**Title:** Squamous Cell Carcinoma of the Skin and Voriconazole Therapy in Lung Transplant Recipients: A Case Series

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**Author contributions**

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**Title:** Squamous Cell Carcinoma of the Skin and Voriconazole Therapy in Lung Transplant Recipients: A Case Series

**Abstract**

Background: Prolonged voriconazole therapy may be associated with skin squamous cell carcinoma (SCC) in lung transplant (LTx) patients. This is of concern given the frequent use of voriconazole in the LTx setting. The impact of voriconazole therapy on the risk of developing skin SCC among an Australian LTx cohort who had an additional risk due to high-level of sun exposure remain unclear.

Aim: This study described the extent and outcomes of new or recurrent skin SCC among LTx patients receiving voriconazole.

Methods: This retrospective cohort study was undertaken at The Alfred Hospital, Australia. Adult LTx recipients with skin SCC who had received voriconazole between 1st July 2003 and 30th June 2010 were included. Medical records and histopathology reports were reviewed. Demographics, clinical characteristics, voriconazole exposure (dose and duration), potential risk factors for skin SCC and manifestations of the skin SCC were recorded. The Naranjo algorithm was used to determine the likelihood of skin SCC being due to voriconazole exposure.

Results: Of the 102 LTx patients receiving voriconazole, 14 (13.7%) had at least one episode of skin SCC: seven (group 1) had skin SCC during or after voriconazole exposure; three (group 2) had skin SCC before commencing voriconazole therapy, which recurred or worsened subsequently; three (group 3) had a history of skin SCC prior to voriconazole being prescribed but no skin SCC was noted during or after voriconazole exposure; and one (group 4) had multiple skin SCCs before LTx and voriconazole use, and developed further skin SCC

post-voriconazole. The median (interquartile range) of voriconazole exposure in group 1, 2 and 3 patients were 119 days (79.5, 693), 1,127 days (665.5, 1129) and 173 days (135.5, 341), respectively. The Naranjo score indicated a probable association between voriconazole use and skin SCC in three patients and a possible relationship in eight.

Conclusions: Prolonged voriconazole exposure may contribute to the development, recurrence and progression of skin SCC in LTx patients.

**Keyword:** voriconazole, lung transplant, skin squamous cell carcinoma

## Introduction

In comparison to the general population, solid organ transplant (SOT) recipients have an increased risk of developing squamous cell carcinoma (SCC), basal cell carcinoma (BCC) and malignant melanoma.[1] The International Society for Heart and Lung Transplantation reported that the incidence of skin malignancy among patients surviving 1, 5 and 10 years post-LTx was 1.0%, 7.8% and 18.2%, respectively.[2]

Several risk factors for developing skin carcinoma among SOT recipients have been identified: high-level of immunosuppression, increased exposure to ultraviolet (UV) radiation, Fitzpatrick skin type I, II, III, advanced age, history of non-melanoma skin cancer or melanoma, and increased number of keratotic skin lesions.[3] The emerging evidence for causal associations between long-term voriconazole exposure and skin SCC[4-11] is of concern given the frequent use of voriconazole prophylaxis, which is commonly administered for months in LTx setting.[12] Also, residing in geographical locations with high-level sun exposure has been identified as an independent risk factor for LTx patients developing skin SCC.[6] Thus, the aim of this case series was to describe the extent and outcomes of new or recurrent skin SCC among LTx recipients who had been prescribed voriconazole, either for prophylactic use or treatment, and to investigate the possible link between skin SCC and voriconazole. This study provides new insights into the impact of voriconazole therapy on the development of skin SCC among Australian LTx cohort, who had an additional risk due to high-level of sun exposure, offering a different perspective from that published by other international LTx centres.

## Methods

This retrospective cohort study was undertaken at The Alfred Hospital, Melbourne, Australia. Adult (i.e. ≥18 years old) LTx patients who had received voriconazole between 1st July 2003 and 30th June 2010 were identified using LTx unit's database and pharmacy dispensing data. Patients' medical records and histopathology reports of biopsy specimens were reviewed. All patient's demographics and clinical characteristics, details of voriconazole exposure (dose and duration), potential risk factors for skin SCC and manifestations of skin SCC were collected by one researcher (CFN) to ensure the consistency of data collection. The Naranjo algorithm (comprising 10 validated questions) was used to determine the association between skin SCC and voriconazole exposure.[13] Each question was assigned a score of +1, +2, 0 or -1 based on the answers (yes, no, unknown or not applicable); the probability of SCC being associated with voriconazole was then determined by the total cumulative score, defined as definite (9-10), probable (5-8), possible (1-4) or doubtful (0).[13] Each patient was followed up from the first onset of skin SCC until 30th June 2011.

The incidence of SCC was self-reported or noted by LTx physicians during review in clinic, and all patients were then referred to dermatology clinic for further follow-up. The study was approved by the Human Research Ethics Committees of The Alfred Hospital and Monash University.

**Immunosuppression protocol and antimicrobial prophylaxis**

Between July 2003 and July 2008, most LTx patients received a cyclosporin-based immunosuppressive regimen post-LTx. From August 2008, tacrolimus replaced cyclosporin. Induction therapy (i.e. immunosuppressant therapy administered usually peri-operatively to reduce the risk of acute rejection and to also delay initiation of maintenance immunosuppression), was not routinely given except in patients with a positive B-cell cross-match or limited renal function. All patients received trimethoprim/sulfamethoxazole (TMP/SMX) for Pneumocystis jirovecii prophylaxis. For cytomegalovirus (CMV) prophylaxis, all at-risk patients received intravenous (IV) ganciclovir, followed by oral valganciclovir ± IV CMV hyperimmuneglobulin, or oral valaciclovir. Administration of voriconazole prophylaxis and treatment were guided by microbiological findings from respiratory specimens, and clinical signs and symptoms.[14]

**Results**

Of the 102 LTx patients receiving voriconazole, 14 (13.7%) had at least one episode of skin SCC: seven had skin SCC during or after voriconazole exposure (group 1); three (2.9%) had skin SCC before commencing voriconazole therapy, which recurred or progressed subsequent to voriconazole administration (group 2); three (2.9%) had a history of skin SCC prior to voriconazole being prescribed but no skin SCC was noted during or after voriconazole exposure (group 3); and one had multiple skin SCC before lung transplantation and voriconazole use, and developed further skin SCC post-voriconazole exposure (group 4).

**Demographics, clinical characteristics and potential risk factors**

Details of the 14 patients are shown in Table 1. All patients were Caucasian, with a median age of 56.5 years at the first skin SCC diagnosis. The majority of the patients were male (10/14, 71.4%). The median (interquartile range) time to first onset of skin SCC was 1,445 (519.5, 2607.5) days post-LTx. All except four patients received standard triple immunosuppressive regimen (i.e. prednisolone, calcineurin inhibitor and anti-metabolite) whilst being prescribed voriconazole (Table 1). During voriconazole therapy, all patients received, concomitantly, a number of photosensitising agents with TMP/SMX being the most common (13/14, 92.8%), followed by statins (6/14, 42.9%). Other potential risk factors for skin SCC are given in Table 1.

**Voriconazole exposure**

Fifteen courses of voriconazole [median (interquartile range) = 2 (1, 3)] were prescribed for group 1 patients, with more than half (8/15) for prophylaxis. The median (interquartile range) cumulative voriconazole dose was 32.1 g (29.8, 199.5) and the median (interquartile range) duration of voriconazole exposure was 119 days (79.5, 693). The median (interquartile range) time to first onset of skin SCC after the first course of voriconazole was 533 days (436, 591). Group 2 patients received a total of five courses of voriconazole, three of which were for prophylaxis. The median (interquartile range) of cumulative dose of voriconazole was 327.8 g (196.3, 389.3) and the median (interquartile range) duration of exposure to voriconazole was 1,127 days (665.5, 1129). Patients in group 3 had a total of six courses of voriconazole, all as prophylaxis. They had lower median (interquartile range) cumulative dose of voriconazole of 39.2 g (36.4, 118.7) and shorter median (interquartile range) duration of voriconazole therapy, 173 days (135.5, 341), compared to group 2 patients. The only patient in group 4 received a cumulative voriconazole dose of 10.0 g over 27 days for prophylaxis.

Serum voriconazole concentrations were monitored in only three patients; median (interquartile range) of 1.35 mg/L (0.8, 1.9) was reported.

**Clinical details of skin SCC, treatments and outcomes**

All patients (n = 14) had their skin SCC lesions surgically excised. Clinical details of skin SCC for the patients in group 1 and group 2 are shown in Table 2. Two patients in group 2 who had invasive skin SCC received radiotherapy. One in group 1 had parotid gland metastasis that required parotidectomy, followed by radiotherapy and chemotherapy with capecitabine. Half of the patients (7/14) died, within a median (range) of 11.6 years (5.8-15.8) post-LTx and 4.2 years (1.8-8.9) post-SCC diagnosis.

**Naranjo algorithm**

According to the Naranjo probability scale, two patients in group 1 and one in group 2 had a score of 5 (probable reaction). The remainder scored in the possible range (a score of 2-4). All group 3 patients had score of 0 (doubtful reaction); while the patient in group 4 had a score of 1 (possible reaction).

**Discussion**

This case series describes a LTx cohort who developed skin SCC lesions after prolonged voriconazole use in an Australian setting. The association between voriconazole therapy and skin SCC has recently been recognised in various immunosuppressed hosts.[4, 5, 7] A strength of the present case series is that it included those who had recurrent or multiple aggressive skin SCC following long-term voriconazole exposure, providing new insights to the current evidence gap.

The most common skin reaction that has been previously reported with the use of voriconazole is drug-related photosensitivity,[15-18] followed by pseudophorphyria,[19, 20] erythematous eruptions,[21] photoaging,[16] Stevens-Johnson syndrome and toxic epidermal necrolysis.[22] The etiology for voriconazole-induced photosensitivity remains unknown. Two mechanisms have been postulated. The photosensitivity reactions could be a direct effect of voriconazole therapy, involving the inhibition of metabolic breakdown of vitamin A (all-trans retinol), leading to an accumulation of phototoxic retinoid compound in the plasma.[23] On the other hand, the phototoxic complications could be an indirect effect of a major

metabolite, voriconazole N-oxide that absorbs the UV A and B spectrum and acts as a vital chromophore.[23]

Patients in earlier publications were reported to have concurrent manifestations of photosensitivity eruptions, followed by multiple actinic keratosis (AK) and skin SCC lesions occurring a few months after the introduction of voriconazole.[4, 5, 7] Thus, it has been speculated that prolonged voriconazole therapy resulted in chronic phototoxicity, which then contributed to the development of skin SCC in transplant patients.[4] Erythema of photo-exposed surfaces, however, was observed in only one patient in our cohort, which preceded the first skin SCC diagnosis by two months.[10] Given the retrospective nature of this study, it is possible that the incidence of voriconazole-induced photosensitivity prior to SCC was not reported in the medical history or by the patients during routine review.

While Singer et al.[8] reported high cumulative voriconazole dose was an independent risk factor for skin SCC in LTx patients, Vadnerker et al.[6] revealed that the occurrence of skin SCC among LTx patients was related to the duration of voriconazole therapy,[6] consistent with Feist et al.[9] and Zwald et al.[11] A recent study revealed that LTx recipients had a 73% increased risk of developing skin SCC post voriconazole exposure; the risk was increased by 3% for each additional 30-day exposure at standard voriconazole dose.[24] In the current case series, the median duration of voriconazole exposure among group 1 patients was approximately 1.5 months longer than the patients in the study by Vadnerker et al., and the median cumulative dose of voriconazole was 46.1 g higher.[6] Similar to Vadnerker et al., the majority of group 1 patients in our cohort had skin SCC lesions located on the head and neck, and were not taking voriconazole at the time of skin SCC diagnosis.[6]

In our cohort, therapeutic drug monitoring (TDM) for voriconazole was conducted in only three patients; none had reported levels above 6 mg/L, the level associated with toxicity.[25] The low uptake of voriconazole TDM is probably due to limited access to timely results (off-site testing), and the lack of clarity related to the role of TDM for voriconazole in LTx recipients during the study period. In recent years, there has been increasing trend towards routine monitoring of serum voriconazole levels among LTx centres.[12] The relationships between voriconazole plasma concentration and skin SCC should be explored in future studies.

Unlike group 1 patients, it appears that group 2 patients had a higher incidence of invasive SCC, with recurrent or progressive skin SCC lesions predominately noted when patients were taking voriconazole. Invasive skin SCC lesions on the scalp with perineural invasion were noted only in case 10 (group 2) following voriconazole prophylaxis. The reason for the differences in skin SCC during or after voriconazole exposure between the two groups cannot be determined. Contributing factors may include the 9-fold increased duration of voriconazole exposure, the 10-fold increased total cumulative dose of voriconazole or the 2-fold longer duration of immunosuppressive therapy among the group 2 patients. More importantly, prolonged use of voriconazole prophylaxis may indicate a more compromised immune system which could have impacted on the risk of developing skin SCC in LTx patients.[10] As such, clinicians should consider discontinuing voriconazole and switching to alternatives such as posaconazole or itraconazole, if prolonged antifungal prophylaxis is required, given the low incidence of skin adverse events associated with these two azoles.[23]

Apart from long-term voriconazole use, high level of sun exposure has been associated with the development of skin SCC in LTx patients.[6] Higher incidence of skin SCC has been noted in areas of significant exposure to UV radiation, a known distinct mutagen of keratinocytes.[6, 23] Australia is one of the countries that has year-round high-level UV radiation,[5] and in our study, all patients had multiple skin SCC lesions located on photo-exposed areas (i.e. scalp, forehead, cheek, lower legs, extensor forearms and dorsum of the hands), in line with other studies.[4, 5] In addition, five patients in this study had extensive sun exposure with a history of sun-burn. The current cohort had a median age of 56.5 years at the first skin SCC diagnosis. Higher rate of skin SCC was noted in older populations;[9] accumulation of high-dose UV radiation over a prolonged period of time could have been the reason behind this observation. In light of this, it would be prudent to give appropriate advice on sun protection (e.g. wear sunscreen and protective clothing) and to undertake prospective skin monitoring in LTx recipients who receive voriconazole therapy for 3 months and above.

Another prominent risk factor for the development of skin SCC among transplant recipients is the level of immunosuppression. Studies have shown that longer duration and more intensive immunosuppressive regimens contribute to a higher risk of developing skin cancer.[1, 3, 26] In our series, all LTx patients had two or more immunosuppressive agents, with a median duration of immunosuppression of nearly 4.0 years prior to the first skin SCC being diagnosed. Unlike the study by Vadnerker et al.,[6] our LTx centre did not routinely use

alemtuzumab induction therapy, which would have further compromised patients' immune systems.

It is possible that the skin SCCs observed in our study were due to patients receiving concomitant photosensitising agents (i.e. TMP/SMX, statins), given the reported association between photosensitising drug exposure and non-melanoma skin carcinoma.[27] However, the types of SCC lesions found in the current cohort are not usually seen with these agents.[4, 28] Additionally, skin carcinoma pre-transplant[9] could be important, such as in case 14, given that this patient had multiple skin SCC lesions before LTx and voriconazole therapy.

In the current study, there were only three patients with a Naranjo score indicating a probable causal relationship between SCC and voriconazole therapy. As this retrospective study has no control arm, the direct causal relationship between drug exposure and skin carcinoma cannot be fully elucidated, but given the clinical implications, further investigation involving large prospective studies is warranted. In summary, prolonged voriconazole exposure may have contributed to the development, recurrence or progression of SCC in LTx patients. The patient who has already had skin SCC should be cause for concern when starting voriconazole as at least 50% of them in this series had recurrence/worsening. The long-term use of voriconazole should be administered with care and routine monitoring for skin SCC should be performed, particularly in those at high risk of skin carcinoma.



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**Table 1** Demographics and clinical characteristics of the LTx patients with skin SCC (n = 14)

| Patient | Age/ gender | Indication for lung transplantation | Voriconazole dose and duration | Immunosuppressant agents during voriconazole use | Other photosensitising agents during voriconazole use | Photosensitivity during voriconazole use | Types of skin cancer lesions* | Survived/ dead at end of follow-up |
|---|---|---|---|---|---|---|---|---|
| (a) Group 1: Had skin SCC during or after voriconazole exposure (n = 7) | | | | | | | | |
| 1† | 45/F | 1) PPH<br>2) BOS<br>3) BOS | 1) 200 mg BD for 397 days<br>2) 200 mg BD for 322 days<br>3) 200 mg BD, then 100 mg BD for 219 days | 1) Pred/Tacro/MMF<br>2) Pred/Tacro/MMF<br>3) Pred/Tacro/Aza | TMP/SMX, Simvastatin | Erythema of photoexposed areas | AK<br>SCC<br>BCC | Dead |
| 2‡ | 66/M | IPF | 1) 200 mg BD for 77 days | 1) Pred/Tacro/MMF | TMP/SMX, atorvastatin | Not documented | AK<br>SCC<br>Bowen's disease<br>BCC | Dead |

**Table 1** Continued

| Patient | Age/ gender | Indication for lung transplantation | Voriconazole dose and duration | Immunosuppressant agents during voriconazole use | Other photosensitising agents during voriconazole use | Photosensitivity during voriconazole use | Types of skin cancer lesions* | Survived/ dead at end of follow-up |
|---|---|---|---|---|---|---|---|---|

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 3†, § | 59/F | Alpha 1-antitrypsin deficiency | 1) 200 mg BD for 7 days<br>2) 100 mg BD , then 200 mg BD for76 days | 1) Pred/Cyclo<br>2) Pred/Cyclo | TMP/SMX | Not documented | SCC<br>Bowen's disease<br>BCC | Dead |
| 4†, \|\| | 51/M | COPD | 1) 200 mg BD for 39 days<br>2) 200 mg BD for 93 days<br>3) 200 mg BD for 317 days | 1) Pred/Cyclo/Aza<br>2) Pred/Tacro/Aza<br>3) Pred/Tacro/Aza/Evero | TMP/SMX, Atorvastatin | Not documented | AK<br>SCC<br>Bowen's disease<br>BCC | Survived |
| 5 | 51/F | Asthma | 1) 200 mg OD for 126 days<br>2) 200 mg OD for 681 days<br>3) 200 mg BD for 145 days | 1) Pred/Tacro<br>2) Pred/Tacro<br>3) Pred/Tacro/MMF | TMP/SMX | Not documented | AK<br>SCC<br>Bowen's disease<br>BCC | Dead |

**Table 1** Continued

| Patient | Age/ gender | Indication for lung transplantation | Voriconazole dose and duration | Immunosuppressant agents during voriconazole use | Other photosensitising agents during voriconazole use | Photosensitivity during voriconazole use | Types of skin cancer lesions* | Survived/ dead at end of follow-up |
|---|---|---|---|---|---|---|---|---|
| 6 | 66/M | COPD | 1) 200 mg BD for 21 days | 1) Pred/Tacro/Aza | TMP/SMX, Atorvastatin | Not documented | AK<br>Bowen's disease | Survived |
| 7† | 53/M | Alpha 1-antitrypsin | 1) 200 mg BD for 45 days<br>2) 100 mg BD, then 50 mg BD | 1) Pred/Cyclo/Aza<br>2) Pred/Tacro | TMP/SMX | Not documented | AK<br>SCC | Survived |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | deficiency | for 74 days | | | | Bowen's disease<br>BCC<br>Lentigo maligna | |

**Table 1** Continued

| Patient | Age/ gender | Indication for lung transplantation | Voriconazole dose and duration | Immunosuppressant agents during voriconazole use | Other photosensitising agents during voriconazole use | Photosensitivity during voriconazole use | Types of skin cancer lesions* | Survived/ dead at end of follow-up |
|---|---|---|---|---|---|---|---|---|
| (b) Group 2: Had skin SCC prior to voriconazole exposure with recurrence or worsened skin SCC when voriconazole was administered (n = 3) | | | | | | | | |
| 8 | 41/M | Secondary pulmonary hypertension | 1) 200 mg BD for 1,127 days | 1) Pred/Tacro/MMF/ Evero | Pravastatin | Not documented | AK<br>SCC<br>Bowen's disease | Survived |
| 9 | 61/M | Emphysema | 1) 200 mg BD, then 100 mg BD for 145 days<br>2) 100 mg BD, then 50 mg BD for 59 days | 1) Pred/Siro<br>2) Pred/Evero | TMP/SMX, Atorvastatin | Not documented | SCC<br>Bowen's disease<br>BCC | Dead |
| 10 | 56/F | Bronchiectasis | 1) 200 mg BD for 217 days<br>2) 100 mg BD, then 150 mg BD | 1) Pred/Tacro/MMF | TMP/SMX | Not documented | SCC<br>Bowen's disease | Survived |

for 914 days

**Table 1** Continued

| Patient | Age/ gender | Indication for lung transplantation | Voriconazole dose and duration | Immunosuppressant agents during voriconazole use | Other photosensitising agents during voriconazole use | Photosensitivity during voriconazole use | Types of skin cancer lesions* | Survived/ dead at end of follow-up |
|---|---|---|---|---|---|---|---|---|
| (c) Group 3: Had skin SCC prior to voriconazole exposure but no recurrence skin SCC after commencing voriconazole (n = 3) | | | | | | | | |
| 11†,§,‖ | 69/M | Bronchiectasis | 1) 100 mg BD for 27 days<br>2) 200 mg BD for 482 days | 1) Pred/Tacro<br>2) Pred/Tacro | TMP/SMX | Not documented | Not Documented | Survived |
| 12 | 57/M | Emphysema | 1) 200 mg BD for 70 days<br>2) 200 mg BD for 28 days | 1) Pred/Cyclo/MMF<br>2) Pred/Cyclo/MMF | TMP/SMX | Not documented | Not Documented | Dead |
| 13 | 60/M | Emphysema | 1) 200 mg BD for 72 days<br>2) 200 mg OD for 101 days | 1) Pred/Cyclo<br>2) Pred/Cyclo | TMP/SMX | Not documented | Not documented | Dead |

**Table 1** Continued

| Patient | Age/ gender | Indication for lung transplantation | Voriconazole dose and duration | Immunosuppressant agents during voriconazole use | Other photosensitising agents during | Photosensitivity during voriconazole | Types of skin cancer lesions* | Survived/ dead at end of |
|---|---|---|---|---|---|---|---|---|

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | voriconazole use | use | | follow-up |
| (d) Group 4: Had skin SCC prior to LTx and voriconazole exposure, and with recurrence skin SCC after voriconazole exposure (n = 1) | | | | | | | | |
| 14‖ | 52/M | COPD | 1) 100 mg BD for 4 days<br>2) 200 mg BD for 23 days | 1) Pred/Cyclo/MMF<br>2) Pred/Cyclo/MMF | TMP/SMX | Not documented | Bowen's disease<br>BCC | Survived |

* Appeared during or after voriconazole exposure

† Had extensive sun exposure or sun-burn prior or during voriconazole therapy

‡ Had an episode of chronic rejection requiring lymphocyte immune globulin

§ Had Fitzpatrick skin type II

‖ Had family or personal history of skin carcinoma

AK = Actinic keratosis; BCC = Basal cell carcinoma: SCC = Squamous cell carcinoma; COPD = Chronic obstructive pulmonary disease; BOS = Bronchiolitis obliterans syndromes; IPF = Idiopathic pulmonary fibrosis; PPH = Primary pulmonary hypertension; Aza = Azathioprine; Cyclo = Cyclosporine; Evero = Everolimus; MMF = Mycophenolate mofetil; Pred = Prednisolone; Siro = Sirolimus; Tacro = Tacrolimus; BD = Twice daily

**Table 2** Details of skin SCC episodes*, †

| | Group 1 patients (n = 7) | Group 2 patients (n = 3) |
|---|---|---|
| Total episodes of skin SCC (median, range) | 37 (5, 1–11) | 16 (5, 4–7) |
| Types of skin SCC lesions while taking voriconazole | | |
| SCC | 1 | 2 |
| SCC in situ (Bowen's disease) | 0 | 3 |
| Types of skin SCC lesions post-voriconazole exposure | | |
| SCC | 6 | 2 |
| SCC in situ (Bowen's disease) | 6 | 2 |
| Location of skin SCC lesions | | |
| Head (e.g. scalp, forehead, ear, lips, nose, eye brow) and neck | 5 | 3 |
| Upper limb (e.g. forearm, hand) | 4 | 1 |
| Trunk (e.g. abdomen, back) | 1 | 0 |
| Lower limb (e.g. leg, foot) | 2 | 0 |
| Invasive or aggressive SCC | 0 | 2 |
| Distant metastasis SCC | 1 | 0 |

* All data are shown as number of patients unless otherwise indicated.

† Details of skin SCC for group 3 patients were not included as no skin SCC was noted during and after voriconazole exposure; while the only one patient in group 4 developed one episode of Bowen's disease post-voriconazole.

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