Minireview

The Oral Fluoropyrimidines in Cancer Chemotherapy

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Abstract

A classic example of a rationally developed class of anticancer drugs, the fluoropyrimidines are now the focus of further rational approaches to cancer chemotherapy as they are transformed into oral formulations. Given alone, oral 5-fluorouracil (5-FU) has erratic absorption and nonlinear pharmacokinetics. However, when oral 5-FU is given as a prodrug and/or paired with a dihydropyrimidine dehydrogenase inhibitor, the resultant 5-FU has linear pharmacokinetics that may approximate the less myelosuppressive continuous i.v. infusion schedule of 5-FU administration without the use of infusion catheters and pumps. We review the preclinical and clinical experience of several of the oral fluoropyrimidines.

Introduction

A classic example of a rationally developed class of anticancer drugs, the fluoropyrimidines are now the focus of further rational approaches to cancer chemotherapy as they are transformed into oral formulations. Modestly effective in the treatment of solid tumors, the fluoropyrimidines are now being refashioned into oral preparations in an attempt to both improve their anticancer activity and minimize their toxicity. This article describes the efforts toward refashioning the most common fluoropyrimidine, 5-FU, into pharmacokinetically predictable oral forms and describes the preclinical and clinical outcomes of those efforts.

5-FU Pharmacokinetics

First synthesized by Heidelberger in the 1950s in an attempt to exploit the increased avidity of tumor cells for uracil, the antimetabolite 5-FU exerts its antitumor effects through several mechanisms including inhibition of RNA synthesis and function, inhibition of thymidylate synthase activity, and incorporation into DNA, leading to DNA strand breaks (1, 2). Until recently, the primary route of administration of 5-FU has been i.v. because of problems with oral dosing. Orally-administered 5-FU is associated with erratic and unpredictable plasma levels with extensive interpatient and intrapatient variability (3). The variability in plasma levels results primarily from extensive first pass metabolism of 5-FU in the gut wall and the liver coupled with variable and schedule-dependent clearance. The primary and rate-limiting enzyme involved in 5-FU metabolism is dihydropyrimidine dehydrogenase (DPD). The role of DPD in the catabolism of 5-FU is depicted in Fig. 1. Although present in tissues throughout the body, DPD has its highest concentration in the liver, and hepatic metabolism of the drug by DPD accounts for most of the clearance of 5-FU; only 5–10% of an administered dose is eliminated unchanged in the urine (2). The observed intrapatient variability in plasma levels of 5-FU may be due in part to the observed circadian variation of DPD activity in humans that results in variable plasma concentrations of the drug throughout the day during prolonged i.v. infusion (4). The interpatient variability in elimination may relate to genetic polymorphism in DPD activity, with 2–4% of the population estimated to be deficient in the enzyme (5, 6).

Given the unpredictable pharmacokinetics of orally-administered 5-FU, the drug has traditionally been administered almost exclusively via the i.v. route, although hepatic arterial infusion and i.p. instillation have been used in special clinical circumstances. 5-FU may be administered by bolus, rapid infusion over minutes to hours, or prolonged infusion over hours to weeks. Several studies have shown that the schedule of administration may result in different antitumor efficacy and different toxicity profiles. A recent meta-analysis examined data from 1219 patients with advanced colorectal cancer treated on one of seven Phase III randomized trials of bolus infusion versus continuous infusion of 5-FU. A small survival advantage (approximately 24 days) and a large toxicity advantage were reported for continuous infusion over bolus infusion (7). Specifically, continuous infusion was associated with far less myelosuppression than bolus administration (4% compared to 31%), but continuous infusion was associated with more hand-foot syndrome than bolus administration (34% compared to 13%). Because orally-administered agents have pharmacokinetics that approximate those of continuous infusion without the patient inconvenience and morbidity associated with indwelling catheters and infusion pumps, investigators have renewed interest in developing oral preparations of fluoropyrimidines that may result in equivalent or greater tumor response rates and less toxicity.

The Oral Fluoropyrimidines

The oral fluoropyrimidines may be divided into three groups: (a) 5-FU prodrugs; (b) 5-FU combined with a DPD inhibitor, and (c) 5-FU prodrugs combined with a DPD inhibitor. We discuss the rationale for each type of agent, and then we discuss specific agents within each group, summarizing both the preclinical and clinical experience. Oral coadministration of leucovorin is being evaluated for possible synergy with each of

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2 The abbreviations used are: 5-FU, 5-fluorouracil; DPD, dihydropyrimidine dehydrogenase; GI, gastrointestinal; UFT, uracil and fluorafur; CDHP, chloro-2,4-dihydroxypropylene; CNS, central nervous system.
these agents, based on its well-documented ability to enhance tumor response to 5-FU (8, 9).

**5-FU Prodrugs**

Prodrugs of 5-FU have been developed that are not substrates for DPD and are therefore absorbed intact through the GI mucosa. These agents must then undergo enzymatic activation by one or more enzyme systems to liberate 5-FU intracellularly. The extent to which these reactions occur in normal versus tumor tissue has the potential to provide some tumor selectivity for these agents.

**Ftorafur**

Ftorafur (Tegafur) is a prodrug [R,S-1-1(tetrahydrofuran-2-yl)-5-FU] that is slowly metabolized to 5-FU through two separate pathways, hepatic cytochrome P-450 enzymes and systemic soluble enzymes (10, 11). Fig. 2 depicts the activation steps of ftorafur.

Capecitabine (n4-pentyloxycarbonyl-5‘-deoxy-5-fluorocytidine; Xeloda) is itself a prodrug of another 5-FU prodrug (doxifluridine) and was designed to minimize the substantial local GI toxicity of doxifluridine without compromising its antitumor efficacy (18). The pharmacologically inactive capecitabine is reliably absorbed unchanged from the GI tract and then converted through three enzymatic reactions to 5-FU. The metabolism of capecitabine is depicted in Fig. 3. It is first converted to 5‘deoxyfluorocytidine in the liver by carboxylesterase and then converted to doxifluridine by cytidine deaminase, a ubiquitous enzyme found in liver, plasma, and tumor tissue. The toxic intermediary doxifuridine is then converted to 5-FU by thymidine phosphorylase, an enzyme that may be more abundant in tumors than in normal tissue, thus potentially resulting in tumor 5-FU concentrations that far exceed plasma levels and produce greater antineoplastic effects with lower toxicity (19, 20). Indeed, investigators have reported that capecitabine administration results in tumor concentrations of 5-FU more than 127 times those attained with i.v. dosing of 5-FU (21). In preclinical studies, capecitabine showed activity against a number of human tumor xenografts (22, 23). Subsequent clinical trials have revealed the drug to be well-tolerated (24–27). From a recent Phase I clinical trial in advanced solid tumor patients, investigators recommended 2510 mg/m²/day capecitabine in two divided doses for 2 weeks followed by a 1-week rest for Phase II testing (28). The dose-limiting toxicities were diarrhea, stomatitis, abdominal pain, and hand-foot syndrome. When paired with leucovorin (60 mg/day), the recommended Phase II dose of capecitabine is substantially lower, 1650 mg/m²/day, although the toxicities are similar (29).

Several Phase II studies have tested the efficacy of capecitabine against specific solid tumors. In a randomized Phase II study of previously untreated advanced breast cancer patients, 2510 mg/m²/day capecitabine (given in two divided doses daily for 2 weeks followed by a 1-week rest) had an efficacy similar to that of traditional cyclophosphamide, methotrexate, 5-fluoro-
orouracil (CMF) therapy (given every 21–28 days; Ref. 30). The same group of investigators also performed a randomized Phase II study of capecitabine and paclitaxel in patients with anthracycline-resistant advanced breast cancer. Capecitabine (given on the same schedule noted above) was similar to paclitaxel (175 mg/m² every 21 days) with respect to response rate and median time to disease progression (31). Whereas the results of these and other studies have led the Food and Drug Administration to grant accelerated approval to capecitabine for use in patients with advanced breast cancer, results will need to be replicated in an adequately powered randomized Phase III trial before definitive conclusions about efficacy can be made.

The drug has also been studied in patients with advanced colorectal cancer. Three doses and schedules that were determined in Phase I trials were tested in the Phase II setting as first-line therapy for patients with advanced colorectal cancer (32). The investigators reported that 2510 mg/m²/day capecitabine given in two divided doses for 14 days followed by a 1-week rest was associated with the highest response rate (9 of 36 patients, 25%) and the longest time to tumor progression (30 weeks) of the three schedules. This dose and schedule became the basis for two Phase III randomized trials of capecitabine (2500 mg/m²/day) versus the standard monthly bolus of 5-FU/leucovorin (450 mg/m²/day 5-FU and 20 mg/m²/day leucovorin) in the first-line treatment of advanced colorectal cancer.

Preliminary results from both Phase III trials suggest that capecitabine is superior to the traditional bolus 5-FU/leucovorin with respect to both response rates and the incidence of life-threatening neutropenia. In a trial of 602 patients, the response rate of patients treated with capecitabine was 26.6% compared to 17.9% for those treated with 5-FU/leucovorin (P = 0.013; Ref. 33). The differences in duration of response (capecitabine, 7.3 months; 5-FU/leucovorin, 9.6 months) and duration of progression-free survival (capecitabine, 5.3 months; 5-FU/leucovorin, 4.8 months) were not significant. The grade 3/4 toxicities produced by capecitabine were hand-foot syndrome (16.2%) and diarrhea (10.8%), whereas the grade 3/4 toxicities related to 5-FU/leucovorin were neutropenia (19.7%), stomatitis (13.4%), and diarrhea (10%). In the second trial of 605 patients, the response rate of patients treated with capecitabine (23.2%) was again superior to that of patients treated with 5-FU/leucovorin (15.5%; P = 0.02; Ref. 34). The differences in duration of response (capecitabine, 9.1 months; 5-FU/leucovorin, 9.7 months) and duration of progression-free survival (capecitabine, 4.4 months; 5-FU/leucovorin, 5.1 months) were also not significant in this study. The grade 3/4 toxicities produced by capecitabine were hand-foot syndrome (17.7%) and diarrhea (15.1%), whereas the grade 3/4 toxicities resulting from 5-FU/leucovorin were neutropenia (25.9%), stomatitis (16.3%), and diarrhea (13.9%). Survival data have not yet been reported from these studies, although it is unlikely that significant differences will emerge. At this point, it seems reasonable to conclude that oral capecitabine is similar to monthly i.v. 5-FU/leucovorin in tumor efficacy and produces a toxicity profile that may be preferred by some patients. However, patients unlikely to be compliant with an oral regimen are probably best treated with i.v. chemotherapy.

DPD-targeted Therapies

As noted previously, DPD is a ubiquitous enzyme that is the immediate rate-limiting step in the degradation of 5-FU. Both preclinical and clinical studies have shown repeatedly that inhibition of DPD is associated with a prolongation of the half-life of 5-FU in plasma (35–37). Patients genetically deficient in DPD are natural examples of this phenomenon because
after receiving standard doses of 5-FU, they have prolonged circulation of the drug and may experience life-threatening toxicity (38, 39). Studies in head and neck and colorectal cancers suggest that patients whose tumors overexpress DPD maybe less likely to respond to standard 5-FU therapy (40, 41). Agents that inhibit DPD activity have been developed and are now increasingly studied in the treatment of cancer because they facilitate oral absorption of 5-FU and prolong its half-life in plasma and may circumvent 5-FU resistance due to tumor overexpression of DPD, which may translate into improved antitumor efficacy.

There are two types of DPD-targeted therapies, those that irreversibly inactivate DPD and those that reversibly inhibit DPD. A uracil analogue, eniluracil (ethynyluracil, BW776, GW776, 776C85), has been shown to irreversibly inactivate DPD both in vitro (42) and in vivo (43). The preclinical and clinical studies showed that eniluracil inhibited >96% of DPD activity for up to 6 h after a single dose (35, 43). The reversible inhibitors of DPD that have been studied in clinical trials are uracil, CDHP, and 3-cyano-2,6-dihydroxypyridine (CNDP).

Combination Therapies

Given the reliable inhibition of DPD produced by these agents, the next logical step was to pair the DPD-targeted therapies with fluoropyrimidines in an attempt to facilitate oral absorption and prolong the half-life of 5-FU. The other potential benefits of using DPD inhibitors are elimination of 5-FU metabolites, which may be responsible for some of the toxic effects of the drug, and inhibition of intratumoral DPD that may increase sensitivity to 5-FU (44).

Eniluracil/5-FU

The combination of oral 5-FU with the oral DPD inhibitor eniluracil holds great promise as a potent antineoplastic therapy. In preclinical animal trials, pretreatment with eniluracil resulted in 100% oral bioavailability of 5-FU and extended its half-life from 9 min to 100 min (35). In humans, Baker et al. noted complete and reliable oral bioavailability of 5-FU after exposure to eniluracil and a prolongation of the half-life of 5-FU (36). These investigators found that in the setting of complete DPD inhibition with eniluracil, 5-FU had linear pharmacokinetics with clearance dependent primarily on creatinine clearance, consistent with renal excretion of 5-FU rather than hepatic metabolism. Indeed, a subsequent Phase I trial found a >10-fold increase in renal 5-FU excretion after exposure to eniluracil (45). In a larger Phase I clinical trial, combinations of eniluracil and 5-FU with or without leucovorin were administered on a daily × 5 schedule to 65 patients with advanced solid tumors (37). These investigators confirmed the pharmacokinetics described in the previous trials and reported that in the setting of complete DPD inhibition by eniluracil, 5-FU had a maximally tolerated dose that was dramatically lower than that seen in conventional 5-FU regimens. The dose-limiting toxicity on this schedule was myelosuppression (neutropenia) without infectious complications, and the investigators recorded only infrequent episodes of severe GI toxicity.

The combination of 5-FU and eniluracil has been evaluated in the Phase II setting against specific solid tumors and has yielded promising results. Mani et al. (46) studied the effects of oral eniluracil (10 mg/m²) and 5-FU (1–1.15 mg/m²/day) given daily for 28 days as a first-line agent in the treatment of patients with advanced colorectal cancer. They reported a response rate of 24% (11 of 45 patients) and rare grade 3 or 4 toxicities. This dose and schedule are the basis for a recently completed Phase III trial comparing eniluracil/leucovorin to a conventional i.v. 5-FU/leucovorin regimen in patients with metastatic colorectal cancer.

S-1

S-1 is a combination of the 5-FU prodrug florafur and two 5-FU modulators, CDHP and oxonic acid, in a molar ratio of 1:0.4:1 (see Fig. 4). As noted above, florafur is converted to 5-FU through hepatic cytochrome P-450s and through cytosolic enzymes, and CDHP is a competitive, reversible DPD inhibitor that prolongs the half-life of 5-FU. Oxonic acid is a pyrimidine phosphoribosyltransferase inhibitor that is intended to mitigate 5-FU-related GI toxicity by preventing the phosphorylation of 5-FU in the digestive tract. After preclinical studies revealed the drug to have antitumor effects in human tumor xenographs in nude mice (47), early Phase I clinical testing determined that the 5-FU generated from the florafur component had linear pharmacokinetics and a half-life of 2–7 h (48). The dose-limiting toxicity was myelosuppression (neutropenia), and the recommended Phase II dose was 75 mg twice daily (49). Additional toxicities were GI (anorexia, vomiting, diarrhea, and stomatitis) and dermatological (rash). Phase II studies in a variety of advanced solid tumors (gastric, colorectal, breast, and head and neck tumors) report high response rates (35–50%) with few patients (<10%) experiencing major toxicities (grade 3), which were primarily hematological (neutropenia, anemia, and thrombocytopenia; Refs. 50–53).

BOF A-2

BOF A-2 (Emitefur) is a second example of a 5-FU prodrug combined with a DPD inhibitor. In this case, the 5-FU prodrug is 1-ethoxymethyl 5-FU, and the DPD inhibitor is 3-cyano-2,6-dihydroxypyridine (combined in a 1:1 molar ratio; Ref. 54). Preclinical studies revealed that the compound resulted in a prolonged 5-FU half-life and produced antitumor responses in murine models (55–57). Subsequent Phase I clinical testing reported the maximally tolerated dose to be 400 mg/m² daily for
4 weeks, and the dose-limiting toxicities were reported to be GI (anorexia, diarrhea, and stomatitis) and hematological (leukopenia and thrombocytopenia; Ref. 58). Early Phase II studies report antitumor effects in several solid tumors including breast, colorectal, gastric, non-small cell lung, and pancreatic tumors (59, 60).

**UFT**

UFT is a 1:4 molar combination of the 5-FU prodrug florafur and the DPD inhibitor uracil that was developed over 20 years ago in Asia. Preclinical studies revealed that the combination of florafur with uracil was associated with higher tumor blood levels of 5-FU than florafur alone, and the difference was associated with greater antitumor activity (61, 62). Combining uracil with florafur also appears to change the drug’s toxicity profile, with a substantial reduction of the CNS toxicity and a mitigation of the GI toxicity that results when florafur is given alone (63). The CNS toxicity of florafur is felt to be mediated by hepatic degradation of 5-FU to α-fluoro-β-alanine by DPD, and uracil blocks this process. In Phase I trials in the United States, UFT has been studied in different schedules (5-day and 28-day schedules) and with and without leucovorin. Pazdur et al. (64) found that the dose-limiting toxicity on the 5-day schedule was granulocytopenia at 900 mg/m²/day, leading to a recommended Phase II dose of 800 mg/m²/day. On the 28-day schedule, however, the dose-limiting toxicity was diarrhea at 450 mg/m²/day, leading to a recommended Phase II dose of 360 mg/m²/day.

In other early trials from the same group, the pharmacokinetics of oral UFT at 375 mg/m²/day on the 28-day schedule were compared with those of 5-FU at 250 mg/m²/day on a continuous infusion 5-day schedule (65). The results revealed similar 5-FU areas under the concentration curve but higher maximal 5-FU concentrations with UFT.

400 mg/m²/day UFT, leading to a recommended Phase II dose of 300 mg/m²/day with 150 mg/day leucovorin. This dose was then tested in a Phase II trial of patients with advanced colorectal cancer and was associated with a 42% tumor response rate and a 24% rate of grade 3 GI toxicities (diarrhea, vomiting, and abdominal cramping) and fatigue (68). Results of two randomized Phase III studies comparing traditional 5-day bolus 5-FU (425 mg/m²/day) and leucovorin (20 mg/m²/day) given every 35 days with oral UFT (300 mg/m²/day) and oral leucovorin (75 or 90 mg/day) for 28 days every 35 days in previously untreated patients with metastatic colorectal cancer have recently been reported (69, 70). In both studies, the oral and i.v. regimens had similar response rates, times to disease progression, and survival. However, in both studies, the oral regimen was associated with far fewer episodes of severe neutropenia compared to the i.v. regimen [3% compared with 31% (P < 0.001) in one study (69), and 1% compared with 56% (P < 0.001) in the other study (70)]. UFT/leucovorin therefore appears to be an acceptable alternative to i.v. 5-FU/leucovorin for treatment of metastatic colorectal cancer. The National Surgical Adjuvant Breast and Bowel Project is currently testing a similar dose and schedule of UFT/leucovorin against a traditional i.v. 5-FU regimen in a Phase III study (C-06) of adjuvant therapy for colon cancer patients.

**Clinical Application**

The choice of which oral fluoropyrimidine to use must be guided both by the patient’s physiological profile and by their tumor’s biochemical profile. Whereas the use of DPD inhibitors requires a reduction in 5-FU dose to avoid severe toxicity, there may be special clinical circumstances where the risks of therapy are further increased by DPD inhibition. For example, patients with renal insufficiency should not be treated with 5-FU and DPD inhibitors because in the face of DPD inhibition, 5-FU clearance is almost entirely renal. Such patients could experience life-threatening 5-FU toxicity due to inability to eliminate the drug by either metabolic or renal clearance. It is also

<table>
<thead>
<tr>
<th>Drug</th>
<th>5-FU prodrug</th>
<th>DPD inhibitor</th>
<th>Potential advantages</th>
<th>Toxicities</th>
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<tr>
<td>Florafur</td>
<td>Yes</td>
<td>No</td>
<td>Reliable absorption</td>
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<td>Capecitabine</td>
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<td>No</td>
<td>Reliable absorption, Tumor selective</td>
<td>GI, hand-foot syndrome</td>
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<td>EU/5-FU</td>
<td>No</td>
<td>Yes</td>
<td>Reliable absorption, Prolonged 5-FU 1/2, Increased tumor sensitivity</td>
<td>Neutropenia (5-day schedule)</td>
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<tr>
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<td>Yes</td>
<td>Reliable absorption, Prolonged 5-FU 1/2, Increased tumor sensitivity</td>
<td>Diarrhea</td>
</tr>
<tr>
<td>S-1</td>
<td>Yes</td>
<td>Yes</td>
<td>Reliable absorption, Prolonged 5-FU 1/2, Increased tumor sensitivity</td>
<td>Neutropenia</td>
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<tr>
<td>BOF A-2</td>
<td>Yes</td>
<td>Yes</td>
<td>Reliable absorption, Prolonged 5-FU 1/2, Increased tumor sensitivity</td>
<td>GI, hematological toxicity</td>
</tr>
</tbody>
</table>

*EU/5-FU, eniluracil/5-FU.*
theoretically possible that DPD inhibitors could reduce the frequency of certain unusual toxicities of 5-FU. As mentioned previously, UFT is associated with less neurological toxicity than fluorafur, perhaps due to the inhibition of formation of toxic 5-FU metabolites. Similarly, it is of interest that hand-foot syndrome appears to be rare with those oral fluoropyrimidines that include a DPD inhibitor, whereas it occurs commonly after capecitabine therapy, suggesting that a toxic 5-FU metabolite might be responsible for this particular toxic effect. Table 1 contains brief summaries of each agent’s potential advantages as well as toxicities.

Knowledge of the biochemical profile or “fluoropyrimidine phenotype” of the tumor might be useful in selecting a particular treatment strategy. For example, tumors that overexpress DPD might benefit most from 5-FU paired with a DPD inhibitor, and those that overexpress thymidine phosphorylase might be most sensitive to capecitabine. As new techniques that allow enzymatic tumor fingerprinting become more widely available, fluoropyrimidine therapy may become even more rationally applied.

Although evaluated primarily in advanced solid tumors, the oral fluoropyrimidines have clinical implications for early-stage tumors as well, if they are found to be as efficacious as infusional 5-FU. As noted previously, UFT with leucovorin is being evaluated for use in the adjuvant setting in patients with localized colon cancer as well as in the neoadjuvant setting in patients with rectal cancer (71). Oral fluoropyrimidines are also being evaluated as radiosensitizers in several Phase I trials of patients with cancers traditionally managed with infusional radio-sensitizing 5-FU (e.g., cervical, head and neck, pancreatic, and rectal cancers; Refs. 71–75).

Summary

The unifying theme for all of the oral fluoropyrimidine therapies is that they are pharmacologically rational renderings of oral 5-FU. Oral 5-FU alone has erratic absorption and non-linear pharmacokinetics. Most of the new oral fluoropyrimidine compounds release 5-FU that has linear pharmacokinetics. Through daily dosing of an oral fluoropyrimidine, investigators hope to approximate the less myelosuppressive continuous i.v. infusion 5-FU without the use of infusion catheters and pumps. These preparations appear to have efficacy in the treatment of several metastatic solid tumors and will need to be scrutinized further in the Phase III setting to determine whether they confer equivalent or superior survival compared with traditional i.v. administered 5-FU. At the very least, oral fluoropyrimidines have the potential to provide the convenience of oral therapy, a more favorable toxicity profile, and equivalent antitumor efficacy compared with standard regimens.

References


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