Multiple Squamous Cell Carcinomas of the Skin After Therapy With Sorafenib Combined With Tipifarnib

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Background: Keratoacanthomas, as well as an actinic keratosis progressing to squamous cell cancer, have been reported in patients who were treated with sorafenib, a multikinase inhibitor known to suppress the actions of Raf kinase and vascular endothelial growth factor receptor.

Observations: We describe a 70-year-old white woman with metastatic renal cell carcinoma who was treated with a combination of sorafenib and tipifarnib (a farnesyltransferase inhibitor). She had no history of skin cancer. However, within 3 months after starting this therapy, she developed 3 erythematous nodules on her legs. Pathologic examination showed deeply invasive, well-differentiated squamous cell carcinomas. The tumors were excised, and sorafenib-tipifarnib treatment was discontinued. No new lesions have developed to date.

Conclusions: Targeted agents, such as sorafenib and tipifarnib, are increasingly being used in the management of visceral malignant neoplasms. A temporal relationship was observed between the initiation of the targeted treatments and the emergence of these cutaneous cancers. Further study of the mechanisms responsible for the rapid appearance of squamous cell cancers in this setting may provide insights into the pathogenesis of skin tumors.

Arch Dermatol. 2008;144(6):779-782

A 70-year-old woman with no history of skin cancer or actinic keratosis was diagnosed as having clear cell renal cell carcinoma (Fuhrman nuclear grade 3) in 1995. She was disease free for 6 years after undergoing a right nephrectomy and an adrenalectomy. Subsequently, she developed metastases to the breast, lung, lumbar spine, left psoas muscle, and left kidney. She underwent a lumpectomy for the metastatic tumor in the breast and radiation therapy for the metastatic renal cell carcinoma in the lumbar spine and psoas muscle. Thereafter, she underwent other treatment regimens, including interferon alfa, capecitabine, and gemcitabine. Her disease continued to progress, and she was referred to the Phase I Program at the University of Texas M. D. Anderson Cancer Center, Houston. After signing informed consent, she was enrolled in a phase 1
study involving a combination treatment of sorafenib (400 mg by mouth twice a day, every day) and tipifarnib (100 mg by mouth twice a day, 21 days on and 7 days off during a 28-day cycle). On treatment day 8, she developed a diffuse macular erythema with a few urticarial plaques that resolved within 2 weeks after she stopped taking the medications and discontinued treatment with prednisone and diphenhydramine hydrochloride. Therapy with both sorafenib and tipifarnib was restarted at half the previous dosages, and there was no recurrence of the skin reaction.

After 3 months of treatment, an erythematous nodule was observed on the medial aspect of the right calf (Figure 1A). Examination of a punch biopsy specimen showed a deeply invasive, well-differentiated squamous cell carcinoma. Two additional erythematous, ulcerated nodules—ranging in diameter from 0.5 to 1.0 cm—developed within the next 2 weeks: one on the right anteromedial region of the right thigh (Figure 1B) and the other on the left pretibial area. Examination of punch biopsy specimens from both lesions also showed deeply invasive squamous cell carcinoma (Figure 2). The tissue sections were initially evaluated by the head of dermatopathology at the M. D. Anderson Cancer Center (V.G.P.); subsequently, the slides were reviewed by 3 additional senior dermatopathologists (P.R.C., A.H.D., and H.L.E.), each of whom concurred with the pathologic diagnoses.

All of the squamous cell carcinomas were treated by wide local excision; the surgical margins were clear of tumor. The patient requested discontinuation of therapy because of the recurring squamous cell carcinomas, de-

Figure 1. Erythematous nodules on the medial aspect of the right calf (A) and the right anterior thigh area (B). The picture of the lesion on the right calf was taken after biopsy.

Figure 2. Biopsy specimen of invasive squamous cell carcinoma (thigh). A, Low-magnification view shows a proliferation of well-differentiated squamous tumor cells infiltrating the deep dermis (hematoxylin-eosin, original magnification ×8). B, High-magnification view of the invasive tumor cells shows atypical keratinocytes with large nuclei, prominent nucleoli, and frequent mitotic figures (arrow) (hematoxylin-eosin, original magnification ×20).
spite stability in the sizes of her metastatic renal cell carcinoma lesions. Follow-up 1 year after therapy was discontinued showed that the patient had not developed any new squamous cell carcinomas and that she had no recurrences of the excised skin cancers.

**COMMENT**

Cutaneous squamous cell carcinoma arises from the epidermis of the skin or mucous membranes. It can occur either de novo or from preexisting conditions such as actinic keratosis, leukoplakia, scars, burns, or squamous cell carcinoma in situ. OUR elderly patient, who denied sun exposure to her legs, developed 3 deeply invasive, well-differentiated squamous cell carcinomas on her lower extremities within 3 months after starting combination therapy with sorafenib and tipifarnib. She had no history of skin cancer or premalignant cutaneous lesions, and there was no recurrence or development of new squamous cell carcinomas after she discontinued therapy.

There has been a recent report of multiple keratoacanthomas developing in 3 patients who were being treated with sorafenib. Some authors consider keratoacanthomas to be a type of squamous cell carcinoma because they behave as a conventional squamous cell carcinoma and can become invasive. Inflammation of actinic keratoses progressing to a squamous cell neoplasm has also been described in 1 patient who was treated with sorafenib. To our knowledge, this type of dermatologic toxic reaction has not been described in patients treated with tipifarnib (Johnson & Johnson Pharmaceutical Research & Development safety database, data on file, unpublished). Therefore, we suspect that the development of our patient’s multiple squamous cell carcinomas was caused by the use of sorafenib alone. However, it is also possible that the effects of sorafenib were amplified by the concurrent administration of tipifarnib.

Current understanding of the pathogenesis of squamous cell carcinoma describes it as a multistep process induced by cumulative exposure to UV radiation, specifically UV-B. Indeed, several mechanisms for the molecular pathogenesis of squamous cell skin cancers have been postulated: mutation of the gene for p53, alteration of genes by human papillomavirus DNA incorporation, inactivation of p16INK4 tumor suppressor gene cell cycle inhibition by epigenetic changes, activation of the oncogenic Ras gene by mutation, and loss of the Patched (PTCH)-sonic/hedgehog pathway by mutation of the PTCH or SMO (smoothened) gene. Central to each of these hypotheses is alteration by mutation or epigenetic change at the DNA level as a result of UV radiation or human papillomavirus. In our case, the patient denied sun exposure to the affected area, rapidly developed skin cancers after initiation of treatment with sorafenib and tipifarnib, and did not experience the appearance of new tumors or the recurrence of her excised cancers after the treatment was discontinued. Therefore, this case is particularly intriguing because it suggests an alternative mechanism of molecular pathogenesis of squamous cell carcinoma—one that is initiated via the signaling pathways affected by the administered agents.

There are several theories to explain why this patient developed multiple squamous cell carcinomas. Dormant squamous cell precursor cells may be present in the population at high frequency but are kept under control by the immune system. It is conceivable that therapy with sorafenib (with or without tipifarnib) resulted in a heretofore undescribed attenuation of the patient’s immune competence, leading to the emergence of the previously dormant cancer precursor cells. Although the use of both sorafenib and tipifarnib can cause lymphopenia and neutropenia, our patient had no signs of immune deficiency.

Sorafenib and tipifarnib are targeted agents that also affect other signal pathways that are relevant to carcinogenesis. Sorafenib inhibits Raf kinase. Tipifarnib is a farnesyltransferase inhibitor, and the Ras oncogene needs to be farnesylated to be active. Therefore, modulation of the Ras/Raf/mitogen-activated protein kinase/ERK kinase (MEK)/extracellular signal-regulated kinase (ERK) signaling circuit, which is a key intracellular signal transduction pathway, would be expected after the administration of this combination. This pathway and its downstream effectors have been implicated in cutaneous squamous cell carcinogenesis, although their down-regulation would have been expected to suppress tumor formation rather than to induce it.

Sorafenib also targets the vascular endothelial growth factor receptor. Agents that inhibit vascular endothelial growth factor receptor and the binding of vascular endothelial growth factor to its receptors have demonstrated antitumor effects in models of squamous cell carcinoma. However, the role of this receptor in the formation of squamous cell cancers is not known.

In summary, we report the presentation of multiple squamous cell carcinomas that developed rapidly after sorafenib and tipifarnib therapy was initiated in a patient who had no history of skin cancer and who did not have cutaneous tumors or recurrence of her treated squamous cells carcinomas after the therapy was discontinued. Contrary to the current theories on development of squamous cell carcinoma, we hypothesize that, in this case, the pathogenic mechanism likely involved protein signaling rather than genetic alteration. Since sorafenib therapy has now become the standard of care for patients with renal cell cancer, dermatologists and oncologists need to be aware of this potential adverse effect. Furthermore, investigation of this phenomenon is needed, as it may provide new insights into the mechanism of cutaneous squamous cell carcinogenesis.

**Accepted for Publication:** October 21, 2007.

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**Author Contributions:** Dr Hong had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. **Study concept and design:** Hong, Reddy, Prieto, Wright, and Kurzrock. **Acquisition of data:** Hong, Reddy, Prieto, Tannir, Cohen, Evans, and Kurzrock. **Analysis and inter-
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Financial Disclosure: Dr Tannir has been a paid consultant for Novartis, Bayer/Onyx, Wyeth, and Pfizer; has received research funding from Pfizer, Lilly Oncology, and Hoffman La Roche; and has served on the speaker’s bureau for Bayer/Onyx, Wyeth, and Pfizer.

Funding/Support: This study was supported in part by grants TRI 25XS068 (Dr Hong) and 5 U01 CA062461 (Dr Kurzrock) from the National Institutes of Health.

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