

Fluorouracil and the New Oral Fluorinated Pyrimidines

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OBJECTIVE: To briefly review the biotransformation and bioavailability of fluorouracil (5-FU); discuss the effects of dihydropyrimidine dehydrogenase (DpD) on the efficacy and toxicity profiles of 5-FU; and review a new class of drugs known collectively as the oral fluorinated pyrimidines, which inhibit or circumvent DpD activity and, when administered with 5-FU, alter its pharmacokinetic and pharmacodynamic properties.

DATA SOURCES: A MEDLINE literature search was conducted (1966–March 1999), using the search terms fluoropyrimidines, fluorouracil, 5-FU, fluorinated pyrimidines, capecitabine, eniluracil, uracil-tegafur, uracil-ftorafur, UFT, S1, BMS-247616, and BOF-A2. Reference lists, bibliographies of pertinent articles, and abstracts from the American Society of Clinical Oncology and the San Antonio Breast Cancer Symposium annual meetings were also identified and reviewed. Both preclinical and clinical literature were reviewed and analyzed.

DATA SYNTHESIS: The new oral fluorinated pyrimidines appear to produce antitumor activity equivalent or superior to that of intravenously administered 5-FU by achieving higher intratumoral 5-FU concentrations or sustained 5-FU exposure. These agents are generally associated with manageable and non-life-threatening toxicities. The oral route of administration facilitates ease of administration and may reduce total healthcare costs associated with 5-FU-sensitive tumors. More studies are needed to assess the therapeutic and economic benefits of the oral fluorinated pyrimidines.

CONCLUSIONS: The bioavailability, efficacy, and toxicity of 5-FU depend on its catabolic rate-limiting enzyme, DpD. The new oral fluorinated pyrimidines inhibit or circumvent DpD activity and, when combined with 5-FU, increase 5-FU's bioavailability and cytotoxic effects and decrease its toxicities. Results of Phase I and II studies in patients with a variety of malignancies suggest positive outcomes, including greater efficacy, less drug-related toxicity, lower costs related to drug administration, and greater patient convenience.

KEY WORDS: BOF-A2, capecitabine, dihydropyrimidine dehydrogenase, DpD, fluorouracil, fluorinated pyrimidines, fluoropyrimidines, eniluracil, 5-ethynyluracil, uracil-tegafur, uracil-ftorafur.

Ann Pharmacother 2001;35:217-27.

ACPE UNIVERSAL PROGRAM NUMBER: 407-000-01-006-H01

Since its synthesis by Heidelberger et al.¹ more than 40 years ago, fluorouracil (5-FU) has become one of the most widely used anticancer drugs in the US for a variety of common malignancies, including cancers of the colon, breast, skin, and head and neck.²⁻⁴ 5-FU has been used as a component of both first-line chemotherapy regimens and in salvage regimens.² Despite extensive clinical experience with 5-FU and its effective antitumor activity, many concerns remain about the optimal use of this agent. These concerns relate to the toxicities of 5-FU, modest single-

agent response rates, wide inter/inpatient pharmacokinetic variability, and the uncertain biochemical factors responsible for the metabolism of 5-FU. Over the years, investigators⁵⁻⁷ have introduced several methods intended to improve the therapeutic index of this drug, including biomodulation with leucovorin and other agents and various administration schedules. Only in the past few years has a better understanding of the biochemistry and clinical pharmacology of 5-FU and other fluoropyrimidines facilitated new strategies to optimize therapeutic outcomes with these agents.

5-FU is a prodrug, which is subject to both anabolism and catabolism. The cytotoxic activity of 5-FU depends on

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its anabolism to nucleotides, which exert their effects through inhibition of thymidylate synthase activity or incorporation into RNA and/or DNA.⁸ The catabolism of 5-FU has been better understood only in recent years. 5-FU is enzymatically inactivated to 5'-6'-dihydrofluorouracil by the enzyme dihydropyrimidine dehydrogenase (DpD), the initial and rate-limiting enzyme in 5-FU catabolism.² Studies^{5,8} have shown that >85% of administered 5-FU is degraded through the catabolic pathway. It appears that varying DpD concentrations in humans may affect 5-FU bioavailability and account for different responses to 5-FU in cancer patients.⁸ The products of 5-FU catabolism have been linked to several 5-FU toxicities, including neurotoxicity.⁴

The discovery of the importance of DpD in 5-FU metabolism encouraged continuing analysis of this enzyme, resulting in the development of several orally administered compounds that inhibit or circumvent DpD activity. These agents, when combined with 5-FU, have the potential to increase the efficacy of 5-FU and reduce certain toxicities, while offering greater ease of administration. Thus, these compounds may offer increased patient convenience and potential cost reductions.

This review discusses the biotransformation and bioavailability of 5-FU and the role of DpD in the transformation. The five oral fluoropyrimidines that inhibit or circumvent DpD activity are discussed individually, with emphasis on their pharmacokinetic/pharmacodynamic profiles

and the potential advantages they offer for safe and effective delivery of 5-FU.

Biotransformation of Fluorouracil

After administration, 5-FU undergoes a series of anabolic and catabolic reactions. As described in Figure 1, anabolic reactions lead to the formation of cytotoxic nucleotides by three pathways identical to that undergone by uracil (Figure 2) in de novo pyrimidine biosynthesis.⁵

The amount of 5-FU available for anabolism is regulated by its catabolism (catabolism rate greatly exceeds anabolism rate). Approximately 85–90% of each dose of 5-FU is cleared by catabolism in the liver and extrahepatic tissues, and <10% undergoes renal excretion.^{5,8,9} DpD reduces the pyrimidine ring to 5'-6'-dihydrofluorouracil, which eventually results in the formation of the neurotoxic, long-lasting metabolite (half-life [t_{1/2}] = 33 h), fluoro-β-alanine.² The antitumor mechanism of action of 5-FU is a consequence of the formation of 5-fluoro-2'-deoxyuridine-5-monophosphate, which binds to and prevents the formation of thymidine monophosphate and ultimately inhibits DNA synthesis. In addition, anabolism of 5-FU to 5-fluorouridine-5'-triphosphate results in incorporation of that metabolite into RNA, resulting in abnormal RNA processing.⁵ Once catabolized, 5-FU is unable to exert an antitumor effect. Inherent DpD concentrations primarily determine the amount of 5-FU anabolized to active metabolites.

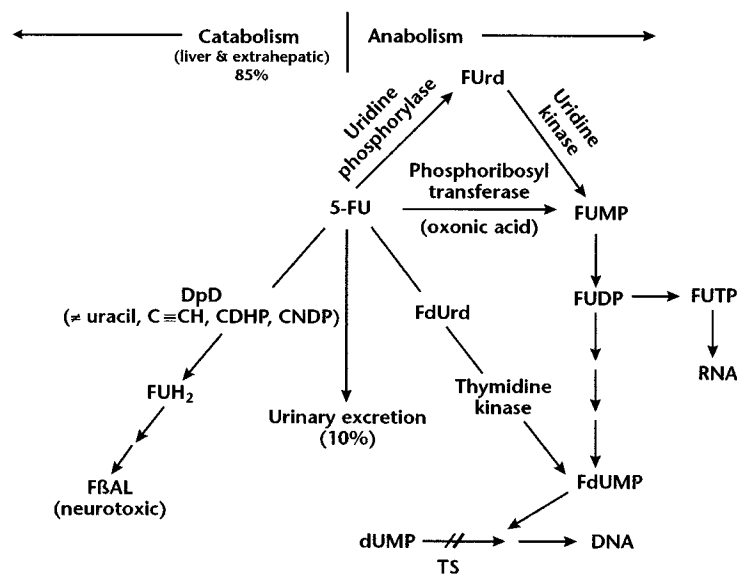


Figure 1. Biotransformation of fluorouracil (5-FU). (1) 5-FU is converted to 5-fluorouridine (FUrd) and 5-fluorouridine-5'-monophosphate (FUMP) by uridine phosphorylase and uridine kinase, respectively. Sequential phosphorylation reactions by corresponding kinases follow, resulting in the formation of 5-fluorouridine-5'-diphosphate (FUDP) and 5-fluorouridine-5'-triphosphate (FUTP), and incorporation into RNA by RNA polymerase; (2) 5-FU is converted directly to FUMP by orotate phosphoribosyltransferase; (3) 5-FU is converted to 5-fluoro-2'-deoxyuridine (FdUrd) by thymidine phosphorylase (TP) and sequentially to 5-fluoro-2'-deoxyuridine-5-monophosphate (FdUMP), which binds to TS and causes inhibition of DNA synthesis and apoptosis. DpD catabolizes >85% of administered 5-FU. DpD is inhibited by uracil, C≡CH, CDHP, and CNDP. C≡CH = ethynyl bond (e.g., 5-ethynyluracil); CDHP = 5-chloro-2,4-dihydroxypyridine; CNDP = 3-cyano-2,6-dihydroxypyridine; DpD = dihydropyrimidine dehydrogenase; FβAL = fluoro-β-alanine; FUH₂ = 5'-6'-dihydrofluorouracil.

Bioavailability of Fluorouracil and the Role of DpD

Although the pKa of 5-FU (8.1) favors absorption in the upper gastrointestinal tract, absorption after oral administration is unpredictable and highly variable in humans. The bioavailability of oral 5-FU has been reported to range from 0% to 80%.² This variation may be due in part to inter/inpatient variations in DpD concentrations, especially in the gastrointestinal mucosa. Significant differences in 5-FU bioavailability have been observed not only in different patients treated with the same oral dose of 5-FU, but also in the same patient after administration of different courses of 5-FU-based therapy.^{2,10}

The bioavailability of 5-FU is also influenced by circadian rhythms; it has been shown^{11,12} that plasma concentrations of 5-FU vary three- to 25-fold depending on the time these concentrations are measured. However, the time of day when peak and trough plasma values occur has been inconsistent between studies.^{11,12} Several investigators^{12,13} have speculated that the inconsistency may be due to a circadian variation in the concentrations of DpD in patients. Indeed, Daher et al.¹⁴ demonstrated

a circadian pattern of DpD activity in human peripheral blood mononuclear cells, with an inverse relationship to plasma 5-FU concentrations.

The wide variations observed in 5-FU clearance, tumor response, and toxicity may be explained in part by genetic differences in DpD concentrations. Severe 5-FU-associated toxicities, including death, have been observed in patients who are DpD deficient.¹⁵⁻¹⁸ Less severe but nonetheless significant toxicities, including myelosuppression, diarrhea, stomatitis, and neurotoxic symptoms, have also been reported after 5-FU therapy in DpD-deficient patients.¹⁹⁻²² Patients who have a homozygous deficiency in DpD are at high risk of developing severe 5-FU toxicity because of a marked reduction in clearance.²³ The $t_{1/2}$ of 5-FU in DpD-deficient patients is extended (>2.5 h vs. 8–22 min), and these patients excrete up to 90% of the dose unchanged in the urine.²¹ Although it is not yet clear whether 5-FU doses can be based on DpD activity, patients with DpD concentrations ≤ 0.1 nmol/min/mg protein appear to be predisposed to severe 5-FU toxicity and may require dose reduction of this agent.²³ Enzyme activity is expressed as nanomoles of total catabolites formed over time per milligram of protein.²² Furthermore, determining DpD activity before administration appears to be prudent because of the potential for severe toxicity.²⁴

In the clinical setting, DpD activity may be assessed with peripheral blood mononuclear cells isolated from heparinized blood; however, this assay is not readily available in most clinical laboratories and is time consuming to perform. Thus, creating a 5-FU product that effectively eliminates or bypasses DpD as a factor in 5-FU metabolism should at least reduce, if not eliminate, these inter/intrapatient variations.

The Oral Fluorinated Pyrimidines

Researchers have endeavored to create compounds that inhibit, inactivate, or circumvent the DpD pathway or enhance the positive effects of 5-FU without increasing its negative effects. Research efforts have resulted in the development of five new agents that appear to enhance the cytotoxic effect of orally administered 5-FU without po-

tentiating the toxic effects. These new, orally administered agents are classified as oral fluorinated pyrimidines, or fluoropyrimidines, and include capecitabine, a 5-FU prodrug that is converted to 5-FU in tumor tissues; eniluracil (ethynyluracil), a selective irreversible inhibitor of DpD; uracil combined with tegafur (ftorafur, FT-207) or UFT, a nonselective DpD inhibitor; and two less well-developed but promising DpD inhibitors, S-1 (BMS-247616) and BOF-A2.

CAPECITABINE

Capecitabine (Xeloda, Hoffman LaRoche, Nutley, NJ), a prodrug of an earlier 5-FU prodrug, 5'-dFUR (doxifluridine; Furtulon, Nippon Roche, Tokyo, Japan), is the first and only oral fluoropyrimidine to be approved for use as second-line therapy in metastatic breast cancer (Figure 3).²⁵ Following oral administration, capecitabine crosses the gastrointestinal mucosal barrier unchanged, reducing the likelihood of gastrointestinal toxicity.²⁶ Once in the liver, capecitabine undergoes sequential conversion to 5'-deoxy-fluorocytidine (5'dFCR) by carboxylesterase, which can then be converted in the presence of hepatic or tumor cytidine deaminase to 5'-dFUR. Within the tumor, 5'-dFUR is converted to 5-FU by the angiogenesis factor thymidine phosphorylase (TP), also called platelet-derived endothelial cell growth factor. Because the final conversion of capecitabine to 5-FU occurs in the tumor, the catabolism of 5-FU in other tissues is bypassed. This, however, does not prevent the catabolism of 5-FU within tumors that contain DpD. A study to determine whether the efficacy of capecitabine and its metabolite 5'-dFUR correlates with DpD and TP in human cancer xenograft models verified that the efficacy of capecitabine depends on the conversion of 5'-dFUR to 5-FU by TP in tumor tissues and, inversely, with tumor DpD concentrations, the enzyme that catabolizes 5-FU to inactive metabolites.²⁷

Capecitabine exhibits dose-linear pharmacokinetics.²⁸ Twelves et al.²⁹ studied the influence of liver dysfunction secondary to liver metastases on the pharmacokinetics of

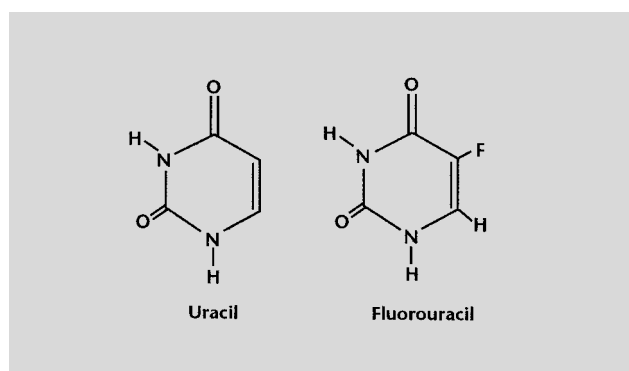


Figure 2. Chemical structures of uracil and fluorouracil.

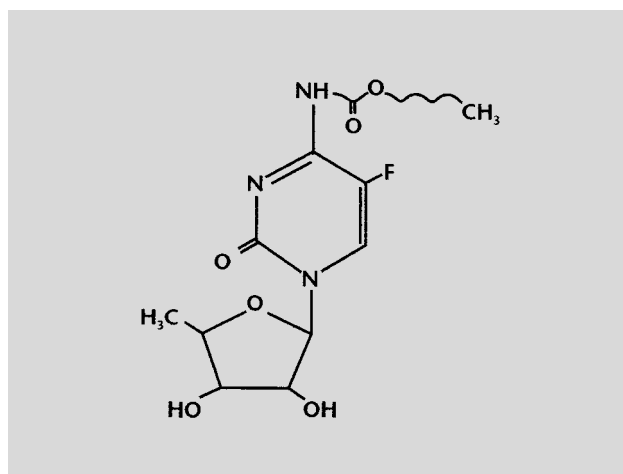


Figure 3. Chemical structure of capecitabine.

capecitabine and its metabolites. In this single-dose study of 14 patients with normal liver biochemistry tests (total bilirubin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase) and 13 with mild to moderate liver damage, plasma concentrations of capecitabine, 5-FU, and 5'-dFUR were higher in patients with liver damage, whereas concentrations of 5'dFCR were lower. However, these effects were not clinically or statistically ($p > 0.07$) significant. Clinicians should use caution when administering capecitabine to patients with mild to moderate hepatic damage; however, no dose adjustments are currently recommended based on results of pretreatment liver biochemical studies.

The complex process of capecitabine metabolism appears to offer several theoretical advantages. First, the 5-FU metabolism is avoided in the gastrointestinal tract, reducing the risk of typical 5-FU-induced gastrointestinal toxicity. Second, because certain tumors contain elevated concentrations of TP, 5-FU is thought to be selectively released in the tumor tissue. Results of a study³⁰ of TP gene expression in colorectal cancer indicated that low concentrations of TP gene expression predicted a high response rate to 5-FU, as well as a longer survival time. The apparent discrepancy between these results and the concept that cells with higher concentrations of TP should be more sensitive to 5-FU may be explained by (1) the regulation of TP protein expression at the translational rather than the gene level, or (2) the conversion of 5'-dFUR to 5-FU being limited by the availability of deoxyribose-1-phosphate in tumors, which has been shown to greatly increase the growth-inhibitory potency of 5-FU. These positive features, however, may be offset by certain negative ones. The concentrations of TP in tumor tissues are highly variable, rendering the conversion of 5-FU in the tumor somewhat unpredictable. Moreover, DpD within the tumor is able to catabolize 5-FU to fluoro- β -alanine, resulting in systemic neurotoxicity. Therefore, the efficacy of capecitabine should theoretically be optimized in tumors with high concentrations of TP and low concentrations of DpD.

Clinical studies of capecitabine in Japan and the US have examined several administration schedules, including a continuous twice-daily dosing schedule,²⁸ as well as intermittent (twice daily for 14 d with a 7-d rest) schedules^{31,32} in multiple solid tumors. Also, capecitabine has been studied as a single agent and in combination with leucovorin.³³ Results of these studies have demonstrated positive antitumor activity in breast and colorectal cancers, at least equal to that produced by conventional 5-FU infusion therapy, with durable responses in many breast cancer patients. The pharmacokinetic parameters of maximum plasma concentration and AUC were found to be predictive of dose-limiting toxicities.³⁴ Dose-limiting toxicities (grade 3 to 4) observed with capecitabine administration in breast and colorectal cancers were diarrhea, nausea/vomiting, abdominal pain, vertigo, and hand-foot syndrome (palmar-plantar erythrodysesthesia).²⁸

Phase II trial results have shown that single-agent capecitabine displays at least comparable efficacy to that pro-

duced by cyclophosphamide, methotrexate, and 5-FU (CMF) combination therapy in patients with advanced breast cancer³¹; additionally, capecitabine was well tolerated when administered to patients with paclitaxel-refractory metastatic breast cancer.³⁵ Moreover, capecitabine activity was comparable to paclitaxel (response rates 36% vs. 21%; median time-to-tumor progression: 92 vs. 95 d) in breast cancer patients and better tolerated in breast cancer patients failing anthracyclines.³⁶ Capecitabine also demonstrated positive antitumor activity in patients with advanced colorectal cancer.³⁷ A dose-finding study by Pronk et al.³⁸ combined capecitabine with docetaxel in 33 patients with colorectal cancer, breast cancer, and cancer of unknown primary origin. Two dose levels were considered tolerable: capecitabine 825 mg/m² given twice daily plus docetaxel 100 mg/m² and capecitabine 1250 mg/m² given twice daily plus docetaxel 75 mg/m². Grades 3 and 4 uncomplicated neutropenia was observed at all dose levels. Nausea and stomatitis were dose limiting at the higher docetaxel doses, and nail dystrophy was problematic with prolonged treatment. Antitumor responses were observed in several tumor types, including colorectal cancer. Combination studies of capecitabine are currently ongoing in breast cancer, colorectal cancer, and other malignancies.

ENILURACIL

Eniluracil (5-ethynyluracil; 776C85, Glaxo Wellcome Inc., Research Triangle Park, NC), a pyrimidine compound with a structure similar to both those of uracil and 5-FU, is a potent inactivator of DpD (Figure 4).³⁹ As a result of this inactivation, eniluracil causes an increase in plasma uracil, which also inhibits the metabolic activity of DpD.⁴⁰ This increase in plasma uracil may potentiate antitumor activity as well as prevent 5-FU toxicity.⁴⁰ The ability of eniluracil to prevent formation of 5-FU catabolites may also contribute to improved efficacy and reduced toxicity.⁴¹ Although eniluracil inactivates DpD rapidly and completely, it does not completely ablate the future production of DpD; recovery to normal concentrations of DpD occurs within a few days following discontinuation of eniluracil.^{42,43}

A Phase I clinical study⁴³ of the safety and pharmacokinetics of eniluracil provided evidence that the bioavailability of 5-FU is increased substantially when 5-FU is administered in combination with eniluracil. The bioavailability of 5-FU combined with eniluracil was $122\% \pm 40\%$ (mean \pm SD) compared with the erratic bioavailability range of 0–80% with 5-FU alone. Interpatient variability in the bioavailability of 5-FU was moderate (coefficient of variation 33%), a marked improvement over 5-FU alone. With the exception of two patients in whom the apparent bioavailability was extraordinarily high (135% and 207%), the variability of oral 5-FU among other patients was much more acceptable (72–122%). The unusually high oral bioavailability may be explained by the administration of lower-than-planned doses, such that intravenous 5-FU dose volumes were extremely small (0.24–0.44 mL). Incomplete injection or adherence of only a small portion of

the infusate to the intravenous tubing could result in an unexpectedly low AUC value following intravenous administration and a fairly sizable error in the calculation of bioavailability. Other possible explanations include 5-FU assay variability and intrasubject variability in 5-FU clearance between intravenous and oral study periods. The $t_{1/2}$ of 5-FU increased from eight to 22 minutes to 4.5 hours with the 5-FU–eniluracil combination. The systemic clearance of 5-FU correlated well with calculated creatinine clearance, which suggests that a renal mechanism of action, rather than the DpD-related liver metabolism, was the principal means of elimination in this study. The principal dose-limiting toxicity was neutropenia, which resolved within seven days.

A Phase I study⁴⁴ consisting of three periods evaluated the safety, pharmacokinetics, and pharmacodynamics of eniluracil in 65 patients with advanced cancer. Patients initially received one of three dosages of eniluracil (0.74, 3.7, or 18.5 mg/m²/d) for seven consecutive days (period 1). After a 14-day washout period, each patient received the assigned initial eniluracil dose daily for three consecutive days with a single intravenous bolus dose of 5-FU (10 mg/m²/d) on day 2. After a second 14-day washout period, patients were treated with the assigned eniluracil dose for seven consecutive days and 5-FU as an intravenous bolus dose on days 2 through 6. The starting dose of 5-FU was escalated until the maximum tolerated dose was determined (period 2). In period 3, oral leucovorin 50 mg on days 2 through 6 was added to determine the maximum tolerated dose of 5-FU with leucovorin in the presence of eniluracil. Several 5-FU doses that can be safely administered with eniluracil with or without leucovorin were identified and recommended for further study. Recommended dosages for further testing using a once-daily for five days schedule were: eniluracil 10 mg/d orally plus 5-FU 25 mg/m²/d intravenously; eniluracil 10 mg/d orally plus 5-FU 20 mg/m²/d intravenously plus leucovorin 50 mg/d orally; and eniluracil 50 mg/d orally plus 5-FU 15 mg/m²/d orally plus leucovorin 50 mg/d orally. Results of this study demonstrated that the maximum tolerated dose of 5-FU, compared with

the conventional dosage of 5-FU (400–600 mg/m²/d), is dramatically decreased (15–25 mg/m²/d) when 5-FU is combined with eniluracil. Measurement of DpD in peripheral blood mononuclear cells showed near-complete DpD inhibition after a single oral dose of eniluracil. The pharmacokinetics of 5-FU in this study are similar to those reported by Baker et al.,⁴³ with a 5-FU $t_{1/2}$ of five to six hours.

A number of Phase II and III studies are evaluating the efficacy of concomitant oral administration of eniluracil and 5-FU in various malignancies, primarily tumors of the gastrointestinal tract.⁴⁵ The purpose of these studies is to determine more predictable and rational dosage regimens for eniluracil plus 5-FU. Encouraging preliminary results have been observed in patients with colorectal cancer receiving a 28-day regimen of oral eniluracil 10 mg twice daily and 5-FU 1–1.15 mg/m² twice daily.⁴⁶

Given the importance of DpD in the metabolism and bioavailability of 5-FU, coadministration of eniluracil with 5-FU could have several beneficial pharmacokinetic and therapeutic outcomes. First, all patients would receive lower doses of 5-FU orally rather than by intermittent bolus or continuous intravenous infusion. Eniluracil's elimination of individual and tumor variations in DpD and the circadian influence on DpD would create a predictable toxicity profile for all patients, especially those who genetically lack DpD, thus increasing the therapeutic index of 5-FU. Additionally, the elimination of 5-FU through predominantly renal excretion instead of hepatic metabolism may contribute to better methods of determining dose adjustments based on renal function. Finally, the antitumor efficacy of 5-FU would be enhanced by shifting its biotransformation from the inactive, neurotoxic catabolic pathway to the active, cytotoxic anabolic pathway.

URACIL/TEGAFUR

UFT (Orzel, Bristol-Meyers Squibb, Princeton, NJ) is an orally administered combination of tegafur and uracil (Figure 5). A prodrug of 5-FU, tegafur is hydroxylated and converted to 5-FU by hepatic microsomal enzymes, leading to a gradual but sustained concentration of 5-FU in tumors.⁴⁷ Uracil biochemically modulates 5-FU by inhibiting DpD, also leading to higher 5-FU concentrations in the blood and enhanced tumor activity.⁴⁸ Unlike eniluracil, which temporarily eliminates DpD, UFT is a competitive inhibitor of DpD, which means that some 5-FU may still be catabolized by DpD. Results of preclinical studies of UFT showed enhanced tumor concentrations of 5-FU and improved antitumor activity.⁴⁸

Japanese investigators^{49–54} studied UFT about 20 years ago, but interpretation of the data was difficult because dissimilar methodologies, criteria, and evaluation standards were used. Results of these studies indicated that UFT was well tolerated and had significant activity in patients with colon, stomach, and breast cancers. Clinical trials of this agent were not initiated in the US until 1990. A number of Phase I trials^{55–61} of UFT have now been conducted in the US and Europe, many of which included patients with co-

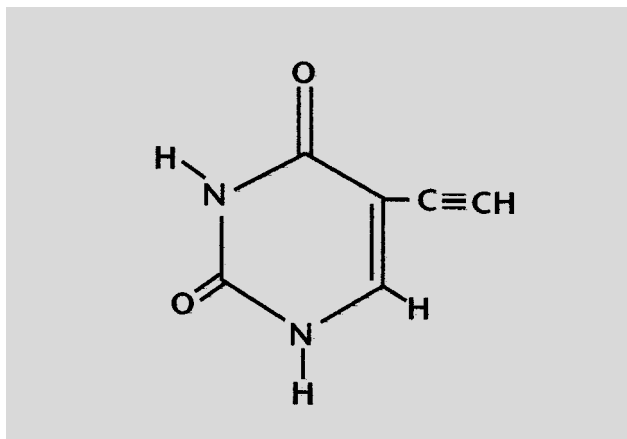


Figure 4. Chemical structure of eniluracil.

lorectal cancer, to evaluate UFT both as a single agent and in combination with leucovorin.

The pharmacokinetics of UFT were analyzed in Phase I, single-agent trials.⁶¹ At all time points, plasma concentrations were highest for tegafur, followed by uracil and 5-FU. Maximum plasma concentrations for tegafur, uracil, and 5-FU were achieved at 0.6–2.1, 0.6–4.1, and 0.7–2.0 hours, respectively. The investigators observed that lower doses of UFT caused more rapid decline of 5-FU and uracil concentrations. In another pharmacokinetic evaluation of UFT,^{57,59} single doses of UFT produced maximum plasma concentrations and AUCs for tegafur, 5-FU, and uracil that increased with escalating UFT doses. 5-FU concentrations were detected throughout a 28-day regimen; however, there was no evidence of significant accumulation of tegafur, uracil, or 5-FU with repeated doses.⁵⁹ Wide interpatient variations in pharmacokinetic parameters of tegafur, uracil, and 5-FU were detected in a Phase I study.⁶⁰ As with intravenous 5-FU, this variability in pharmacokinetic parameters may be related to interpatient variability of DpD. In general, there was no significant difference between the parameters as measured on day 1 or day 28 during treatment. There was, however, significant variation in the maximum plasma concentration and AUC of 5-FU in this study. Results of a Phase II study⁶² of patients with relapsed or refractory colorectal cancer showed that the bioavailability and pharmacokinetics of leucovorin are not affected by concurrent administration of UFT.

Several Phase II studies^{63–66} analyzed the combination of UFT with leucovorin in patients with colorectal cancer. In these trials, patients had received no prior chemotherapy for advanced disease, and they were administered UFT two or three times daily plus oral leucovorin in divided doses, usually on a 28-day regimen. Grade 3 or 4 diarrhea and vomiting were reported in each of these trials; however, myelosuppression occurred minimally or not at all. The results of these studies suggest that oral UFT plus oral leucovorin are generally well tolerated, and responses are

similar to those achieved with intravenous 5-FU plus intravenous leucovorin.

Patients with Dukes' stage B2 or C colon cancer who received UFT and leucovorin as adjuvant therapy experienced overall survival rates of 94% (B2 patients) and 87% (C patients).⁶⁷ After a median follow-up of three years, 11% of stage B2 and 30% of stage C patients relapsed; relapses were not related to dose reductions or early termination of chemotherapy. Mok et al.⁶⁸ conducted a Phase III trial evaluating oral UFT as maintenance therapy after completion of standard adjuvant chemotherapy (5-FU plus levamisole or 5-FU plus leucovorin) in colorectal cancer patients. Preliminary results of this study revealed only modest improvement in the five-year survival rate and the five-year disease-free survival rate in patients treated with a prolonged course of oral UFT following standard adjuvant therapy.

Of the newer oral fluoropyrimidines, UFT has been studied the most extensively. Several randomized, Phase III trials⁴⁷ are currently evaluating an oral UFT–leucovorin regimen compared with parenteral 5-FU–leucovorin in patients with colorectal cancer. These trials are expected to yield results that will offer further insight into the overall efficacy and safety of the oral UFT regimen, as well as its effects on symptomatic relief, quality of life, and pharmacoeconomic outcomes.

S-1

S-1 (BMS-247616; Bristol-Meyers Squibb, Princeton, NJ) is an oral fluoropyrimidine that combines the prodrug tegafur and two 5-FU modulators, 5-chloro-2,4-dihydropyridine (CDHP) and potassium oxonate, in a molar ratio of 1:0.4:1 (Figure 6).⁶⁹ CDHP is 200 times more potent than uracil in inhibiting DpD.⁴⁵ This novel combination of pharmacologic agents results in potent antitumor efficacy and low toxicity.⁷⁰ Exposure to 5-FU following tegafur administration is mediated by hepatic microsomal enzymes, whereas CDHP, a competitive inhibitor of DpD, prolongs 5-FU $t_{1/2}$.⁶⁹ Additionally, preclinical studies have shown that the potassium oxonate component selectively inhibits 5-FU phosphorylation, particularly in the gastrointestinal tract, thus affording protection from the risk of diarrhea and other gastrointestinal toxicities.^{69,71}

In preclinical studies, S-1 demonstrated a significantly higher tumor growth inhibition in human colorectal tumor models implanted in rats compared with UFT ($p < 0.05$); additionally, S-1 significantly increased life span (mean survival for S-1 was 16 d longer than that for the untreated group vs. 8 d longer with UFT).⁷² A Phase I trial of S-1 determined a maximum tolerated dose of 80 mg/m²/d; the dose-limiting toxicity was diarrhea.⁷³

Results of both early Phase II trials of S-1 in patients with advanced gastric cancer⁷⁴ and late Phase II trials in patients with advanced colorectal cancer⁷⁵ confirmed the impressive antitumor effects and mild toxicity of this compound. Ohtsu et al.⁷⁴ reported a 49% overall response rate and a median survival time of 250 days in 51 patients with advanced gastric cancer. Toxicities were generally mild,

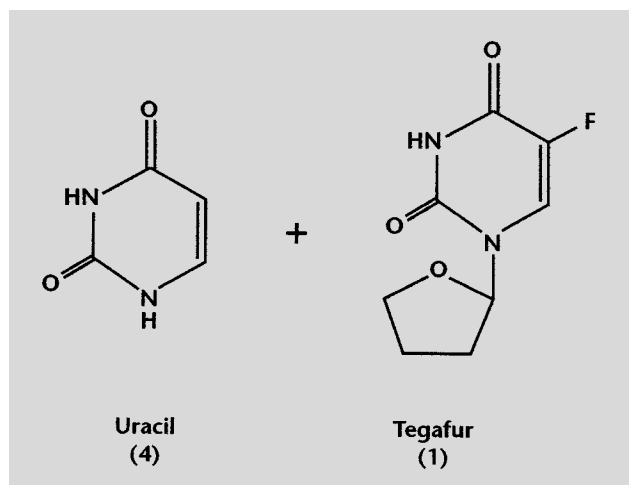


Figure 5. Chemical structure of UFT.

with a 5.8% occurrence of grade 3/4 anemia and neutropenia, as well as a 2.5% incidence of grade 3/4 proteinuria and diarrhea. Baba et al.⁷⁵ evaluated 64 colorectal cancer patients receiving 40, 50, or 60 mg of S-1 twice daily based on body surface area for four consecutive weeks of a six-week cycle; a minimum of two cycles were administered. Of 62 assessable patients, 35.5% responded. Major grade 4 toxicities included leukopenia (4.8%), neutropenia (12.9%), thrombocytopenia (8.1%), anemia (6.5%), and anorexia (4.8%).

Hirata et al.⁷⁶ investigated the pharmacokinetics of S-1 in patients with advanced cancer, using a standard dosage of 80 mg/m²/d in a 28-day oral regimen. Findings of this study indicated that the pharmacokinetics of orally administered S-1 are comparable to those of continuous 5-FU intravenous infusion.

EMITEFUR

A two-drug combination, BOF-A2 (emitefur) consists of the 5-FU prodrug 1-ethoxymethyl 5-fluorouracil (EM-FU) and the DpD inhibitor 3-cyano-2,6-dihydroxypyridine (CNDP) in a 1:1 molar ratio.^{69,77} EM-FU is relatively resistant to degradation and is metabolized to 5-FU by the liver microsomes. In vitro, CNDP is approximately 2000 times more potent than uracil in inhibiting the degradation of 5-FU, without significantly affecting the anabolic pathways of 5-FU.⁴⁵

Results of preclinical investigations⁶⁹ have confirmed antitumor activity of BOF-A2 in murine models and resulted in a prolonged 5-FU $t_{1/2}$. Most clinical studies of BOF-A2 have been performed in Japan; US studies have demonstrated typical 5-FU-related toxicities.^{69,77} Investigators are currently evaluating the optimal dose and schedule, as well as concomitant drug therapy (e.g., leucovorin).

Managing Adverse Effects of Oral Fluoropyrimidines

Toxicities associated with the oral fluoropyrimidines are generally well tolerated. Certain pharmacokinetic considerations determine the pattern of 5-FU toxicity; therefore,

the oral fluoropyrimidines may attenuate toxicities secondary to 5-FU bolus injection.⁷⁷ Moreover, the toxicity profiles may differ between the compounds that compete with or irreversibly inhibit DpD (i.e., UFT, eniluracil, S-1, BOF-A2) and those that do not (i.e., capecitabine).⁷⁷ No comparative trial data are available for the individual oral fluoropyrimidines, and individual toxicity profiles appear to differ among these agents. For example, UFT and leucovorin are not associated with significant myelosuppression, mucositis, hand-foot syndrome, or alopecia; diarrhea is the dose-limiting toxicity. With chronic administration of capecitabine, the dose-limiting toxicities are mucositis, diarrhea, and hand-foot syndrome, which usually occur after approximately one month of therapy. For eniluracil and 5-FU, bone marrow suppression is the dose-limiting toxicity. Early findings suggest that diarrhea is also the dose-limiting toxicity of S-1 and BOF-A2. Although limited data exist to compare toxicity profiles of the oral fluorinated pyrimidines with 5-FU and leucovorin, some observations can be made from clinical trial results. With intermittent bolus injections of 5-FU, the dose-limiting toxicity is myelosuppression, but when given with leucovorin, significant diarrhea, mucositis, and neutropenia occur, of which approximately 20–30% of patients require hospitalization. Delivery of 5-FU by continuous intravenous infusion is associated primarily with stomatitis and hand-foot syndrome.

Table 1 shows the adverse effects reported to occur most frequently with 5-FU and the new oral fluoropyrimidines.^{77,78} Diarrhea, for example, is common with several of the oral fluoropyrimidines as well as with 5-FU. This adverse effect can generally be controlled with standard doses of anti-diarrheals, such as loperamide or octreotide.⁷⁹ Treatment of hand-foot syndrome, a dose-limiting toxicity observed in several clinical trials of capecitabine, is symptomatic and includes the frequent use of hand creams, udder balm, or possibly oral vitamin B₆.^{78,80} Prevention of nausea/vomiting generally includes prophylaxis with an antiemetic, possibly in combination with dexamethasone.⁷⁸ Readers are referred to published practice guidelines for the proper severity grading and treatment options for diarrhea, nausea, and vomiting.^{79,81}

In addition to overall compliance with treatment, patients should be educated about the major adverse effects associated with individual chemotherapeutic regimens and taught to alert their caregivers of related changes.

Therapeutic and Economic Implications

The conventional routes of administration of 5-FU are bolus injection and continuous infusion. Although continuous infusion of 5-FU is believed to be more efficacious because of prolonged tumor exposure to the drug, this route of administration is also more expensive and less convenient than bolus injection. In the past, oral administration of 5-FU was avoided

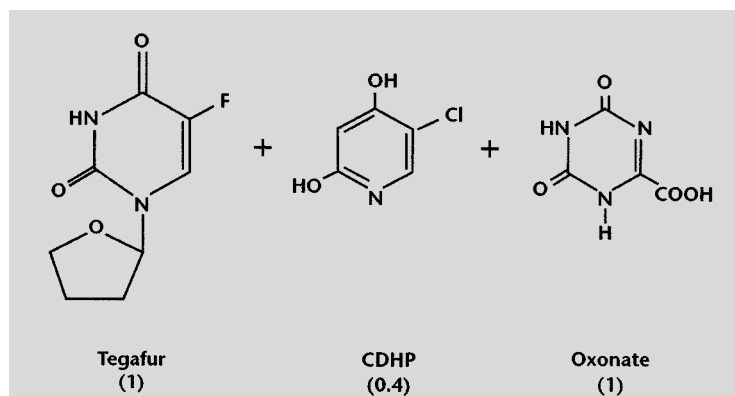


Figure 6. Chemical structure of S-1. CDHP = 5-chloro-2,4-dihydroxypyridine.

because it is poorly absorbed and has erratic bioavailability. The oral fluoropyrimidines, which effectively inhibit or circumvent DpD activity, improve the therapeutic index of 5-FU by prolonging 5-FU exposure and facilitating reduced toxicities through their altered pharmacokinetic/pharmacodynamic profiles. In addition to fewer toxicity-related treatment costs, these new agents will eliminate the equipment and labor required for continuous intravenous infusion of 5-FU, and thus lower costs. Overall, oral 5-FU-containing chemotherapy regimens are expected to be more easily implemented and less expensive, as well as more convenient for patients. Additional issues related to cost, such as reimbursement and patient compliance, need to be addressed in the near future.

Summary

5-FU was introduced more than 40 years ago and continues to be widely used for a number of common malignancies. The traditional route of administration for 5-FU has been intravenous, either by bolus injection or continuous infusion; oral administration of 5-FU has resulted in erratic absorption and relatively poor clinical results because of the effects of the rate-limiting enzyme DpD on its catabolism. During the last few decades, much has been learned about the metabolic pathways of 5-FU, including the effects of the DpD enzyme on the pharmacokinetics, efficacy, and toxicity of 5-FU administration. This research resulted in the recent discovery and development of new oral fluoropyrimidine modulators and prodrugs that inhibit or bypass the catabolic activity of DpD, thus enhancing the efficacy of 5-FU and simplifying its administration.

Results of preclinical and clinical studies suggest beneficial pharmacokinetic and therapeutic outcomes with the oral fluoropyrimidines. These compounds appear to produce antitumor activity superior to that of intravenous 5-FU by achieving higher intratumoral 5-FU concentrations or sustained 5-FU exposure at lower peak concentrations than those observed with intravenous bolus schedules of 5-FU. These protracted oral administration schedules reduce the occurrence of toxic effects associated with high-peak plasma concentrations such as neutropenia and stomatitis. Most of the new oral fluoropyrimidines demonstrate linear

pharmacokinetics of 5-FU, approximating the less myelosuppressive continuous intravenous infusion schedule without the use of infusion catheters and pumps. Additionally, these agents are generally associated with manageable and non-life-threatening toxicities. The enhanced antitumor efficacy, prolonged exposure to 5-FU, and convenient use that characterize the oral fluoropyrimidines translate to potentially positive clinical outcomes. Although more studies are needed to evaluate the pharmacoeconomics of the oral fluoropyrimidines, preliminary data suggest that these therapies may be economically beneficial because of reduced administration costs and toxicity-related hospitalizations.

These new agents appear to have efficacy in the treatment of several solid tumors, primarily breast and gastrointestinal cancers, and will need to be further evaluated in Phase III trials to determine whether they confer equivalent or superior survival compared with traditional 5-FU regimens. The choice of which oral fluoropyrimidine to use must be guided by both the patient's physiologic profile and the tumor's biological profile. For example, patients with renal insufficiency with 5-FU and DpD inhibitors require a dose adjustment of 5-FU because, in the face of DpD inhibition, 5-FU clearance is almost entirely renal. Additionally, tumors that overexpress DpD may benefit most from 5-FU paired with a DpD inhibitor, while those that overexpress TP might be most sensitive to capecitabine. At the very least, the oral fluoropyrimidines have the potential to provide convenience of treatment, a more favorable toxicity profile, and equivalent antitumor efficacy compared with current 5-FU regimens.

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Table 1. Common Adverse Effects of 5-FU and Oral Fluoropyrimidines^a

Adverse Effect	5-FU	Capecitabine	Eniluracil	UFT	S-1	BOF-A2
Diarrhea	X	X	X	X	X	X
Nausea/vomiting	X	X	X			X
Neutropenia	X		X		X	
Mucositis and stomatitis	X	X				
Hand-foot syndrome		X				
Anemia					X	

5-FU = fluorouracil; UFT = uracil + tegafur.
^aAdapted from MacDonald⁷⁷ and Berg.⁷⁸

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EXTRACTO

OBJETIVO: Discutir brevemente la biotransformación y biodisponibilidad de 5-fluorouracilo (5-FU), discutir los efectos de la dehidrogenasa de dihidropiridina (DpD), y reseñar un nuevo grupo de fármacos conocidos en su conjunto como pirimidinas fluoradas orales las cuales inhiben o evitan la actividad de la DpD y que cuando se administran con 5-FU varían las propiedades farmacocinéticas y farmacodinámicas de éste.

MÉTODOS: Se llevó a cabo una búsqueda bibliográfica (1966–1999) a través de MEDLINE utilizando los siguientes términos de búsqueda: fluoropyrimidines, 5-fluorouracil, 5-FU, fluorinated pyrimidines, capecitabine, emiluracil, uracil-tegafur, uracil-florafur (UFT), S1, BMS-247616, y BOF-A2. También se localizaron y revisaron las listas de referencias bibliográficas de los artículos correspondientes y los resúmenes de los congresos anuales de la American Society of Clinical Oncology y del San Antonio Breast Cancer Symposium. Se revisó y analizó tanto la literatura preclínica como clínica.

HALLAZGOS Y DISCUSIÓN: La biodisponibilidad, eficacia, y toxicidad de 5-FU depende de su enzima catabólico-limitante DpD. Las nuevas pirimidinas fluoradas inhiben o evitan la actividad de DpD y, cuando se combinan con 5-FU, aumentan la biodisponibilidad y efectos citotóxicos de éste y disminuyen su toxicidad. Los resultados de los estudios de fases I y II en pacientes con diversos tipos de cáncer sugieren resultados positivos que incluyen una mayor eficacia, menor toxicidad relativa al producto, menor costo de tratamiento con el fármaco, y un grado mayor de conveniencia para el paciente.

CONCLUSIONES: Las nuevas pirimidinas fluoradas orales parecen producir una actividad contra tumores equivalente o superior a la de 5-FU administrado por vía intravenosa, alcanzando niveles intratoracales de 5-FU más altos o una exposición más sostenida al 5-FU. Estos agentes están generalmente asociados con perfiles de toxicidad manejables y que no comprometen la vida. La vía de administración oral facilitará la administración del fármaco y puede reducir el costo total del tratamiento de los tumores sensibles al 5-FU. Es necesario realizar más estudios para certificar el beneficio terapéutico y económico de las pirimidinas fluoradas orales.

Homero A Monsanto

RÉSUMÉ

OBJECTIF: Revoir les données relatives à la biotransformation et à la biodisponibilité du 5-fluorouracile (5-FU); discuter des effets de la dihydropyrimidine déshydrogénase (DpD) sur l'efficacité et la toxicité du 5-FU et passer en revue une nouvelle classe de médicaments connus sous le nom de fluoropyrimidines orales, lesquelles inhibent ou contournent l'activité de la DpD et qui, lorsqu'elles sont administrées avec le 5-FU, en modifient les propriétés pharmacocinétiques et pharmacodynamiques.

MÉTHODES: Une recherche MEDLINE couvrant la période 1966–1999 a été effectuée. Les termes de recherche utilisés ont été : fluoropyrimidines, 5-fluorouracile, 5-FU, pyrimidines fluorées,

capécitabine, eniluracile, uracile-tegafur, uracile-ftorafur (UFT), S1, BMS-247616, et BOF-A2. Des listes de références, des bibliographies d'articles ainsi que des résumés de la Société américaine d'oncologie clinique et du symposium annuel de San Antonio sur le cancer du sein ont été passés en revue. Les données provenant de la documentation scientifique préclinique et clinique ont également été revues et analysées.

RÉSULTATS: La biodisponibilité, l'efficacité et la toxicité du 5-FU dépendent de l'enzyme DpD. Les nouvelles fluoropyrimidines orales inhibent ou contournent l'activité de la DpD et lorsqu'elles sont combinées au 5-FU, en augmentent la biodisponibilité, les effets cytotoxiques et en réduisent les effets indésirables. Les résultats d'études de phases I et II chez des patients atteints de divers cancers suggèrent des effets positifs, incluant une plus grande efficacité, une plus faible

incidence d'effets indésirables, des coûts d'administration moins élevés et une plus grande facilité d'utilisation pour le patient.

DISCUSSION: Les nouvelles fluoropyrimidines orales produisent une activité antitumorale équivalente, voire même supérieure à celle du 5-FU administré par voie intraveineuse, en permettant l'atteinte de taux intratumoraux plus élevés de 5-FU ou en favorisant une exposition continue au 5-FU. L'utilisation de ces médicaments est généralement associée à la survenue d'effets indésirables traitables et non menaçants pour la vie du malade. La voie orale facilite l'administration et peut contribuer à réduire le coût total du traitement des tumeurs sensibles au 5-FU. D'autres études sont requises afin d'évaluer les bénéfices thérapeutiques et économiques des fluoropyrimidines orales.

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