

INCIDENCE OF CUTANEOUS SQUAMOUS CELL CARCINOMA IN PATIENTS RECEIVING VORICONAZOLE THERAPY FOR CHRONIC PULMONARY ASPERGILLOSIS

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Background

Voriconazole (VORI) has been associated with cutaneous squamous cell carcinoma (cSCC) in transplant recipients, but the risk in the immunocompetent is not known. (1)

Patients with chronic pulmonary aspergillosis (CPA) have chronic lung disease without significant immunosuppression and are often treated with VORI for prolonged periods.(2)

Our aim was to define the risk and clinical presentations of cSCC in patients with CPA treated with VORI.

Methods

All patients with CPA referred to the National Aspergillosis Centre (2009-March 2019) were included retrospectively.

The start of observation was taken as the day VORI was started for patients who received VORI, and the first attendance for patients who did not receive VORI. The last observation point was the last clinic appointment or death for patients who did not develop cSCC, and the date of cSCC diagnosis in those who did.

VORI use was recorded as a binary variable; patients receiving VORI for less than 28 days were considered non-exposed.

Age, sex, underlying diseases, degree of immunosuppression, photosensitivity, mean of the last five VORI levels, location of cSCC, treatment and outcome were recorded for all patients with cSCC.

The crude incidence rate and age-specific incidence rate of cSCC in patients who received VORI were calculated.

Cox regression was performed to compare incidence of cSCC..

Results

❖ 668/1111 patients received VORI. Mean age was 66.6 years (range 21-96) and 42.8 % were female. Mean follow up duration was 29.3 months (IQR 35.0) for patients who did not have VORI and 33.1 months (IQR 42.0) for those who did.

❖ There were 12 cases of cSCC (Table 1). All patients were white and all had photosensitivity prior to cSCC. Mean duration of therapy was 36.7 months and mean time from start of therapy to cancer diagnosis was 47.2 months.

Table 1. Clinical features of cases of cSCC in patients with CPA according to voriconazole use

Age, sex	Underlying condition	VORI duration and mean levels (mg/L) ¹	Time to cSCC	cSCC type and location	Outcome
49, M	Sarcoidosis on prednisolone 5mg	4y 3m 1.92	4y 3m	Moderately differentiated left forehead	Resected. No relapse, Radiotherapy
69, M	Metastatic hepatocellular carcinoma on sorafenib Asthma	4y 6m 4.19	4y	Moderately differentiated scalp	Resected with local flap. Two new scalp SCCs 10m later, resected. New lesions 20m later, awaiting biopsy, died from unrelated cause
69, M	Sarcoidosis on prednisolone 5mg	4y 7m 1.74	4y 7m	Scalp	Resected. No relapse
80, M	COPD	2y 11m 2.04	2y 11m	Right ear, cervical lymph node metastases	Resected. Required plastic surgery with reconstruction
81, M	Bronchiectasis	3y 4m 1.78	3y 4m	Left ear	Resected. Two further SCCs of hand 4y later, awaited resection, died from unrelated cause
67, M	COPD	4y 1m 0.93	4y 1m	Well differentiated right ear	Resected. Recurrence 6m later, resected. SCC on right temple 12m later, resected.
80, M	Non-specific interstitial pneumonia on prednisolone 12.5mg and cyclosporine	7m 1.57	7m	Two lesions. Unknown area	Resected
77, M	Previous TB Right upper lobectomy	3y 8m 2.59	7y 1	Unknown area	Resected
67, M	Lung squamous cell carcinoma treated with cisplatin/etoposide and radiotherapy	4y 5m 3.75	4y 7m	Cheek	Resected
85, M	COPD Bronchiectasis	16 days	6y 7m	Scalp	Resected. Second SCC 6m later, resected. Third SCC 18m later, resected
78, F	COPD Prednisolone 10mg	6 days	4y 11m	Left calf	Resected, required skin graft
75, F	ABPA Bronchiectasis	12 days	6y 1m	Poorly differentiated right cheek	Resected

1. Mean of last five measurements of voriconazole levels before cSCC diagnosis. Levels recorded only for patients for whom voriconazole use had a temporal association with cSCC development (patients 1-9). y: years, m: months, M: male, F: female, cSCC: cutaneous squamous cell carcinoma, VORI: voriconazole

❖ The crude incidence rate was 4.88 per 1000 person/years in patients who received VORI and 2.79 per 1000 person/years in those who did not. Age-adjusted incidence rates on VORI were 13.3 per 1000 person/years in those aged >74, 5.24 per 1000 person/years in those aged 65-74 and 2.33 per 1000 person/years on those younger than 65.

❖ On Cox regression, age (p=0.01, HR 1.09, 95% CI 1.02-1.16) was significantly associated with cSCC. Male gender (p=0.082, HR 3.97, 95% CI 0.84-18.90) and VORI use (p=0.659, HR 1.35, 95% CI 0.35-5.20) were associated with an increased risk but did not reach statistical significance.

Conclusions

- ▶ VORI use beyond 28 days did not lead to a significantly increased risk of cSCC in a large cohort of patients with chronic pulmonary aspergillosis.
- ▶ The degree of immunosuppression may increase the risk of cSCC.
- ▶ Photosensitivity always preceded cancer diagnosis.
- ▶ VORI-related cSCC did not have specific or more aggressive features.
- ▶ There was no link with high VORI serum levels.

References

- 1) Kolaitis NA et al. Transplant Internat 2017;30:41-8
- 2) Denning DW et al. Eur Respir J 2016;47:45-68.

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