Dihydropyrimidine dehydrogenase inhibition as a strategy for the oral administration of 5-fluorouracil: utility in the treatment of advanced colorectal cancer

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Dihydropyrimidine dehydrogenase (DPD), the rate-limiting enzyme in 5-fluorouracil (5-FU) catabolism, has been a key target for the development of novel oral fluoropyrimidines. DPD-inhibiting oral fluoropyrimidines showing promise in early clinical studies included UFT (the 5-FU prodrug, tegafur, plus the DPD substrate, uracil), eniluracil (an irreversible DPD inhibitor that improves the oral bioavailability of 5-FU) and S-1 (tegafur plus a reversible DPD inhibitor, 5-chloro-2,4-dihydroxypyridine, and oxonic acid). However, results from phase II/III trials evaluating these agents as first-line therapy for metastatic colorectal cancer have been disappointing. Although DPD-inhibiting oral fluoropyrimidines have some activity in colorectal cancer and oral administration provides significant convenience advantages, the inferior efficacy of UFT/leucovorin and eniluracil/5-FU versus 5-FU/leucovorin in phase III trials does not support the use of these compounds. A feasible regimen for the phase III development of S-1 outside Japan has not been defined. Thus the DPD-inhibiting oral fluoropyrimidines have failed to fulfill their early promise: clinical data indicate that none of these compounds is likely to improve outcomes for patients with metastatic colorectal cancer. ***Anti-Cancer Drugs*** **14:695–702 © 2003 Lippincott Williams & Wilkins.**

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Introduction

5-Fluorouracil (5-FU) remains the most widely prescribed therapeutic agent for the treatment of colorectal cancer. 5-FU is administered predominantly as an i.v. therapy, with studies showing that protracted or continuous infusion 5-FU is associated with a modest survival advantage, as well as a significant increase in response rate compared with bolus administration [1,2]. With a view to improving convenience, and avoiding the complications and discomfort associated with daily i.v. administration, considerable efforts have been directed towards developing a viable oral fluoropyrimidine.

The development of oral formulations of 5-FU has been hampered by the poor and unpredictable bioavailability of 5-FU, which ranges from 0 to 80% with wide inter- and intra-patient variability [3]. The key enzyme in the catabolism of 5-FU, dihydropyrimidine dehydrogenase (DPD) (Fig. 1), is estimated to account for the breakdown of more than 80% of 5-FU [4] and shows broad inter-patient variability [5]. When DPD is inhibited, renal excretion becomes the principal route of 5-FU elimination [6]. DPD is widely distributed in many tissues, and the DPD activities of the intestinal mucosa and liver contribute to the low systemic exposure to 5-FU following oral administration [7]. As the rate-limiting enzyme in the breakdown of 5-FU, DPD has been identified as a key target for the development of novel oral therapeutic strategies.

The inhibition of DPD has the potential to reduce inter-patient variability in the catabolism of 5-FU and enable predictable oral administration. A number of oral fluoropyrimidines incorporating agents that inhibit DPD have been developed to provide alternatives to i.v. 5-FU. The aim of the DPD-inhibiting fluoropyrimidines (DIFs) is to mimic continuous infusion 5-FU, while avoiding the requirement for central venous access and infusion pumps. This paper reviews the clinical development and current status of DIFs as therapy for metastatic colorectal cancer.

UFT (tegafur plus uracil)

Tegafur (1-[2-tetrahydrofuranyl]-5-fluorouracil) is an oral 5-FU prodrug, which is most commonly administered in combination with a DPD inhibitor. It is slowly converted to 5-FU by the cytochrome P450 pathway, thus avoiding breakdown by DPD in the small bowel [8]. The original clinical evaluation of tegafur was undertaken using short duration i.v. schedules [9–11]. Although some antitumor

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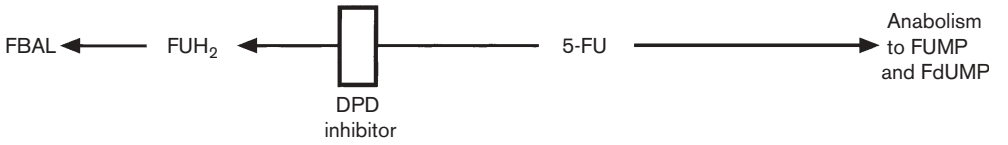
Fig. 1



Metabolic conversion of 5-FU.

activity was demonstrated, clinical utility was limited by severe neurotoxicity caused by the tegafur metabolite, butyrolactone. Regardless of the route of administration (oral or i.v.), tegafur was associated with a high incidence of severe neurotoxicity at the doses required for antitumor activity [11–15]. However, development continued in Japan, where research focused on the oral administration of the drug at lower doses in combination with the DPD inhibitor, uracil [16]. Uracil is a DPD substrate that competitively inhibits the catabolism of 5-FU, thereby reducing 5-FU clearance, and increasing plasma and intratumoral 5-FU concentrations [17]. The addition of the DPD inhibitor improved the bioavailability of tegafur and enabled lower doses of tegafur to be administered, thus reducing the incidence of neurotoxicity.

Preclinical investigations showed that combination of tegafur and uracil in a 1:4 ratio (UFT) yielded the maximal benefit to risk ratio [9]. Clinical evaluation of UFT in Japan demonstrated promising antitumor activity and stimulated worldwide interest in the drug. However, as the Japanese clinical studies of UFT did not formally establish the maximum tolerated dose (MTD) and rationale for schedule selection, clinical development of the drug in the US and Europe required formal phase I/II evaluation.

The principal dose-limiting toxicities associated with oral UFT are myelosuppression [18] or gastrointestinal toxicities [19], depending upon the administration schedule. Pharmacokinetic analyses showed that UFT was associated with an increased elimination half-life, higher peak plasma concentrations and similar area under the concentration curve (AUC) compared with infused 5-FU [20]. UFT was also evaluated in combination with leucovorin (LV), as preclinical studies had shown that, like i.v. 5-FU, co-administration with LV enhanced the activity of UFT [21]. Pharmacokinetic analyses have demonstrated that the ingestion of food significantly reduces the oral bioavailability of UFT/LV causing a 37–76% decrease in the C_{max} and AUC for uracil and 5-FU [22]. Therefore, it is recommended that food should not be consumed within 1 h before or after every dose of oral UFT/LV.

The clinical development programme for UFT/LV has utilized 3-times-daily dosing. With this schedule, long-lasting grade 3/4 diarrhea was observed in 71% of patients treated with UFT 350 mg/m^2 plus LV 150 mg, days 1–28 every 35 days [23]. This led to a reduction in the dose to 300 mg/m^2, at which grade 3/4 diarrhea occurred in 11% of patients, indicating a narrow therapeutic index. It could be anticipated that patient compliance and convenience would be improved with a twice-daily regimen. However, a twice-daily regimen with UFT 300 mg/m^2/day plus LV 30 mg twice daily, days 1–28 every 35 days, was associated with a higher incidence of grade 3/4 diarrhea (26%) [24].

Phase III studies

Two large, phase III trials have compared the efficacy of UFT/LV with i.v. 5-FU/LV as first-line treatment for metastatic colorectal cancer. One trial was conducted in the US, Canada and Europe [25] and the other in Europe [26] (Table 1). Both trials evaluated the same UFT/LV regimen (UFT 300 mg/m^2/day with LV 75 or 90 mg/day administered for 5 days every 28 days). However, the i.v. 5-FU/LV comparator regimens differed. The international trial used the regulatory standard, the Mayo Clinic regimen (i.v. 5-FU 425 mg/m^2/day plus LV 20 mg/m^2 daily on days 1–5, every 28 days), while the European trial used a non-regulatory standard, modified (35-day) Mayo Clinic regimen, in which the planned 5-FU dose intensity was 25% lower than with the standard regimen.

The international trial, which enrolled 816 patients, was designed to demonstrate statistical equivalence in survival between patients treated with oral UFT/LV and i.v. 5-FU/LV (with the protocol defining that equivalence could not be concluded if survival was reduced by 20% or more with UFT/LV compared with 5-FU/LV) [25]. The per-protocol final analysis of survival after 640 deaths was not able to demonstrate equivalence with UFT/LV, based on the margins of the confidence interval (CI) for the hazard ratio (HR = 0.933; 95.6% CI: 0.794–1.097) (Table 2). In a subsequent, unplanned analysis (HR = 0.964; 95.6% CI: 0.826–1.125), after 700 deaths were recorded, equivalence could be concluded based on the protocol definition of equivalence. Of note, disparity in the survival data, which favored sites outside the US (survival

Table 1 Efficacy and safety of oral UFT/LV versus i.v. 5-FU/LV as first-line therapy for metastatic colorectal cancer

	UFT/LV versus Mayo Clinic regimen [25,27]				UFT/LV versus modified Mayo Clinic regimen[b] [26]			
	UFT/LV ($n = 409$)	5-FU/LV ($n = 407$)	HR[a]	p value	UFT/LV ($n = 190$)	5-FU/LV ($n = 190$)	HR[a]	p value
Response rate (%)	12	15	–	0.232	11	9	–	0.593
Median TTP (months)	3.5	3.8	0.823	0.011	3.4	3.3	0.941	0.591
Median survival (months)	12.4	13.4	0.933	0.391	12.2	10.3	1.14	0.226
Grade 3/4 toxicities (%)								
diarrhea	21	16	–	NS	18	11	–	NS
mucositis/stomatitis	1	19	–	<0.001	2	16	–	<0.001
leukopenia	<1	19	–	<0.001	13	57	–	<0.001
neutropenia	1	56	–	<0.001	3	31	–	<0.001

[a]5-FU/LV : UFT/LV.
[b]35-day schedule with 25% reduced planned dose intensity compared with standard 28-day Mayo Clinic regimen.
NS = not significant.

Table 2 Survival analyses: phase III trial of UFT/LV versus 5-FU/LV (Mayo Clinic regimen)

	Median survival [95% CI] (months)		HR (5-FU/LV : UFT/LV)	*P* value	Reference
	UFT/LV	5-FU/LV			
Planned interim analysis (453 deaths)	12.4 [10.9–13.6]	13.2 [11.6–15.4]	0.873 [98.3% CI: 0.696–1.095]	0.178	[27]
Protocol-defined analysis (631 deaths)	NR	NR	0.924 [95.6% CI: 0.785–1.086]	NR	[27]
Final analysis (640 deaths)	12.4 [11.1–13.6]	13.4 [11.6–15.4]	0.933 [95.6% CI: 0.794–1.097]	0.391	[25]
Unplanned analysis (700 deaths)	12.4 [11.2–13.6]	13.4 [11.6–15.4]	0.964 [95.6% CI: 0.826–1.125]	0.630	[25]

NR = not reported.

for UFT/LV was 3.4 months shorter at the median in the US compared with the Mayo Clinic regimen), led to the FDA expressing concerns about the true impact of UFT/LV on survival [27]. Moreover, UFT/LV resulted in significantly inferior time to disease progression compared with i.v. 5-FU/LV ($p = 0.011$) with a HR (5-FU/LV : UFT/LV) of 0.823 (95.1% CI: 0.708–0.958). The HR indicates that the risk of a patient experiencing disease progression with UFT/LV was increased by 22% compared with 5-FU/LV. In the worst-case scenario, the upper limit of the CI indicates that the risk of disease progression could be increased by 41% with UFT/LV compared with 5-FU/LV and in the best case could be 4% worse with UFT/LV. Furthermore, considering that time to disease progression (TTP) as a direct, drug-related efficacy endpoint was inferior and that the protocol-defined analysis of survival did not allow equivalence to be concluded, the later survival analysis showing equivalence between the treatment arms may have been influenced by effective post-study treatment. In addition, a lower response rate for UFT/LV compared with i.v. 5-FU/LV (12 versus 15%) was also observed.

UFT/LV was associated with significant improvements in safety compared with 5-FU/LV, including lower incidences of neutropenia, stomatitis ($p < 0.001$ for both) and diarrhea ($p < 0.05$). However, analysis of the published data [25] by Fisher's exact test [28] showed a trend for increased incidence of grade 3 or 4 diarrhea with UFT plus LV (21 versus 16% with 5-FU/LV; $p = 0.057$), based on a safety population of 406 patients for UFT plus LV and 396 for the Mayo Clinic regimen [29,30]. This high incidence of grade 3 or 4 diarrhea (21%) has also been observed in a phase III adjuvant trial (26%) [31]. In addition, hyperbilirubinemia was observed more frequently in patients receiving UFT/LV ($p < 0.001$).

As discussed above, the European trial, which enrolled 367 patients, used a comparator regimen with a 25% lower planned dose intensity of 5-FU compared with the standard Mayo Clinic regimen [26]. In the absence of sufficient published survival data with this regimen, the appropriateness of this comparator was strongly questioned by the FDA [27]. Therefore, any comparison of UFT/LV with this low-dose-intensity regimen does not provide generally applicable data to define the role of UFT/LV in the treatment of colorectal cancer. Unsurprisingly, the response rate for this suboptimal 5-FU/LV regimen was low (9%) and similar to that achieved with UFT/LV (11%) in this trial, as well as in the international trial (12%). Time to disease progression was similar in the two treatment arms (median 3.4 and 3.3 months for the UFT/LV and i.v. 5-FU/LV arms, respectively, HR = 0.941, $p = 0.591$). Survival in the UFT/LV arm was similar to that observed with the low-dose-intensity Mayo Clinic regimen (median 12.2 versus 10.3 months, respectively, HR = 1.144, $p = 0.226$). Median survival in the UFT/LV arm was similar to that observed in the international trial (12.2 and 12.4 months, respectively). The safety profile of UFT/LV mirrored that observed in the international trial.

Phase III studies: summary

The pivotal, phase III trials comparing UFT and 5-FU/LV as first-line therapy for metastatic colorectal cancer confirmed the favorable toxicity profile for UFT/LV, with reduced incidences of neutropenia, stomatitis ($p < 0.001$) and diarrhea ($p < 0.05$), but failed to establish definitively equivalent efficacy with the standard 5-FU/LV (Mayo Clinic regimen). UFT/LV has failed to receive regulatory approval in the US as first-line therapy for metastatic colorectal cancer.

Eniluracil/oral 5-FU

Eniluracil (5-ethynyluracil; GW776C85) is a 'suicide substrate' that irreversibly inhibits DPD [32] and improves dramatically the oral bioavailability of 5-FU [33]. Co-administration of 5-FU with eniluracil increases the half-life and decreases the clearance of 5-FU [6]. Following administration of 5-FU alone, more than 50% of the 5-FU dose is recovered in the urine as α-fluoro-β-alanine (FBAL). In the presence of eniluracil, the principal 5-FU elimination pathway is renal excretion of intact 5-FU rather than DPD-related catabolism with less than 2% of the administered dose excreted in the urine as FBAL. Due to the key role of renal excretion, caution should be exercised when administering eniluracil/5-FU to patients with impaired renal function. In addition, extreme caution is necessary when treating patients with standard doses of i.v. 5-FU following exposure to eniluracil, as the long-lasting inactivation of DPD (greater than 4 weeks) has led to fatalities when patients received i.v. 5-FU [34,35].

A phase I/pharmacokinetic study showed that oral eniluracil plus oral 5-FU, administered twice daily for 28 of 35 days, had a similar toxicity profile to that of continuous infusion 5-FU [6]. The principal DLT was diarrhea and the dose recommended for further evaluation was oral 5-FU 1 mg/m^2 twice daily in combination with eniluracil 20 mg twice daily for 28 days followed by a 7-day rest period. In phase II studies, eniluracil/5-FU demonstrated promising efficacy and safety in patients with metastatic colorectal cancer [36,37].

Phase III studies

The encouraging activity of eniluracil/oral 5-FU observed in early clinical trials was not confirmed in subsequent phase III evaluation [38,39]. Two large, independent, phase III trials involving more than 1400 patients demonstrated that as first-line treatment for metastatic colorectal cancer, the efficacy of eniluracil/5-FU is inferior to that observed with i.v. 5-FU/LV (Mayo Clinic regimen) (Table 3). One trial was conducted predominantly in Europe [38] and the other trial was conducted in North America [39]. Both trials compared the safety and efficacy of oral eniluracil 11.5 mg/m^2 plus oral 5-FU 1.15 mg/m^2 (both twice daily for 28 days every 35 days) with the standard Mayo Clinic regimen (i.v. 5-FU 425 mg/m^2, LV 20 mg/m^2 daily for 5 days every 28 days).

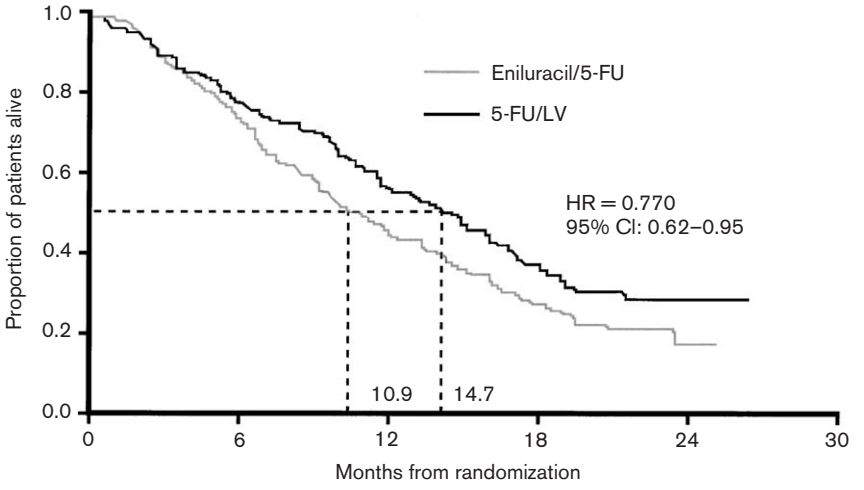
In the European study, the overall safety profile of eniluracil/5-FU was favorable compared with 5-FU/LV, with significantly lower incidences of grade 3/4 mucositis ($p < 0.001$), neutropenia ($p < 0.001$) and leukopenia ($p = 0.002$). However, the efficacy of eniluracil/5-FU regimen was inferior to that of i.v. 5-FU/LV. Although not statistically significant, the response rate was lower in the eniluracil/5-FU arm than in the 5-FU/LV arm (12 versus 14%). The HR for progression-free survival was 0.831 (95% CI: 0.69–1.00), which suggests a strong trend towards the inferiority of eniluracil/5-FU compared with 5-FU/LV. In addition, overall survival was statistically inferior with eniluracil/5-FU compared with 5-FU/LV (HR = 0.770; 95% CI: 0.62–0.95), with median overall survival of 10.9 months with eniluracil/oral 5-FU versus 14.7 months with 5-FU/LV (Fig. 2). The HRs indicate that patients receiving eniluracil/5-FU had a 17%

Table 3 Efficacy and safety of oral eniluracil/5-FU versus i.v. 5-FU/LV (Mayo Clinic regimen) as first-line therapy for metastatic colorectal cancer [38,39]

	European study [38]				North American study [39,59]			
	Eniluracil/5-FU ($n = 268$)	5-FU/LV ($n = 263$)	HR[a]	p value	Eniluracil/5-FU ($n = 485$)	5-FU/LV ($n = 479$)	HR[a]	p value
Response rate (%)	12	14	–	NS	12	13	–	0.845
Progression-free survival (months)	4.4	5.3	0.831	NS	4.6	5.2	0.832	0.011[b]
Median survival (months)	10.9	14.6	0.770	statistically inferior	13.3	14.5	0.880	0.31[b,c]
Grade 3/4 toxicities (%)								
diarrhea	7	10	–	NS	19	16	–	0.354
nausea	NR	NR	–	–	3	7	–	0.012
mucositis	1	13	–	<0.001	1	12	–	<0.001
granulocytopenia/neutropenia	2	32	–	<0.001	5	47	–	<0.001
febrile neutropenia	NR	NR	–	–	0	9	–	<0.001
leukopenia	2	8	–	0.002	NR	NR	–	–
thrombocytopenia	4	1	–	0.037	3	2	–	–

[a]5-FU/LV : eniluracil/5-FU.
[b]Log-rank p value.
[c]Although not statistically significant, survival did not meet the protocol-specified statistical criteria for equivalence to 5-FU/LV.
NS = not significant; NR = not reported.

Fig. 2



Overall survival: eniluracil/5-FU versus 5-FU/LV (European study). (Modified from [38].)

increased risk of experiencing disease progression and a 23% increased risk of dying compared with those receiving i.v. 5-FU/LV.

In the North American study, the toxicity profiles of the two regimens were similar to those observed in the European study. In addition, in this study grade 3/4 hyperbilirubinemia was significantly more frequent with eniluracil/5-FU than with 5-FU/LV (22 versus 9%; $p < 0.001$), and the incidences of grade 3/4 nausea (3 versus 7% with 5-FU/LV; $p = 0.012$) and febrile neutropenia (0 versus 9% with 5-FU/LV; $p < 0.001$) were significantly reduced. The response rates for eniluracil/5-FU and 5-FU/LV were similar (12 and 13%, respectively), but progression-free survival with eniluracil/5-FU was significantly inferior compared with 5-FU/LV ($p = 0.01$). Median progression-free survival was 4.6 months with eniluracil/5-FU versus 5.2 months with 5-FU/LV. Although overall survival with eniluracil/5-FU was not statistically significantly different from that achieved with 5-FU/LV ($p = 0.314$), it did not fulfill the protocol-specified statistical criteria for equivalence because the lower boundary of the 95% CI for the HR was below 0.8 (HR = 0.880; 95% CI: 0.75–1.03). Median overall survival was 13.3 months with eniluracil/5-FU versus 14.5 months with 5-FU/LV.

Phase III studies: summary

Early studies suggested that eniluracil/5-FU was a promising new, oral fluoropyrimidine, achieving good efficacy with a tolerable dose regimen in patients with metastatic colorectal cancer. The phase III studies demonstrated improved tolerability of eniluracil/5-FU compared with 5-FU/LV (Mayo Clinic regimen). However, the inferior efficacy observed with this tolerable regimen in these two well-designed, randomized studies does not support the use of this DIF as first-line therapy for colorectal cancer. As a result, the clinical development of eniluracil/5-FU has been abandoned.

S-1

S-1 is another DIF that has been evaluated as therapy for colorectal cancer, although phase III development is not being pursued currently. This agent comprises a fixed mixture (1 : 0.4 : 1 molar ratio) of tegafur and two biomodulators: 5-chloro-2,4,-dihydroxypyridine (CDHP) and oxonic acid. CDHP is a reversible DPD inhibitor that is 200 times more potent than uracil. Oxonic acid is intended as an inhibitor of 5-FU phosphorylation in the gastrointestinal tract, with the aim of reducing gastrointestinal side effects.

Following evaluation of S-1 in Japan, a formal clinical evaluation programme for the agent began in Europe in the 1990s. A Dutch phase I study investigated S-1 administered twice daily for 28 of 35 days [40]. Diarrhea was the principal DLT. The antitumor activity was modest, with partial responses in only two of 28 patients (7%).

Phase II studies

More promising efficacy was demonstrated in a Japanese phase II study investigating the twice-daily regimen (40 mg/m^2 twice daily for 28 days followed by a 14-day rest period) as first-line therapy for metastatic colorectal cancer [41]. Partial responses were observed in 22 of 62 evaluable patients (35%), with median overall survival of 12.0 months. In this study, hematological toxicities

predominated, with grade 3/4 neutropenia and thrombocytopenia occurring in 13 and 8% of patients, respectively.

The results of an EORTC phase II study of S-1 in patients with metastatic colorectal cancer have raised questions about the safety of this DIF [42]. In this study, the initial S-1 starting dose (40 mg/m^2 twice daily days 1–28 followed by a 7-day rest period) resulted in unacceptable toxicity, with serious treatment-related adverse events occurring in six of 16 patients (38%) during the first treatment cycle and four patients (25%) discontinuing treatment due to toxicity. Therefore, for the second part of the trial ($n = 31$), the starting dose was reduced to 35 mg/m^2 twice daily. During this second phase, diarrhea remained the most common treatment-related grade 3/4 adverse event, occurring in 35% of patients. Partial responses were observed in two (13%) of the 16 patients treated with S-1 40 mg/m^2 and seven (23%) of the 31 patients treated with S-1 35 mg/m^2.

Summary

Clinical data indicate that, despite the presence of oxonic acid, grade 3/4 diarrhea is the predominant toxicity associated with S-1. Before further development of this compound is pursued, additional studies are required to identify the optimal dosing schedule for this DIF and clarify the differing toxicity profiles observed in the Japanese and European studies.

The current status of the DIFs

During preclinical and early clinical studies, regimens incorporating DPD inhibitors showed considerable promise. In addition, the theoretical advantage of overcoming DPD-related 5-FU-resistance in colorectal cancer using DPD inhibitors was attractive to investigators. However, the results from phase III trials evaluating the DIFs as first-line therapy for metastatic colorectal cancer have been disappointing. The inferior efficacy demonstrated by both UFT/LV and eniluracil/5-FU (including inferior overall survival) compared with i.v. 5-FU/LV (Mayo Clinic regimen) in randomized, phase III trials does not support the use of these compounds in their explored regimens. In addition, a feasible dose and regimen for the phase III development of S-1 outside Japan has not yet been defined. The DIFs have therefore failed to fulfill their early promise. Although some activity has been demonstrated, clinical data indicate that none of these compounds is likely to make a significant impact on therapeutic outcomes for patients with metastatic colorectal cancer.

Recently, numerous phase I studies investigating the DIFs in combination regimens have been reported at major oncology meetings. As oral agents, DIFs have the potential to replace i.v. 5-FU/LV and simplify combination regimens with oxaliplatin or irinotecan. However, as with single-agent DIFs, large phase II and phase III randomized trials are required to establish the true potential of these combinations. Preliminary studies indicate that the limitations observed in single-agent studies may also limit the utility of the DIFs in combination regimens [43–47].

Is there a future for oral fluoropyrimidines?

There is a medical need for oral formulations capable of mimicking infused 5-FU. Oral agents have the potential to enhance patients' quality of life by enabling home-based therapy that avoids the inconvenience, pain and discomfort associated with i.v. therapy. In addition, studies have shown that the majority of patients prefer oral chemotherapy to i.v. therapy, as long as efficacy is not compromised [48,49].

DPD inhibition has not been the only strategy for design of oral fluoropyrimidines. The prototype for a non-DPD-inhibiting oral fluoropyrimidine is the rationally designed agent capecitabine, which avoids degradation in the gut via its carbamate side chain [50]. Furthermore, the enzymatic activation of capecitabine generates 5-FU preferentially in tumor tissue through exploitation of the significantly higher activity of thymidine phosphorylase in tumor compared with healthy tissue. Capecitabine has achieved superior response rates and equivalent overall survival and time to disease progression compared with i.v. 5-FU/LV (Mayo Clinic regimen) in phase III trials as first-line therapy for colorectal cancer [51–53]. Furthermore, the safety profile of capecitabine is improved compared with i.v. 5-FU/LV. Based on these data, capecitabine has been approved in the US and Europe as first-line therapy for metastatic colorectal cancer.

In the future, the highly active oral fluoropyrimidine, capecitabine, is likely to replace i.v. 5-FU as the backbone of treatment for metastatic colorectal cancer. Ongoing combination trials are identifying additional roles for capecitabine as a more convenient component of combination regimens [54–58].

References

1 Meta-analysis Group in Cancer. Efficacy of intravenous continuous infusion of fluorouracil compared with bolus administration in advanced colorectal cancer. *J Clin Oncol* 1998; **16**:301–308.

2 Lokich JJ, Ahlgren JD, Gullo JJ, Philips JA, Fryer JG. A prospective randomized comparison of continuous infusion fluorouracil with a conventional bolus schedule in metastatic colorectal carcinoma: a Mid-Atlantic Oncology Program study. *J Clin Oncol* 1989; **7**:425–432.

3 Fraile RJ, Baker LH, Buroker TR, Horowitz J, Vaitkevicius VK. Pharmacokinetics of 5-fluorouracil administered orally, by rapid intravenous and slow infusion. *Cancer Res* 1980; **40**:2223–2228.

4 Heggie GD, Sommadossi JP, Cross DS, Huster WJ, Diasio RB. Clinical pharmacokinetics of 5-fluorouracil and its metabolites in plasma, urine and bile. *Cancer Res* 1987; **47**:2203–2206.

5 McLeod HJ, Sludden J, Murray GI, Keenan RA, Davidson AI, Park K, *et al.* Characterisation of dihydropyrimidine dehydrogenase in human colorectal tumours. *Br J Cancer* 1998; **77**:461–465.

6 Baker SD, Diasio RB, O'Reilly S, Lucas VS, Khor SP, Sartorius SE, *et al.* Phase I and pharmacologic study of oral fluorouracil on a chronic daily

schedule in combination with the dihydropyrimidine dehydrogenase inactivator eniluracil. *J Clin Oncol* 2000; **18**:915–926.
7 Naguib FNM, El-Kouni MH, Sha S. Enzymes of uracil catabolism in normal and neoplastic human tissues. *Cancer Res* 1985; **45**:5402–5412.
8 Au JL, Wu AT, Friedman MA, Sadee W. Pharmacokinetics and metabolism of ftorafur in man. *Cancer Treat Rep* 1979; **63**:343–350.
9 Fujii S, Kitano S, Ikenaka K, Shirasaka T. Effect of coadministration of uracil or cytosine on the antitumor activity of clinical dose of 1-(2-tetrahydrofuryl)-5-fluorouracil and level of 5-fluorouracil in rodents. *Gann* 1979; **70**: 209–214.
10 Friedman MA, Ignoffo RJ. A review of the United States clinical experience of the fluoropyrimidine, ftorafur (NSC-1458958). *Cancer Treat Rev* 1980; **7**:205–213.
11 Valdivieso M, Bodey GP, Gottlieb JA, Freireich EJ. Clinical evaluation of ftorafur (pyrimidine-deoxyribox N_1-2′-furanidyl-5-fluorouracil). *Cancer Res* 1976; **36**:1821–1824.
12 Bjerkeset T, Fjosne HE. Comparison of oral ftorafur and intravenous 5-fluorouracil in patients with advanced cancer of the stomach, colon or rectum. *Oncology* 1986; **43**:212–215.
13 Palmeri S, Gebbia V, Russo A, Armata MG, Gebbia N, Rausa L. Oral tegafur in the treatment of gastrointestinal tract cancer: a phase II study. *Br J Cancer* 1990; **61**:475–478.
14 Ron IG, Lotan A, Inbar MJ, Chaitchik S. Advanced colorectal carcinoma: redefining the role of oral ftorafur. *Anticancer Drugs* 1996; **7**:649–654.
15 Nogue M, Segui MA, Saigi E, Batiste-Alentorn E, Arcusa A, Boleda M, *et al.* Protracted treatment with tegafur and low dose oral leucovorin in patients with advanced colorectal carcinoma. *Cancer* 1998; **83**:254–258.
16 Taguchi T, Nakano Y, Jikuya K, Fujii S, Ikenaka K, Fuku-Shima M, *et al.* Effect of uracil on the antitumor activity of ftorafur. *Jpn J Cancer Chemother* 1978; **5**:1161–1165.
17 Kawaguchi Y, Nagayame S, Masuda H, Yasuda A. Studies on the metabolism of 1-(2′-tetrahydrofuranyl)-5-fluorouracil and uracil coadministered orally to tumor-bearing rats. *Gann* 1980; **17**: 889–899.
18 Pazdur R, Lassere Y, Diaz-Canton E, Bready B, Ho DH. Phase I trials of uracil–tegafur (UFT) using 5 and 28 day administration schedules—demonstration of schedule dependent toxicities. *Anticancer Drugs* 1996; **7**:728–733.
19 Muggia FM, Wu XY, Spicer D, Groshen S, Jeffers S, Leichman CG, *et al.* A phase I and pharmacokinetic study of oral UFT a combination of the 5-fluorouracil prodrug tegafur and uracil. *Clin Cancer Res* 1996; **2**: 1461–1467.
20 Ho DH, Pazdur R, Covington W, Brown N, Huo YY, Lassere Y, *et al.* Comparison of 5-fluorouracil pharmacokinetics in patients receiving continuous 5-fluorouracil infusion and oral uracil plus N_1-(2′-tetrahydrofuryl)-5-fluorouracil. *Clin Cancer Res* 1998; **4**:2085–2088.
21 Rustum YM. Mechanism-based improvement in the therapeutic selectivity of 5-FU prodrug alone and under conditions of metabolic modulation. *Oncology* 1997; **54**(**suppl 1**):7–11.
22 Damle B, Ravandi F, Kaul S, Sonnichsen D, Ferreira I, Brooks D, *et al.* Effect of food on the oral bioavailability of UFT and leucovorin in cancer patients. *Clin Cancer Res* 2001; **7**:517–523.
23 Pazdur R, Lassere Y, Rhodes V, Ajani JA, Sugaman SM, Patt YZ, *et al.* Phase II trial of uracil and tegafur plus oral leucovorin: an effective oral regimen in the treatment of metastatic colorectal carcinoma. *J Clin Oncol* 1994; **12**:2296–2300.
24 Thomas MB, Langlaben A, Rinaldi D, Anthony L, Irwin D, Lassere Y, *et al.* A phase II study of UFT plus leucovorin given as a twice-daily (BID) regimen in the treatment of patients (Pts) with metastatic colorectal cancer (MCC). *Proc Am Soc Clin Oncol* 2001; **20**:142a (abstr 564).
25 Douillard J-Y, Hoff PM, Skillings JR, Eisenberg P, Davidson N, Harper P, *et al.* Multicenter phase III study of uracil/tegafur and oral leucovorin versus fluorouracil and leucovorin in patients with previously untreated metastatic colorectal cancer. *J Clin Oncol* 2002; **20**:3605–3616.
26 Carmichael J, Popiela T, Radstone D, Falk S, Borner M, Oza A, *et al.* Randomized comparative study of tegafur/uracil and oral leucovorin versus parenteral fluorouracil and leucovorin in patients with previously untreated metastatic colorectal cancer. *J Clin Oncol* 2002; **20**:3617–3627.
27 *NDA Pipeline* 1999; **18**:V-95–V-100.
28 Benner S. *63rd US Federal Drug Administration Oncology Advisory Board Meeting Slides*. Available from URL: http:www.fda.gov/ohrms/dockets/ac/99/slides/3540/3540s1d/index.htm.
29 Cunningham D, James RD. Integrating the oral fluoropyrimidines into the management of advanced colorectal cancer. *Eur J Cancer* 2001; **37**: 826–834.
30 Twelves CJ, Cassidy J. Which endpoints should we use in evaluating the use of novel fluoropyrimidines regimens in colorectal cancer? *Br J Cancer* 2002; **86**:1670–1676.
31 Smith IE. Epirubicin, cyclophosphamide, and UFT plus oral calcium folinate in advanced breast cancer. *Oncology (Huntingt)* 1999; **3**(**7 suppl 3**): 82–85.
32 Porter DJT, Chestnut WG, Merill BM, Spector T. Mechanism-based inactivation of dihydropyrimidine dehydrogenase by 5-ethynyluracil. *J Biol Chem* 1992; **267**:5236–5242.
33 Baccanari DP, Davis ST, Knick VC, Spector T. 776C85: effects on the pharmacokinetics and antitumour activity of 5-fluorouracil. *Proc Natl Acad Sci* 1993; **90**:11064–11068.
34 Okuda H, Ogura K, Kato A, Takubo H, Watabe T. A possible mechanism of eighteen patient deaths caused by interactions of sorivudine, a new antiviral drug, with oral 5-fluorouracil prodrugs. *J Pharmacol Exp Ther* 1998; **287**:791–799.
35 Yan J, Tyring SK, McCrary MM, Lee PC, Haworth S, Raymond R, *et al.* The effect of sorivudine on dihydropyrimidine dehydrogenase activity in patients with acute herpes zoster. *Clinical Pharmacol Ther* 1997; **61**:563–573.
36 Schilsky RL, Bukowski R, Burris III H, Hochster H, O'Rourke M, Wall JG, *et al.* A multicenter phase II study of a five-day regimen of oral 5-fluorouracil plus eniluracil with or without leucovorin in patients with metastatic colorectal cancer. *Ann Oncol* 2000; **11**:415–420.
37 Mani S, Hochster H, Beck T, Chevlen EM, O'Rourke MA, Weaver CH, *et al.* Multicenter phase II study to evaluate a 28-day regimen of oral fluorouracil plus eniluracil in the treatment of patients with previously untreated metastatic colorectal cancer. *J Clin Oncol* 2000; **18**:2894–2901.
38 Van Cutsem E, Sorensen J, Cassidy J, Daniel F, Harper P, Bailey N, *et al.* International phase III study of oral eniluracil (EU) plus 5-fluorouracil (5-FU) versus intravenous (IV) 5-FU plus leucovorin (LV) in the treatment of advanced colorectal cancer (ACC). *Proc Am Soc Clin Oncol* 2001; **20**:131a (abstr 522).
39 Schilsky RL, Levin J, West WH, Wong A, Colwell B, Thirlwell MP, *et al.* Randomized, open-label, phase III study of a 28-day oral regimen of eniluracil plus fluorouracil versus intravenous fluorouracil plus leucovorin as first-line therapy in patients with metastatic/advanced colorectal cancer. *J Clin Oncol* 2002; **20**:1519–1526.
40 van Groeningen CJ, Peters GJ, Schornagel JH, Gall H, Noordhuis P, de Vries MJ, *et al.* Phase I clinical and pharmacokinetic study of oral S-1 in patients with advanced solid tumors. *J Clin Oncol* 2000; **18**:2772–2779.
41 Ohtsu A, Baba H, Sakata Y, Mitachi Y, Horikoshi N, Sugimachi K, *et al.* Phase II study of S-1, a novel oral fluoropyrimidine derivative, in patients with metastatic colorectal carcinoma. *Br J Cancer* 2000; **83**:141–145.
42 Van den Brande J, Schöffski P, Schellens J, Roth AD, Duffaud F, Weigang-Kohler K, *et al.* EORTC Early Clinical Studies Group early phase II trial of S-1 in patients with advanced or metastatic colorectal cancer. *Br J Cancer* 2003; **88**:648–653.
43 Garcia-Girón C, Feliu J, Vincent JM, Madronal C, Fonseca E, Constela M, *et al.* Phase II trial of oxaliplatin–UFT–leucovorin (OXA-UFT-LV) combination in first line treatment of advanced colorectal cancer (ACC). *Proc Am Soc Clin Oncol* 2000; **19**:293a (abstr 1148).
44 Cruz J, Méndez M, Alfonso PG, Gonzalez E, Pujol E, Castañon C, *et al.* A phase II study of weekly irinotecan (CPT-11) and oral uracil and ftorafur (UFT) plus folinic acid (FA) as first line treatment in advanced colorectal cancer (CRC). *Eur J Cancer* 2001; **37**(**suppl 6**):S295 (abstr 1090).
45 Alonso V, Escudero P, Zorrilla M, Isla MD, Herrero A, Mayordomo JI, *et al.* Phase I trial of weekly irinotecan combined with UFT as second-line treatment for advanced colorectal cancer. *Eur J Cancer* 2001; **37**: 2385–2391.
46 Yip D, Karapetis C, Strickland A, Steer C, Holford C, Harper P. A phase I trial of escalating dose eniluracil/oral 5-fluorouracil plus oxaliplatin (Oxa) in patients with advanced gastrointestinal malignancies. *Proc Am Soc Clin Oncol* 2001; **20**:82b (abstr 2079).
47 Speyer JL, Hochster H, Chachoua A, Farrell K, Cosmidis A, Muggia F. A phase I/II study of eniluracil/5-FU plus oxaliplatin (FOX-E) in patients with pre-treated colorectal cancer. *Proc Am Soc Clin Oncol* 2001; **20**:144a (abstr 574).
48 Borner M, Schöffski P, de Wit R, Caponigro F, Comella G, Sulkes A, *et al.* Patient preference and pharmacokinetics of oral modulated UFT versus intravenous fluorouracil and leucovorin: a randomised crossover trial in advanced colorectal cancer. *Eur J Cancer* 2002; **38**:349–358.
49 Liu G, Franssen E, Fitch MI, Warner E. Patient preferences for oral versus intravenous palliative chemotherapy. *J Clin Oncol* 1997; **15**:110 – 115.
50 Miwa M, Ura M, Nishida M, Sawada N, Ishikawa T, Mori K, *et al.* Design of a novel oral fluoropyrimidine carbamate, capecitabine, which generates 5-

fluorouracil selectively in tumours by enzymes concentrated in human liver and cancer tissue. *Eur J Cancer* 1998; **34**:1274–1281.

51 Hoff PM, Ansari R, Batist G, Cox J, Kocha W, Kuperminc M, *et al.* Comparison of oral capecitabine versus intravenous fluorouracil plus leucovorin as first-line treatment in 605 patients with metastatic colorectal cancer: results of a randomized phase III study. *J Clin Oncol* 2001; **19**:2282–2292.

52 VanCutsem E, Twelves C, Cassidy J, Allman D, Bajetta E, Boyer M, *et al.* Oral capecitabine compared with intravenous 5-fluorouracil plus leucovorin (Mayo Clinic regimen) in patients with metastatic colorectal cancer: results of a large phase III study. *J Clin Oncol* 2001; **19**: 4097–4106.

53 Twelves C. Capecitabine as first-line treatment in colorectal cancer: pooled data from two large, phase III trials. *Eur J Cancer* 2002; **38**(**suppl 2**): S15–S20.

54 Dunst J, Reese T, Sutter T, Zuhlke H, Hinke A, Kolling-Schlebusch K, *et al.* Phase I trial evaluating the concurrent combination of radiotherapy and capecitabine in rectal cancer. *J Clin Oncol* 2002; **20**:3983–3991.

55 Schleucher N, Tewes M, Achterrath W, Cao S, Frings S, Wilke H, *et al.* Extended phase I study of capecitabine and weekly irinotecan as first-line chemotherapy in metastatic colorectal cancer. *Eur J Cancer* 2001; **37**(**suppl 6**):S290 (abstr 1073).

56 Kerr DJ, Ten Bokkel Huinink WW, Ferry DR, Rea DW, Boussard BM, Oulid-Aissa D, *et al.* A phase I/II study of CPT-11 in combination with capecitabine as first-line chemotherapy for metastatic colorectal cancer (MCRC). *Proc Am Soc Clin Oncol* 2002; **21**:161a (abstr 643).

57 Diaz-Rubio E, Evans TRJ, Tabernero J, Cassidy J, Sastre J, Eatock M, *et al.* Capecitabine (Xeloda®) in combination with oxaliplatin: a phase I, dose-escalation study in patients with advanced or metastatic solid tumors. *Ann Oncol* 2002; **13**:558–565.

58 Tabernero J, Butts CA, Cassidy J, Conroy T, de Braud F, Díaz-Rubio E, *et al.* Capecitabine and oxaliplatin in combination (Xelox) as first line therapy for patients (pts) with metastatic colorectal cancer (MCRC): results of an international multicenter phase II trial. *Proc Am Soc Clin Oncol* 2002; **21**:133a (abstr 531).

59 Levin J, Schilsky R, Burris H, Wong A, Colwell B, Thirlwell M, *et al.* North American phase III study of oral eniluracil (EU) plus oral 5-fluorouracil (5-FU) versus intravenous (IV) 5-FU plus leucovorin (LV) in the treatment of advanced colorectal cancer (ACC). *Proc Am Soc Clin Oncol* 2001; **20**:132a (abstr 523).