

[2]Other antifungals include itraconazole and fluconazole.

Table 2

UAP-P Cohort Keratinocyte Cancer and Antifungal Exposure Data

	Overall (N = 396)
Total Patients with Post-transplant KC, N (%)	29 (7.3)
BCC	12 (41.3)
SCC	28 (96.6)
Anatomic Location of First Post-transplant KC, N (%)[1]	
Head/neck or forearms/hands	30 (75.0)
All other sites	8 (20.0)
Unknown	2 (5.0)
Post-transplant Antifungal Use	
Ever posaconazole	393 (99.2)
Ever voriconazole	55 (13.9)
Ever isavuconazole	99 (25.0)
Posaconazole only	264 (66.7)
Posaconazole or voriconazole only	32 (8.1)
Posaconazole or isavuconazole only	73 (18.4)
Relative Risk of KC for Posaconazole	RR (p-value)
Versus voriconazole[2]	0.46 (.0965)
Versus isavuconazole[3]	1.75 (.3560)
Relative Risk of SCC for Posaconazole	RR (p-value)
Versus voriconazole[2]	0.44 (.0774)
Versus isavuconazole[3]	1.66 (.4061)

KC, keratinocyte cancer; BCC, basal cell carcinoma; SCC, squamous cell carcinoma; RR, relative risk

[1]Accounts for multiple KCs diagnosed simultaneously on the same date

[2] Calculated as posaconaozle only / posaconazole and voriconazole only

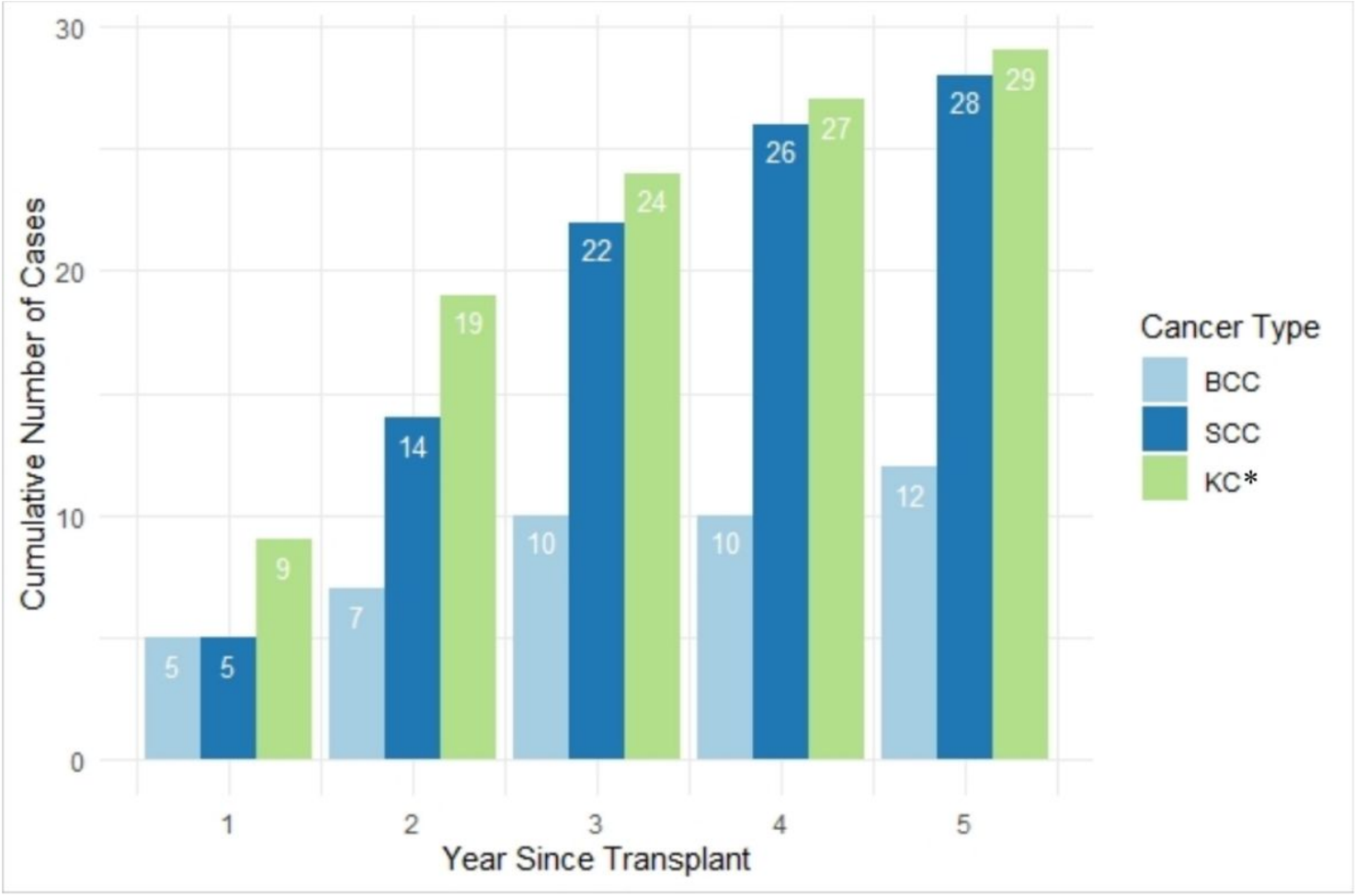
[3] Calculated as posaconaozle only / posaconazole and isavuconazole only

Table 3
Multivariable Proportional Hazards Regression Models for Developing Post-Transplant Squamous Cell Carcinoma

Variable	Reference Category	Hazard Ratio	p-Value
Male Sex	Female	1.55	0.0708
White Race	All Other	7.10	< .0001
Age at Transplant[1]			
55–62 years	≤ 55 Years	2.32	0.0196
63–67 years	≤ 55 Years	1.92	0.0794
> 67 years	≤ 55 Years	2.01	0.0905
UAP-P Cohort	TAP Cohort	0.86	0.6294
UAP-V Cohort	TAP Cohort	2.06	0.0111
Restrictive Parenchymal Lung Disease	All Other	1.25	0.3670
ATG Induction	Basiliximab	0.78	0.3959
Pre-transplant KC	No	3.15	0.0002

ATG, anti-thymocyte globulin; KC, keratinocyte cancer
[1]Age at transplant in quartiles

Figures



*KC is reported as the cumulative number of patients with any post-transplant KC. Patients with both SCC and BCC are only counted once for KC.

Figure 1

Cumulative Number of Patients with Post-Transplant Keratinocyte Cancer in the UAP-P Cohort

Cumulative numbers of patients by post-transplant year with keratinocyte cancer (KC) overall, and for squamous cell carcinoma (SCC) and basal cell carcinoma (BCC). SCC was more common than BCC, and over time, nearly all patients with KC developed SCC.

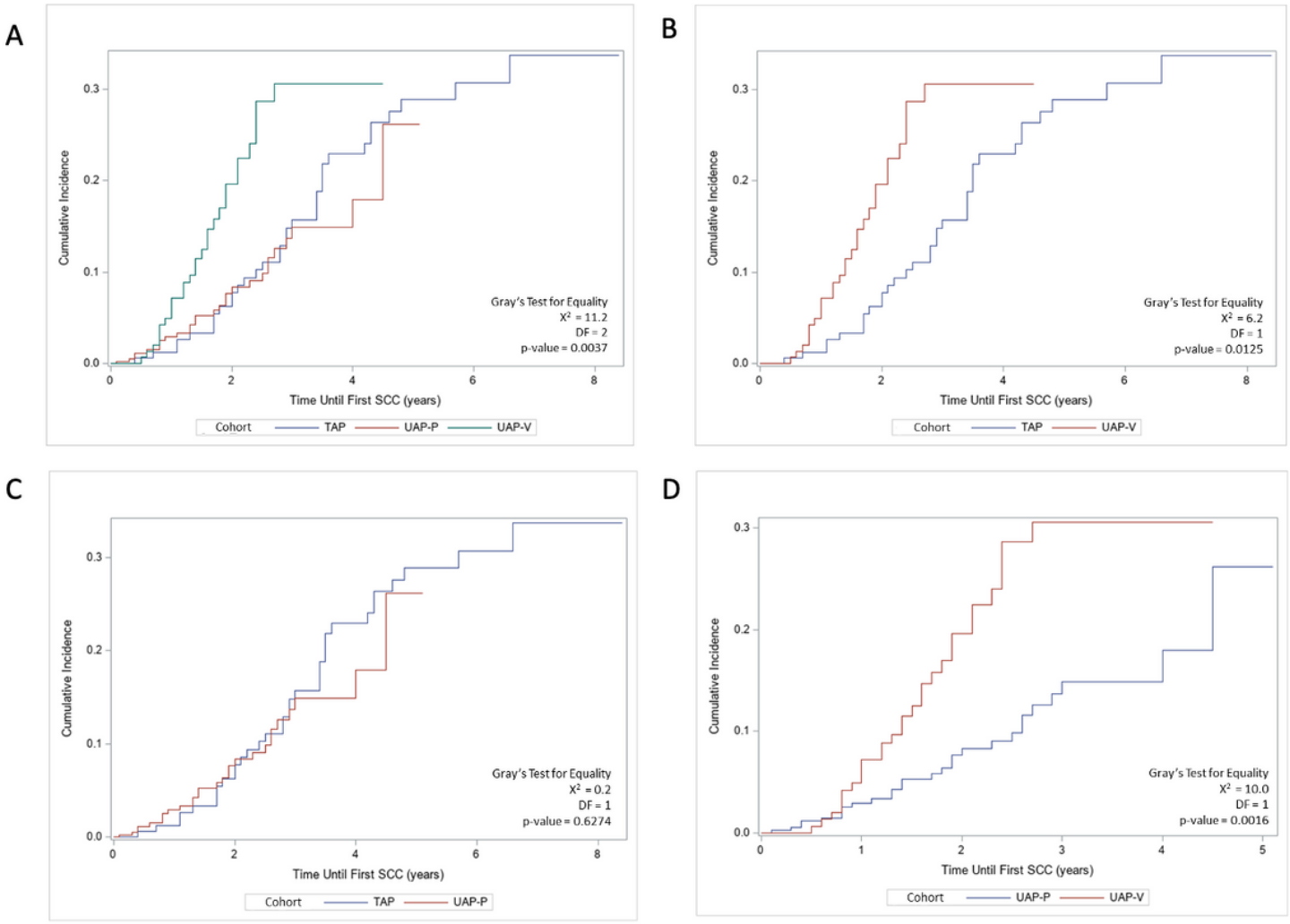


Figure 2

Cumulative Incidences of First Post-Transplant Squamous Cell Carcinoma by Cohort

Cumulative incidence curves of squamous cell carcinoma (SCC) for targeted antifungal prophylaxis (TAP), universal antifungal prophylaxis with voriconazole (UAP-V), and universal antifungal with posaconazole (UAP-P) cohorts. A) all cohorts, B) TAP and UAP-V, C) TAP and UAP-P, and D) UAP-P and UAP-V. The UAP-V cohort had a higher cumulative incidence than the TAP and UAP-V cohorts, whereas the UAP-P and TAP cohorts were not different in their cumulative incidences.

Supplementary Files

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- SupplementalFigure1.docx