Case Report: Hand–Foot Syndrome Induced by the Oral Fluoropyrimidine S-1

Shari A. Elasmar, Everardo D. Saad and Paulo M. Hoff

Department of Gastrointestinal Medical Oncology and Digestive Diseases, The University of Texas M. D. Anderson Cancer Center, Houston, Texas, USA

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Hand–foot syndrome (HFS) is a relatively common side effect of fluorouracil (5-FU) chemotherapy that has also been associated with the oral fluoropyrimidine capecitabine. Interestingly, HFS is virtually unknown to result from treatment with UFT, a combination of tegafur and uracil. Tegafur is a prodrug of 5-FU and is a component of S-1, another oral fluoropyrimidine active in a variety of solid tumors. We know of only one previously described case of S-1-induced HFS and the case reported here is the first to provide full documentation of this occurrence. The pathophysiology of chemotherapy-induced HFS remains unknown and very little pathological information is available. Treatment consists of topical emollient therapy, although pyridoxine has occasionally been beneficial. The study of HFS may provide an important insight into the pharmacology of fluoropyrimidines and allow for effective preventive strategies for this side effect of chemotherapy.

INTRODUCTION

S-1 is a novel oral fluoropyrimidine that was developed in Japan and is currently being investigated in Europe and the USA (1). S-1 consists of tegafur, 5-chloro-2,4-dihydroxypyridine (CDHP) and potassium oxonate at a fixed molar ratio of 1:0.4:1. Tegafur is a prodrug of fluorouracil (5-FU), which is the cytotoxic component of this combination. CDHP is a potent reversible inhibitor of dihydropyrimidine dehydrogenase (DPD), the chief catabolic enzyme of 5-FU. Potassium oxonate selectively inhibits orotate phosphoribosyltransferase, the enzyme responsible for 5-FU activation in the gastrointestinal tract, thus reducing the gastrointestinal toxicity of the combination (2). The known adverse effects of S-1 include diarrhea, myelosuppression, nausea, vomiting, stomatitis, anorexia, hyperbilirubinemia and asthenia (1,3–7). Four studies have reported skin rashes associated with S-1 (4–7). Additionally, two of our patients also developed skin rash, which was a diffuse maculopapular erythema in one case and hyperpigmentation in another; none of our patients developed hand–foot syndrome (HFS) after treatment with S-1 (1). Sakata et al. reported a single case of grade 2 HFS in a phase II study of S-1 in 51 patients (5), but we know of no other cases in which S-1 induced this condition.

HFS, also known as palmar–plantar erythrodysesthesia, has been clinically described as a condition affecting the palms of the hands and the soles of the feet. Patients experience various degrees of dysesthesia, painful erythema and edema that may be followed by dry or moist desquamation of the skin involved. In more severe cases, these symptoms interfere with the normal activities of daily living. A grading system for HFS has been developed that incorporates both clinical and functional domains (8). Drugs that have been associated with HFS include 5-FU, capecitabine, cytarabine, doxorubicin, epirubicin, fluorodeoxyuridine (FUDR), hydroxyurea, mercaptopurine, cyclophosphamide, docetaxel and vinorelbine (9). We fully document a case of HFS that was apparently caused by S-1.

CASE REPORT

A 64-year-old female was diagnosed with stage III adenocarcinoma of the sigmoid colon after undergoing a left hemicolectomy in April 1992. She received adjuvant chemotherapy with 5-FU and levamisole for 12 months until April 1993. The patient remained disease-free until December 1995, when liver metastases were discovered on computed tomography (CT) scan. The patient then received two courses of FUDR, cisplatin and interferon by hepatic intra-arterial infusion. She underwent left hepatic lobectomy and cryoablation of a right lobe lesion in March 1996, followed by five courses of intra-arterial 5-FU
and leucovorin. In April 1997, additional CT scans revealed recurrent liver metastases and the patient was treated with two courses of irinotecan in September 1997. In October 1997, CT scans revealed a complete response, but liver metastases were again found in January 1998. The patient underwent radiofrequency ablation of the liver metastases in February 1998 and was followed closely until April 1999, when retroperitoneal lymphadenopathy and pulmonary nodules were detected. On 19 April 1999, she was enrolled in a phase I study of S-1 and initially received the drug at a dosage of 50 mg twice daily. One course consisted of treatment for 5 days, followed by a 2-day rest, for four consecutive weeks. During the first course, she experienced grade 3 nausea and diarrhea, which prompted a dosage reduction to 40 mg twice daily. Thereafter, the patient tolerated the S-1 therapy well. After the eighth course, the clinician noted very mild erythema of the hands that was consistent with grade 1 HFS. After the ninth course, the patient complained of erythema of her palms, fingers and soles. She also stated that the skin on her fingers and on her soles had peeled off and that the underlying dermis felt very stiff and tight. She denied any pain or paraesthesia. Although she was able to sew and button, she related several instances when she had dropped items without feeling it. The clinician who conducted the physical examination noted palmar and plantar erythema and dry desquamation of the palms, fingers and soles that was consistent with grade 2 HFS (Fig. 1). She had no dysesthesia to touch. Because the patient’s only concurrent medications were multivitamins and celecoxib, the HFS was attributed to S-1. The next dose of chemotherapy was withheld and she was instructed to apply lotion to her hands and feet and to take oral vitamin B₁₂. By the time the patient was seen in the clinic 6 days later, her HFS had improved to grade 1. She received the next course of S-1 at 20 mg in the morning and 40 mg in the evening and has not experienced recurrence of HFS to date.

**DISCUSSION**

We report a case of HFS that was apparently induced by S-1. The study of this side effect may help to elucidate the pharmacology of fluoropyrimidines and allow for effective preventive strategies for HFS resulting from chemotherapy.

5-FU has been known to cause HFS since the association was first described by Lokich and Moore in 1984 (10). Compared with bolus infusion, continuous infusion with 5-FU is associated with a higher incidence of this side effect (11). In addition, the continued prolonged exposure to 5-FU provided by the oral administration of capecitabine leads to rates of HFS as high as 68% (8). It is unknown whether HFS induced by fluorinated pyrimidines is due to 5-FU itself or to one of its metabolites (12). Interestingly, HFS is virtually unknown to occur in patients receiving UFT, another oral prodrug of 5-FU that combines tegafur and uracil, a selective inhibitor of DPD, at a fixed molar ratio of 1:4 (13). UFT has been extensively used in Japan and Europe and more recently in the USA. UFT-induced skin toxicity characterized by maculopapular rash has been reported (14). Similarly, the use of oral tegafur alone caused skin rash in 10% of patients treated in an early phase I study (15). In one series of four patients treated with tegafur alone, hyperpigmentation of the extremities appeared during treatment and lasted for ~2 months after discontinuation of tegafur (16). In the same series, biopsies of the skin revealed hyperpigmentation of the basal layer of the epidermis (16).
One patient in our phase I study also developed skin hyperpigmentation (14).

The pathophysiology of HFS is largely unknown and few cases have been investigated with biopsies. Pathological changes described thus far include vacuolar degeneration of basal keratinocytes, dermal perivascular lymphocytic infiltration, apoptotic keratinocytes and dermal edema (17,18). Treatment of HFS consists of topical emollient therapy and discontinuation of the offending drug. Vitamin B₆ (pyridoxine) has been used empirically and there is anecdotal evidence of its efficacy in controlling 5-FU-induced HFS (19,20). In a randomized study of spontaneously occurring canine non-Hodgkin’s lymphoma, pyridoxine was more effective than placebo in preventing or ameliorating liposomal doxorubicin-induced toxicity to the skin (21). We know of only one small controlled study, published in abstract form, that examined the efficacy of pyridoxine in preventing HFS in humans. Twenty-six patients already on therapy with 5-FU received pyridoxine or placebo for prevention of a first episode or recurrent episodes of HFS. More patients in the pyridoxine arm than in the control arm experienced amelioration of symptoms (22).

The incidence of S-1-induced HFS cannot be reliably estimated at this time. None of the 16 patients treated in our first phase I study developed HFS (1) and the only reported case of this side effect occurred among 51 patients with gastric cancer treated in a Japanese phase II study (5). Other phase II studies from Japan have been reported only in abstract form, which did not provide a detailed analysis of toxicity. In these studies, no cases of HFS were described among a total of 53 patients with tumors of the head and neck and breast (23,24). Recently published phase II studies, one with 50 gastric tumor patients and the other with 62 colorectal cancer patients, reported skin rash and pigmentation toxicities but not HFS (6,7).

Our patient developed HFS only after eight cycles of therapy, suggesting a cumulative toxic effect. This theory is supported by the worsening of HFS between courses 8 and 9, which contrasts sharply with our own experience with capcitabine, wherein the HFS was seen predominantly during the first two courses (9). In our study of 41 patients, only two of the 28 patients (7.1%) who developed HFS experienced the first episode after the third cycle of capcitabine.

S-1 should be included in the list of chemotherapy drugs that may cause HFS. Although the incidence is currently unknown, this toxicity seems to be rather uncommon. The pathophysiology of S-1-induced HFS may differ somewhat from that of capcitabine-induced HFS. Continued research may lead to the discovery of more effective strategies to prevent and treat this complication of chemotherapy and allow for a better understanding of the biology and pharmacology of fluoropyrimidines.

References