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Lack of association between excretion of sorafenib in sweat and hand-foot skin reaction

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Abstract

Study objective—To determine if sweat excretion of sorafenib is associated with hand-foot skin reaction (HFSR).

Design—Prospective pilot study

Setting—Outpatient clinic of a research institution

Patients—Two patients with HFSR (grade 1) and two healthy volunteers

Measurements and Main Results—We measured sorafenib concentrations in sweat samples collected from patients with HFSR using liquid chromatography (LC)/mass spectrometry (MS)/MS. Sorafenib concentrations in these samples were undetectable based on our assay sensitivity of 5 ng/mL.

Conclusion—Our results suggest that HFSR is not associated with excretion of sorafenib in sweat. Further studies are needed to understand the mechanism of HFSR, a treatment-limiting adverse effect of multi-kinase inhibitors.

Keywords

sorafenib; hand-foot skin reaction; hand-foot syndrome; sweat

Introduction

Hand-foot skin reaction (HFSR) is a common toxicity associated with sorafenib. Pain and disability associated with HFSR caused by sorafenib and sunitinib affects up to 62% of patients and can limit treatment dose and duration.^{1–4} In phase II studies, patients treated with sorafenib for prostate cancer and lung cancer experienced dose reductions for HFSR toxicity (10% and 31%, respectively).¹

Similar to HFSR, hand-foot syndrome (HFS) is characterized by acral erythematous plaques and dysesthesia but is associated with certain traditional chemotherapeutics, including cytarabine, liposomal doxorubicin, 5-fluorouracil, and capecitabine. The anatomical distribution and histological changes of eccrine glands observed in traditional HFS have led others to propose that sweat excretion of these toxic drugs is associated with HFS.⁵ HFS

from conventional cytotoxic agents is distinguished from HFSR associated with multi-kinase inhibitors by the tendency of patients with HFS to have more extensive, acute erythema with swelling of the hands, feet, and occasionally intertriginous skin, followed by blistering desquamation. HFSR from multi-kinase inhibitors is often localized to smaller areas of the palms and soles with more superficial blistering and callus formation.

Based on the similar anatomical distribution of HFS from conventional chemotherapies and HFSR from multi-kinase inhibitors, we hypothesized that sweat excretion of sorafenib might play a role in the development of HFSR. We sought to investigate the mechanism of HFSR by analyzing sweat in patients who developed HFSR while on sorafenib. Our ultimate goal is to identify modalities that prevent or treat HFSR.

Methods

Patients and study design

This prospective pilot study was performed in the outpatient clinic of a research institution (Center for Cancer Research, National Cancer Institute (NCI), National Institutes of Health, Bethesda, Maryland). Subjects were recruited under an NCI institutional review board-approved protocol. All participants provided written informed consent.

Patients with sorafenib-associated HFSR grade 1 (Common Terminology Criteria for Adverse Events v3.0) and healthy volunteers were recruited to participate. Sweat was collected from hands of two patients with HFSR: a) a 62-year-old female with ovarian cancer and active grade 1 HFSR on day 30 of sorafenib 200mg twice daily and bevacizumab 5mg/kg biweekly and b) a 62-year-old male with prostate cancer and prior grade 2 HFSR, which improved after treatment was held for grade 3 hypophosphatemia, and with active grade 1 HFSR on day 197 of sorafenib 400mg twice daily. Both patients were taking sorafenib at the time of sweat collection. Sweat samples were also collected from the hands of two healthy volunteers.

Sorafenib plasma levels were collected from the second patient described above. No pharmacokinetic blood samples were collected from the ovarian cancer patient. Neither patient received prior HFS-associated chemotherapeutics.

Sweat collection

Sweat stimulation was conducted by pilocarpine iontophoresis. Sweat was collected through a standard capillary macroduct method that is used for cystic fibrosis sweat-testing (Wescor Macroduct[®] kit, Wescor, Inc., Logan, Utah).⁶ Immediately after collection, sweat was transferred to a small sealable container, which was stored at -80°C .

Quantitation of sorafenib in sweat

A liquid chromatography (LC)/mass spectrometry (MS)/MS method, originally developed and validated for studying sorafenib in plasma⁷ was used for analysis of sweat samples. For this analysis sweat samples were measured against plasma calibrators. Acetonitrile was added to sweat in a ratio of 1:10. Sweat samples from healthy volunteers were spiked with known concentrations of sorafenib (2, 5 and 10 ng/mL) to determine the lower quantifiable limit (LOQ), which was determined to be 5 ng/mL (Figure 1). Sorafenib in sweat samples was found to be stable for at least 180 days, when stored at -80°C .

Results

The chromatograms of sweat samples from sorafenib-treated patients with HFSR did not reveal detectable sorafenib (Figure 2). The sorafenib plasma concentrations for both patients were assumed to be at steady-state based on sorafenib half-life of 25–48 h⁸ and sample collection days of 30 (patient (a) above) and 197 (patient (b) above). The plasma concentration for the patient with prostate cancer was 7468.6 ng/mL during sweat collection.

Discussion

The multi-kinase inhibitors sorafenib and sunitinib are generally well-tolerated and treatment with these agents results in increased progression-free survival in patients with renal cell cancers, gastrointestinal stromal tumors (sunitinib), and hepatocellular carcinomas (sorafenib).^{2–4, 9, 10} HFSR is a common toxicity associated with sorafenib and sunitinib use, and may lead to interruptions in treatment and reductions of doses. In this study, we investigated the sweat excretion of sorafenib to determine if the presence of drug in sweat was associated with HFSR. Our findings indicate that HFSR is not associated with sorafenib sweat concentrations measuring ≤ 5 ng/mL. The results of this study are limited by the number of subjects included and the limit of detection of the assay.

Sorafenib is a lipophilic compound with an experimental hydrophobicity (logP) value of 3.8.¹¹ Eccrine sweat glands are abundant on the palms of the hands and soles of the feet and produce sweat comprised mainly of water, various salts, and minute amounts of lipids, urea and other organic molecules. Based on the composition of sweat, the lipophilicity of sorafenib suggests that this drug is unlikely to be excreted via eccrine sweat glands. Sunitinib, another agent associated with HFSR, is also lipophilic (logP 2.5).¹¹ Conversely, most medications associated with traditional HFS are relatively hydrophilic, including doxorubicin (logP –0.5), fluorouracil (logP –0.8), cytarabine (logP –2.8), hydroxyurea (logP –1.6), and capecitabine (logP 0.4).¹¹ Of note, excretion of doxorubicin in sweat has been associated with HFS.⁵

Histologic examination of HFSR lesions has demonstrated focal horizontal zones of necrotic keratinocytes, dilated blood vessels, mild perivascular lymphohistiocytic inflammation, and eccrine gland abnormalities including dilatation and dysmorphic eccrine cells.^{12, 13} The multi-kinase inhibitors target platelet-derived growth factor receptor (PDGFR) and c-KIT, which are both expressed in eccrine glands. Within the limits of detection, our findings fail to demonstrate an association of HFSR with sorafenib sweat excretion. An alternative hypothesis is that the leakage of drug from blood capillaries damaged by subclinical trauma and inhibition of vascular repair pathways may cause HFSR, which is partly supported by the worsening severity of HFSR with increased activity and friction. Sorafenib and sunitinib are known to target receptor tyrosine kinases expressed by endothelial cells (PDGFR, c-KIT, and vascular endothelial growth factor receptor). Furthermore, combined anti-vascular endothelial growth factor therapy with sorafenib and bevacizumab is associated with a higher incidence of HFSR.¹ However, to our knowledge there are no published studies which confirm this mechanism.

Conclusion

The presence of HFSR in these patients is not associated with sorafenib sweat excretion. Further studies are needed to understand the mechanism of HFSR.

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Figure 1. Chromatograms for sweat samples from healthy volunteers which were externally spiked with three concentrations of sorafenib (A) 2 ng/mL (B) 5 ng/mL and (C) 10 ng/mL. (IS: internal standard).

Fig 2. Chromatograms for sweat samples from (A) patient on day 30 of sorafenib and bevacizumab with grade 1 hand-foot skin reaction (HFSR) and (B) patient on day 197 of sorafenib with grade 1 HFSR.