Can Inhibiting Dihydropyrimidine Dehydrogenase Limit Hand-Foot Syndrome Caused by Fluoropyrimidines?

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Abstract

Hand-foot syndrome (HFS) is a cutaneous adverse event that occurs in some patients treated with fluoropyrimidines. Although it is not life threatening, HFS can severely disrupt the daily lives of patients. HFS appears more frequently with 5-fluorouracil (5-FU) delivered by continuous infusion or with the 5-FU oral derivative capecitabine than with bolus 5-FU therapy. HFS is a leading cause of treatment interruption, dosage reduction, or, even, therapy discontinuation for patients on a capecitabine regimen. Interestingly, addition of a dihydropyrimidine dehydrogenase (DPD) inhibitor, such as uracil, 5-chloro-2,4-dihydroxypyridine, or eniluracil, to the fluoropyrimidine treatment regimen significantly diminishes the incidence of HFS. DPD inhibitors were initially combined with fluoropyrimidines to increase the efficacy of the drugs by impairing the DPD-mediated catabolism of 5-FU. However, with the accumulating findings from clinical trials that show the benefits of DPD inhibition on decreasing the risk of HFS, consideration should be given to changing the recommendations for the treatment of cancer patients with fluoropyrimidines to include DPD inhibitor components as standard therapy.

5-Fluorouracil (5-FU) remains one of the most commonly used cancer chemotherapeutics nearly 50 years after its introduction. 5-FU, alone or in combination therapy, is commonly given for cancers of the head and neck, breast, cervix, and gastrointestinal tract. Incorporation of 5-FU into anabolic pathways within the cell results in cell death, primarily by the conversion of 5-FU into 5FdUMP, which binds and forms a stable complex with thymidylate synthase (1). Further enzymatic activity of thymidylate synthase is impaired, disrupting RNA and DNA synthesis and stability. Numerous adverse side effects have been reported by patients in response to 5-FU treatment, including myelosuppression, cardiac toxicity, mucositis, diarrhea, and hand-foot syndrome (HFS; refs. 2, 3).

In the United States, preferences for 5-FU administration have gradually shifted from bolus i.v. injection to infusion via a pump. However, more recently, orally delivered derivatives and prodrugs have been developed to provide an alternative to the inconvenience of i.v. administration and alleviate some of the adverse side effects that result from the 5-FU treatment regimen (Fig. 1; refs. 3–5). Capecitabine is an oral prodrug that is ultimately converted to 5-FU by thymidine phosphorylase and uridine phosphorylase. Both enzymes have been shown to have elevated expression in solid tumors, allowing for a locally increased concentration of the active drug at the site of the cancer (6, 7). Other 5-FU–based therapies include uracil/tegafur (UFT; molar ratio, 4:1), S-1 [tegafur, 5-chloro-2,4-dihydroxypyridine (CDHP), potassium oxonate; molar ratio, 1:0.4:1], and eniluracil/5-FU treatment, all of which combine 5-FU or its oral derivative, tegafur, with an inhibitor of dihydropyrimidine dehydrogenase (DPD). DPD is the initial and rate-limiting enzyme in the catabolism of endogenous pyrimidines uracil and thymine into β-alanine (8). Likewise, DPD is responsible for the catabolic degradation and removal of >80% of given 5-FU in cancer patients (9). Chemically inhibiting DPD activity with uracil, CDHP, or eniluracil reduces interpatient and intrapatient variability, raises plasma levels of bioavailable 5-FU, and lengthens the time of pharmacologic exposure to the drug.

Both oral and infusional fluoropyrimidine treatments have an improved safety profile when compared with bolus administration of 5-FU. Patients have decreased hematologic and nonhematologic toxicity using capecitabine, UFT, and eniluracil (10–12). However, HFS occurs more frequently in patients treated with capecitabine or on a continuous infusion 5-FU protocol compared with bolus 5-FU administration (2, 10, 13–15). Although HFS is not life threatening, the condition negatively affects quality of life and can severely limit daily activities. Additionally, development of HFS leads to disruption of treatment schedule and often leads to dosage reduction. Whereas dose modification does not seem to significantly influence drug efficacy, in rare cases hospitalization or the discontinuation of capecitabine therapy can result from HFS (16–19). Notably, combination therapy of 5-FU with a DPD inhibitor significantly reduces the occurrence of
HFS, which suggests that the toxicity may be due to a by-product of DPD catabolism of the drug.

**Symptoms and Pathology of HFS**

HFS, or palmar-plantar erythrodysesthesia, is an adverse cutaneous reaction to many chemotherapeutics, but is a common toxicity of fluoropyrimidines and liposomal doxorubicin (15, 20). Symptom grading guidelines have been developed by both the WHO and the National Cancer Institute (14, 15). Grade 1 is characterized by dysesthesia or paresthesia of the palms and soles. With grade 2 symptoms, patients experience discomfort when walking or holding objects and painless redness or swelling. Progression to grade 3 involves painful erythema and swelling that limits normal activity. Grade 4 HFS is defined by desquamation, ulceration, and blistering of the skin, accompanied by severe pain. The recommendation for treatment of HFS entails temporary disruption of therapy until symptoms resolve or decrease to grade 1 (21). When treatment is resumed, a dose reduction is generally required to minimize the chances of the syndrome reoccurring.

HFS is dosage- and schedule-dependent. Continuous infusion administration of 5-FU is associated with a higher incidence of HFS (6.6-71.9%, median 35%; refs. 2, 13, 22, 23) than bolus 5-FU administration (0.5-46.5%, median 6.2%; refs. 2, 12, 13, 16, 17, 22–25). Capecitabine attempts to mimic continuous infusion 5-FU administration through slower, controlled release due to the necessary processing of the drug to an active metabolite. HFS occurs in 15.5% to 68.3% (median, 53.5%) of patients treated with capecitabine (16, 17, 24, 26–29).

The molecular pathophysiology of fluoropyrimidine-induced HFS remains unclear, although several theories on the mechanism of toxicity have been proposed. Expression levels

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**Fig. 1.** Metabolic pathways of capecitabine and tegafur. A, capecitabine is converted into active metabolite in situ by thymidine phosphorylase or uridine phosphorylase. Further 5-FU catabolism is initiated by DPD, eventually yielding FBAL, a catabolite implicated in HFS etiology. B, tegafur is activated by CYP2A6, forming 5-hydroxytegafur, an unstable intermediate which spontaneously converts to 5-FU.
of thymidine phosphorylase and uridine phosphorylase, the enzymes responsible for ultimately converting capecitabine to active 5-FU, have been shown to be elevated in keratinocytes, which could result in inflammation from the accumulation of the drug in skin cells (30–32). Alternatively, capecitabine may be collected and secreted by eccrine sweat glands, which are highly concentrated on the palms and soles (33). Histologic analysis from involved tissues has been reported (34, 35). Punch biopsies from patients experiencing HFS due to liposomal doxorubicin or capecitabine have shown hyperkeratosis, parakeratosis, hypergranulosis, mild perivascular lymphohistiocytic infiltration, and mild vacuolar degeneration in the basal layer of the epidermis. However, the eccrine sweat glands were found to be normal in one patient with capecitabine-induced HFS (35).

Catabolites produced by the metabolism of 5-FU and capecitabine have also been implicated in causing patient toxicities, including HFS. DPD initiates the degradation of bioavailable 5-FU by reducing it to 5,6-dihydro-5-fluorouracil. Dihydropyrimidinase and β-ureidopropionase continue the catabolism, resulting in the formation of α-fluoro-β-alanine (Fig. 1). To investigate their role in HFS etiology, HaCaT cells, a human keratinocyte line, was exposed to these catabolites (4). 5,6-Dihydro-5-fluorouracil and α-fluoro-β-alanine were shown to have minimal cytotoxic effect on HaCaT cells. However, as keratinocyte apoptosis is rarely evident in histologic analysis of HFS patient samples, it is unclear whether this study adequately addresses the effect of 5-FU catabolites on cutaneous tissues. More compelling evidence comes from reports of DPD-deficient patients treated with fluoropyrimidines. Although these patients are at increased risk of severe toxicity from 5-FU and its derivatives, including grade 4 myelosuppression and death, HFS is rarely reported as an adverse side effect in these patients (36). Interestingly, α-fluoro-β-alanine and another 5-FU catabolite, fluoroacetic acid, have also been implicated in causing neurotoxicity (37–39).

**DPD Inhibitors and HFS**

Clinical studies comparing the efficacy and safety of 5-FU to third-generation and fourth-generation derivatives have suggested that inhibiting DPD activity can reduce the incidence of HFS (Fig. 2). Patients treated with continuous infusion 5-FU or capecitabine are consistently reported to have greater risk of developing HFS of all grades (6.6-71.9%, median 35.5%) than patients on DPD inhibitor–associated fluoropyrimidine treatments (0-15%, median 2%; refs. 11, 12, 25, 29, 40–57). Furthermore, HFS induced by continuous infusion 5-FU or capecitabine is more often of grade 3 or grade 4 (2-18%, median 2%; refs. 11, 12, 25, 29, 40–57). Whereas HFS is occasionally caused by UFT, S-1, or 5-FU/eniluracil, it is nearly always grade 1 or grade 2; patients very rarely develop severe HFS when on a UFT, S-1, or 5-FU/eniluracil regimen.

5-FU derivative drugs like UFT and S-1 or combination therapy of 5-FU/eniluracil contain compounds that inhibit DPD to increase levels of the drug available for anabolic pathways by impairing the catabolic pathway. The effect of adding uracil or CDHP to tegafur, a 5-FU derivative, on reducing the incidence of HFS, or similar cutaneous reactions, was shown by several case reports of patients treated with tegafur alone developing HFS (58–60). Uracil in UFT acts as a natural competitor with 5-FU for binding to DPD. S-1 contains CDHP, a reversible inhibitor of DPD that is more potent than uracil. In contrast, eniluracil binds and irreversibly inhibits DPD. Clinical trials using these drugs showed marked reduction in the number of patients presenting with symptoms of HFS.

UFT was developed in Japan in the late 1970s (61). Whereas it is licensed in Japan and much of Europe, UFT has not been approved for use in the United States due, in part, to Food and Drug Administration questions regarding the demonstrable noninferiority of the combination drug compared with 5-FU (62). However, the results of phases II and III studies in the United States and abroad provide evidence that HFS rarely afflicts patients treated with UFT. A phase III trial compared 407 patients receiving bolus 5-FU/leucovorin to 409 patients receiving UFT/leucovorin for metastatic colorectal cancer. Five percent of patients on bolus 5-FU/leucovorin developed HFS, whereas only 2% of patients treated with UFT/leucovorin reported HFS (12). A separate phase III study of 380 metastatic colorectal cancer patients (190 received bolus 5-FU/leucovorin, 190 received UFT/leucovorin) achieved similar results: 2% of 5-FU/leucovorin treated patients reported HFS compared with no cases in the UFT/leucovorin treatment arm (25). In a report of patients treated with oral UFT/leucovorin or bolus 5-FU/leucovorin, none of the 31 advanced colorectal cancer patients completing the study developed HFS (57). Phase II studies of combination therapy of UFT/leucovorin with irinotecan (TEGAFIRI) or oxaliplatin (TEGAFOX) to treat colorectal cancer have also shown minimal incidence of HFS. A trial of TEGAFIRI with 28 patients reported no cases of HFS (41). Likewise, a study of 41 patients alternating between TEGAFIRI and TEGAFOX regimens also reported no cases of HFS (42). More recently, a randomized trial comparing TEGAFIRI to TEGAFIRI reported no HFS on the TEGAFIRI protocol (68 patients), whereas 9.6% of patients on TEGAFIRI (73 patients) reported only grade 1 or grade 2 symptoms (40). Two consecutive phase II trials directly comparing UFT/leucovorin to capecitabine for treating colorectal cancer patients indicated the regimens were of similar efficacy, as measured by time to progression and median survival (29). The incidence of nausea and diarrhea caused by UFT/leucovorin and capecitabine were also similar. However, the study reported no cases of HFS in 77 patients on UFT/leucovorin but 34 cases (54%) in 63 patients treated with capecitabine.

S-1, a combination of tegafur, CDHP, and potassium oxonate, was also developed in Japan over 10 years ago (63). Like UFT, it has not yet been approved for use in the United States. Most phase II studies of S-1 have shown that HFS is a rare side effect, although there have been isolated case reports (56, 64). One trial of 40 colorectal cancer patients administered S-1, of which six developed mild grade 1 HFS (48). Several phase II studies from Japan reported on patients with different solid tumors (51, 52, 56). Only 1 of 51 (2%) gastric cancer patients, 6 of 62 (9.7%) colorectal cancer patients, or 0 of 12 (0%) with gastric, colorectal, or breast cancer reported grade 1 or grade 2 HFS. Rates of HFS were similar in phase II studies of S-1 conducted in Europe with Caucasian patients (53–55). Three of 30 (10%) gastric cancer patients, 4 of 47 (8.5%) colorectal cancer patients, and 0 of 28 patients with a variety of solid tumors developed mild HFS. S-1, in combination with
cisplatin, was used to treat 56 patients with non–small cell lung cancer with no reports of HFS (50). S-1 plus cisplatin was also used to treat 47 gastric and 72 gastroesophageal cancer patients in separate studies. Combined, only three patients reported grade 1 HFS (2.5%; refs. 47, 49).

Eniluracil was studied in the late 1990s and early 2000s as an alternative DPD inhibitor (65). Early trials suggested that 5-FU/eniluracil was effective in treating several types of solid tumors with decreased toxicity. Phase II trials with 33, 106, and 84 breast cancer patients reported grade 1 or grade 2 HFS at a rate of 15%, 5%, and 2%, respectively (43, 45, 46). Similarly, 2 of 55 (4%) colorectal cancer patients and <5% of 45 hepatocellular cancer patients reported grade 1 HFS in phase II studies (11, 44). Despite an improved safety profile, further research was abandoned after two large phase III trials suggested 5-FU/eniluracil had inferior efficacy compared with 5-FU/leucovorin (66, 67). However, Adherex Technologies, Inc., recently began reinvestigating the utility of 5-FU/eniluracil in the clinical setting. Their in vitro studies suggest that the inferior efficacy of eniluracil may be due to dose-dependent competitive inhibition of uridine phosphorylase, a key enzyme in the 5-FU anabolic pathway (68). These results imply that altering the ratio of eniluracil could improve the efficacy to levels equivalent or superior to 5-FU/leucovorin, with decreased toxicity.

**Implications for Treatment**

Inhibition of DPD has emerged as a promising target to reduce the incidence of HFS in cancer patients treated with fluoropyrimidine-based therapy. Although HFS is not life threatening, it can significantly impair a patient’s daily activity and decrease their quality of life (14, 15). Furthermore, with fewer toxic side effects, patients can remain on chemotherapy for a longer period of time, thus deriving greater potential benefit from treatment. Economic analysis also determined that UFT/leucovorin is more cost-effective than 5-FU/leucovorin due to the decreased number of out-patient visits, laboratory resources, and concomitant medications required (69).

Interestingly, two cases of a partially DPD-deficient patients treated with capecitabine developing HFS symptoms have been published (70, 71). Whereas one patient reported mild grade 1 HFS, the other reported a variant form of HFS, with characteristics consistent with grade 3 symptoms on his palms. Both patients had low, but detectable, DPD activity, however.

Because UFT and S-1 were developed and have been primarily used in Asia, investigation of ethnic differences in response rates and toxicity have been minimal. Several studies have suggested that the area under the curve of 5-FU in Caucasian patients treated with S-1 was significantly higher than that of Japanese patients, leading to recommendations that Caucasian patients receive a lower maximum dose of the drug (51, 72, 73). This difference may be due to variations among different ethnicities in the rate of occurrence of polymorphisms in CYP2A6, the cytochrome P450 enzyme responsible for converting tegafur into 5-FU (74, 75). However, other reports have found that the pharmacokinetics for 5-FU were similar in the Japanese and Western patients given tegafur, as part of S-1 or UFT/leucovorin, when the measurements were adjusted for body size (76, 77). Efficacy was similar, and HFS rarely occurred in either population. Whereas enzymatic measurements have suggested the African-American population may have decreased DPD activity compared with a Caucasian control population (78), one center reported that HFS occurred more frequently in African-Americans treated with capecitabine than in Whites (35). Clearly, further research is needed on the efficacy and safety of these drugs, including the incidence of HFS, in patients of different ethnicities.

**Fig. 2.** Incidence of HFS in patients on fluoropyrimidine treatments. **A,** patients treated with continuous infusion 5-FU or capecitabine have significantly higher risk of developing all grades of HFS compared with patients on bolus 5-FU or combination therapy including a DPD inhibitor, like UFT, S-1, or 5-FU/eniluracil. **B,** severe grade 3 or grade 4 symptoms are extremely rare in patients with UFT, S-1, or 5-FU/eniluracil-induced HFS.
Few studies have been published comparing UFT or S-1 with capecitabine, but the available evidence indicates that efficacy rates and toxicity profiles are comparable, except for the significantly lower incidence of HFS with either UFT/leucovorin or S-1 treatment. Future studies should address whether combining capecitabine treatment with a DPD inhibitor could decrease the incidence of HFS. HFS affects a large percentage of patients and is one of the most common dose-limiting toxicities on a capecitabine regimen. Although a degree of dosage modification does not affect capecitabine efficacy for treatment, HFS is a painful adverse side effect, which may be easily eliminated. Alternatively, indication for use of a fluoropyrimidine/DPD inhibitor combination therapy could be beneficial for patients with intolerable HFS while on capecitabine treatment. Additional research would be needed to determine the dosage of capecitabine that could be safely delivered to patients if given in conjunction with a DPD inhibitor. The use of current capecitabine doses with a DPD inhibitor would likely result in severe, life-threatening toxicities.

It should also be noted that chemical DPD inhibitors may also interfere with the anabolic pathways that activate 5-FU. As mentioned previously, eniluracil has been reported recently to interfere with the anabolic pathways that activate 5-FU. As a DPD inhibitor. The use of current capecitabine doses with a DPD inhibitor would likely result in severe, life-threatening toxicities.

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Fluoropyrimidines remain a mainstay of cancer chemotherapy. Innovations and discoveries have led to improved efficacy of 5-FU when given as an infusion, a prodrug, or in a compound with companion agents while making treatments safer and more convenient for patients. Significant toxicities remain, however. Although HFS is among the less serious side effects, it can have considerable negative influence on patient welfare. Mounting evidence suggests that HFS may be caused by products of DPD-initiated catabolic degradation of 5-FU. Newer generation 5-FU drugs incorporating DPD inhibitors have the potential to diminish the incidence and severity of HFS and, thus, improve the standard of care provided to cancer patients.

## Conclusions

Fluoropyrimidines remain a mainstay of cancer chemotherapy. Innovations and discoveries have led to improved efficacy of 5-FU when given as an infusion, a prodrug, or in a compound with companion agents while making treatments safer and more convenient for patients. Significant toxicities remain, however. Although HFS is among the less serious side effects, it can have considerable negative influence on patient welfare. Mounting evidence suggests that HFS may be caused by products of DPD-initiated catabolic degradation of 5-FU. Newer generation 5-FU drugs incorporating DPD inhibitors have the potential to diminish the incidence and severity of HFS and, thus, improve the standard of care provided to cancer patients.

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