RESEARCH LETTER

Fluorouracil and Other Predictors of Morpheaform Basal Cell Carcinoma Among High-Risk Patients: The Veterans Affairs Topical Tretinoin Chemoprevention Trial

Although basal cell carcinoma (BCC) overall is less aggressive than other forms of skin cancer, the morpheaform subtype is particularly concerning because of its benign appearance and aggressive subclinical spread. We sought to evaluate risk factors for its development on the face or ears in a high-risk population of veterans with at least 2 prior keratinocyte carcinomas in the Veterans Affairs Topical Tretinoin Chemoprevention (VATTC) Trial.

Methods | The VATTC Trial included 1131 high-risk veterans followed up for 2 to 6 years, as described elsewhere.1 We determined risk factors for time to first morpheaform BCC (mBCC) within the entire study population via Cox regression (measured by hazard rate ratio [HRR]) and also compared the risk of developing mBCC relative to that of developing nonmorpheaform BCC (nmBCC) via logistic regression (measured by odds ratios [ORs]). All variables with P values < .15 in the univariate models were included in the multivariate backward stepwise regression models. The study was approved by multiple ethics and oversight committees; informed consent was obtained for this study.

Results | Participants had a mean age of 72 years, were followed up for a mean of 3.6 years, and had a mean of 3.6 keratinocyte carcinomas during the 5 years before enrollment. An mBCC developed in 50 participants (10% of those in whom any BCC developed). The 1-, 3-, and 5-year cumulative risks of mBCC were 1.2%, 4.1%, and 5.4%.

In univariate Cox regression, the most important risk factor for mBCC was the number of BCCs in the 5 years before enrollment (HRR, 7.06; P < .001). Other significant predictors included a history of ever using fluorouracil, sun sensitivity, and the number of actinic keratoses at baseline. The Long Beach, California, center was also a positive predictor for mBCC (HRR, 3.53; P = .01). In the multivariate Cox model (Table 1), the number of BCCs in the 5 years before enrollment and a history of ever using fluorouracil were the only 2 predictors of mBCC when study site was not considered. When study site was included, these 2 variables were retained, and the Oklahoma City, Oklahoma, center became a significant predictor.

Univariate logistic regression revealed that the most important risk factor for mBCC vs nmBCC was a history of ever using fluorouracil (OR, 2.49; P = .004). Other significant predictors included the number of BCCs in the 5 years before enrollment and sun sensitivity, but not the number of actinic keratoses at baseline. When study site was considered, the Long Beach center was associated with increased risk of mBCCs vs nmBCCs. In the multivariate logistic regression model (Table 1), a history of ever using fluorouracil was the strongest independent predictor for mBCC vs nmBCCs when study site was not considered (OR, 2.48; P = .009); the number of BCCs in the prior 5 years was marginally significant (P = .050). When study site was included, the Long Beach center was a significant predictor, and the number of BCCs in the prior 5 years was not.

Among patients in whom at least 2 BCCs developed during the study and whose first BCC was morpheaform, the odds were nearly 12 times greater that the second BCC would also be morpheaform compared with patients whose first BCC was nonmorpheaform (Table 2) (P = .002)

Discussion | Patients with a history of treatment with fluorouracil had a higher risk of developing mBCC, even though fluo-

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Table 1. Multivariate Modelsa

<table>
<thead>
<tr>
<th>Predictor</th>
<th>HRR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multivariate Cox regressionb</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not controlling for study site</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BCCs in prior 5 y</td>
<td>9.71 (2.94-32.04)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>History of ever using fluorouracil</td>
<td>2.76 (1.24-6.17)</td>
<td>.01</td>
</tr>
<tr>
<td>Controlling for study site</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BCCs in prior 5 y</td>
<td>10.48 (3.17-34.62)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>History of ever using fluorouracil</td>
<td>2.81 (1.22-2.07)</td>
<td>.001</td>
</tr>
<tr>
<td>Study site 635 (Oklahoma City)</td>
<td>2.58 (1.07-6.21)</td>
<td>.03</td>
</tr>
<tr>
<td>Multivariate logistic regressionb</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not controlling for study site</td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of ever using fluorouracil</td>
<td>2.48 (1.26-4.88)</td>
<td>.009</td>
</tr>
<tr>
<td>BCCs in prior 5 y</td>
<td>2.64 (1.00-6.99)</td>
<td>.050</td>
</tr>
<tr>
<td>Controlling for study site</td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of ever using fluorouracil</td>
<td>2.22 (1.10-4.47)</td>
<td>.02</td>
</tr>
<tr>
<td>Study site 600 (Long Beach, California)</td>
<td>4.42 (2.22-8.81)</td>
<td>&lt; .001</td>
</tr>
</tbody>
</table>

Abbreviations: BCCs, basal cell carcinomas; HRR, hazard rate ratio.

a Multivariate models included variables with P < .15 in the univariate models.
b Cox regression variables included BCCs in prior 5 years, actinic keratoses at baseline, history of ever using fluorouracil, use of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker during the study, sun sensitivity index, ethnicity of grandparents, total occupational decades outdoors in sun at age 30 years or older, total recreational months outside at age 13 to 17 years, use of products with sun protection factor higher than 15 on face or ears in prior 6 months, and the Long Beach and Oklahoma City study sites.

c Logistic regression variables included sex, BCCs in prior 5 years, actinic keratoses at baseline, history of ever using fluorouracil, sun sensitivity index, total recreational months outside at age 13 to 17 years, total recreational months outside in prior 5 years, ethnicity of grandparents, and the Long Beach and Oklahoma City study sites.
Fluorouracil use was not associated with increased risk of BCC overall in this study. Fluorouracil treatment may eliminate some superficial BCCs but leave mBCCs intact, which might explain why fluorouracil was associated with mBCCs but not BCCs overall; it has been shown to be up to 90% effective for superficial BCC. On the other hand, surgery is currently the only recommended treatment for mBCC; less aggressive treatments are not as effective.

Fluorouracil may also have destroyed cancer cells at the surface while deeper pockets remained viable and later proliferated, resulting in mBCCs. Some studies suggested that mBCCs tend to occur on areas of previous nmBCCs.

Strengths of this study include a large sample size of veterans from 6 locations with a mean follow-up duration of 3.6 years. Patients were examined semiannually by board-certified dermatologists. End points were verified by electronic medical records for completeness and by central dermatopathology reviews for diagnosis, which have been shown to be reliable.

Limitations include a study population of primarily elderly men with at least 2 prior keratinocyte carcinomas, which may limit the generalizability of our results. Index event bias may shift results toward the null. We cannot eliminate possible recall bias, although it was minimized because predictors, such as prior BCCs and baseline actinic keratoses, were identified through medical record review and dermatological examination. Prospective ascertainment of variables also minimizes recall bias.

The findings of our study underscore key risk factors for mBCC in a high-risk population. Fluorouracil treatment was associated with increased risk of mBCC in the entire study population and also the subgroup in whom any BCC developed during the study. The possibility that fluorouracil treatment may predispose to development of mBCC warrants further investigation.

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Table 2. Distribution of First and Second Postenrollment BCCs

<table>
<thead>
<tr>
<th>First BCC</th>
<th>Morpheaform</th>
<th>Nonmorpheaform</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morpheaform</td>
<td>4</td>
<td>10</td>
<td>14</td>
</tr>
<tr>
<td>Nonmorpheaform</td>
<td>10</td>
<td>295</td>
<td>305</td>
</tr>
<tr>
<td>Total</td>
<td>14</td>
<td>305</td>
<td>319</td>
</tr>
</tbody>
</table>

Abbreviation: BCC, basal cell carcinoma.

* P = .002 (Fisher exact test); odds ratio, 11.8 (difference in type distribution of second BCC based on type of first BCC).

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Acquisition of data: Xiong, Weinstock.
Analysis of data: All authors.
Drafting of the manuscript: Xiong, Korgavkar, Weinstock.
Critical revision of manuscript for important intellectual content: All authors.
Statistical analysis: Xiong, Weinstock.
Obtained funding: Weinstock.
Administrative, technical, or material support: DiGiovanna, Weinstock.
Study supervision: Weinstock.

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OBSERVATION

Atypical Lentigines in a Man With Mixed African American and White Race/Ethnicity Receiving Long-term Voriconazole Therapy

Voriconazole, an antifungal agent frequently used in systemic fungal infections, has been implicated in phototoxicity and photoaging. Chronic voriconazole phototoxicity and accelerated photoaging may contribute to the development of melanoma and squamous cell carcinoma. We describe the development of multiple lentigines and atypical melanocytic lesions in a dark-skinned man receiving long-term voriconazole therapy.

Report of a Case | A man in his 40s with mixed African American and white race/ethnicity, Fitzpatrick skin type IV, and history of pulmonary sarcoidosis and secondary pulmonary aspergillosis presented for a follow-up dermatologic examination. Unremarkable findings from a skin examination had been noted 3 years previously. The patient returned for dermatologic examination and was noted to have new hyperpigmented lesions on his forearms that were present for a few months. At the time, the patient had been receiving voriconazole, 200 mg twice daily, for 32 months for treatment of his fungal disease. In addition, the patient had a history of long-term prednisone use (varying doses of up to 60 mg/d) since 2008 to manage his pulmonary sarcoidosis. Because of progressively deteriorating pulmonary function and intermittent, worsening hemoptysis, an evaluation for lung transplant was initiated.

The patient had no history of atypical melanocytic lesions, and there was no family history of melanoma. The patient reported sun exposure with no history of increased occupational exposure or sunburns.

Physical examination revealed numerous hyperpigmented macules clinically consistent with lentigines on his face, with darker and multicolored macules on his sun-exposed forearms (Figure 1A). Other signs of chronic sun exposure were absent. Biopsies of the most clinically suspicious hyperpigmented lesions were obtained and were remarkable for epidermal hyperplasia with pigmentation along the basal layer consistent with a lentiginous growth pattern. The largest, darkest lentiginous macule (Figure 1B) demonstrated single atypical melanocytes crowding in the lower epidermal layers without exhibiting a normal nesting pattern (Figure 2), while other lesions had moderate cytologic atypia (not shown). The atypical lesions were excised, and the patient was counseled on appropriate sun protection measures and self-skin examination, with close dermatologic follow-up.

Discussion | Voriconazole inhibits fungal 14 α-demethylase, a cytochrome p450 enzyme essential to ergosterol biosynthesis of fungal cell membranes and is first-line therapy for the treatment of invasive aspergillosis. It has multiple cutaneous adverse effects, including UV-A photosensitivity manifesting as erythema, blistering, pruritus, cheilosis, eczema, and lentigo formation.