Pergamon

European Journal of Cancer, Vol. 34, No. 10, pp. 1509–1513, 1998

Printed in Great Britain
0959-8049/98/$—see front matter

PII: S0959-8049(98)00226-3

Clinical Oncology Update

Oral Fluoropyrimidines in the Treatment of Colorectal Cancer

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5-Fluorouracil (5-FU) has been the mainstay of systemic therapy for colorectal cancer since its initial development 40 years ago. Efforts to improve the therapeutic index of 5-FU have included alteration of schedule and addition of biochemical modulators. An understanding of 5-FU mechanisms of action has resulted in major therapeutic advances in the past 10 years; however, a plateau has been reached in the efficacy of 5-FU, mandating a paradigm shift for those involved in colorectal cancer drug development. One direction vigorously pursued is the development of orally administered fluoropyrimidines that maintain or improve upon the effectiveness of intravenous 5-FU. In this paper the preclinical and clinical development of oral fluoropyrimidines and their modulators is reviewed, including UFT, capecitabine, ethynyluracil and S-1. © **1998 Elsevier Science Ltd. All rights reserved.**

Key words: colorectal cancer, oral chemotherapy, 5-fluorouracil, tegafur, capecitabine, ethynyluracil, S-1
Eur J Cancer, Vol. 34, No. 10, pp. 1509–1513, 1998

INTRODUCTION

5-FLUOROURACIL (5-FU) HAS been the mainstay of systemic therapy for colorectal cancer since its initial development 40 years ago [1, 2]. Randomised trials have demonstrated clinical benefit in adjuvant and advanced disease settings [3–5]. Efforts to improve the therapeutic index of 5-FU have included alteration of schedule [6, 7], and addition of biochemical modulators [2, 8]. An understanding of 5-FU mechanisms of action has resulted in major therapeutic advances in the past 10 years; however, a plateau has been reached in the efficacy of 5-FU, mandating a paradigm shift for those involved in colorectal cancer drug development.

One direction vigorously pursued is the development of orally administered fluoropyrimidines that maintain or improve upon the effectiveness of intravenous (i.v.) 5-FU. There are several potential advantages to oral administration, including patient convenience and reduced costs associated with drug preparation and administration. Although patients would prefer an oral agent rather than an intravenous one, there is unwillingness to sacrifice response rate or duration of response [9].

5-FU shows incomplete and unpredictable oral absorption [10]. This problem may be overcome by the oral administration of other fluoropyrimidines that are absorbed intact and subsequently converted to 5-FU. Alternatively, 5-FU may be coadministered orally with drugs that inhibit its degradation in the gastrointestinal tract. In this paper, the current status of oral fluoropyrimidines in clinical development is reviewed.

Received 25 Mar. 1998; accepted 1 Apr. 1998.

UFT

UFT is a combination of uracil and tegafur (1-[2-tetrahydrofuranyl]-5-FU, ftorafur) in a fixed molar ratio of 4:1 (Figure 1). Tegafur is a 5-FU prodrug that was synthesised in Latvia in 1966 and initially developed for i.v. use. Because of dose-limiting central nervous system and gastrointestinal toxicity with i.v. administration at subtherapeutic doses, the clinical development of tegafur was interrupted [11, 12]. However, it was observed that with oral administration, the therapeutic index of tegafur improves. Tegafur is rapidly and completely absorbed after oral administration. It is converted to 5-FU by two mechanisms: a hydrolytic pathway mediated by hepatic microsomal enzymes and by soluble enzyme hydrolysis. Peak plasma levels of 5-FU are achieved at 30–120 min.

5-FU is rapidly metabolised with a half-life of 5–20 min [10]. The rate-limiting enzyme in the degradative pathway is dihydropyrimidine dehydrogenase (DPD). Uracil is a normal substrate for DPD and can compete with 5-FU, thereby reducing 5-FU clearance. In tumour-bearing rats, the antitumour activity of tegafur is enhanced by co-administration of uracil and this effect is maximised at a uracil:tegafur molar

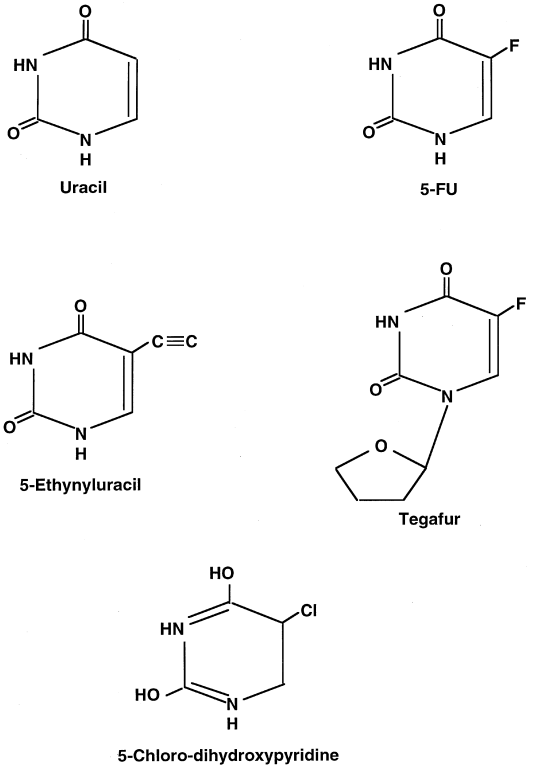

Figure 1. Structures of uracil and analogues used in the treatment of colorectal cancer.

ratio of 4:1 [13]. In addition, the ratio of 5-FU in tumour compared with plasma or normal tissue is enhanced [14, 15]. These preclinical studies formed the basis for the introduction of UFT into clinical trials. In Japan, oral UFT has been studied in a wide variety of malignancies, with a spectrum of activity and response rates similar to those observed with 5-FU [16].

In a further effort to maximise the therapeutic efficacy of tegafur, UFT has been developed in a regimen with oral leucovorin. A predominant mechanism of 5-FU cytotoxicity is the inhibition of thymidylate synthase (required for DNA synthesis) by the catabolite 5-fluorodeoxyuridine monophosphate (FdUMP). Intracellular reduced folates serve as a cofactor in this reaction and potentiate the binding of FdUMP to its target enzyme. Leucovorin (LV, folinic acid) can serve as a pharmacological source of reduced folates. In colorectal cancer, the addition of LV improves the therapeutic efficacy of 5-FU [3, 4, 17].

Given the clinical evidence that a protracted venous infusion of 5-FU may be superior and better tolerated than bolus dosing [7, 18], the UFT–leucovorin combination is being developed as a 28 day schedule with daily oral dosing, in an effort to mimic the pharmacology of continuous infusion 5-FU. Four phase I studies were conducted to determine the toxicity and maximum tolerated dose (MTD) of daily oral UFT when administered with LV. In each study, UFT and LV were administered in three divided doses daily for 28 days, followed by a 1 week rest period, repeated as 35 day cycles. Two studies employed a daily LV dose of 15 mg and two studies used a daily dose of 150 mg. In these trials, the MTD of UFT was 350 mg/m^2/d (mg refers to tegafur) [19–21]. The dose-limiting toxicities (DLTs) were diarrhoea, nausea/vomiting and fatigue. Transient hyperbilirubinaemia was also reported [19].

Peak 5-FU plasma levels are achieved generally 30 min after an oral dose of UFT, with low but detectable levels at 5 h. With a dose of 200 mg of UFT (the morning dose for most patients treated with 300–350 mg/m^2/day) the peak serum 5-FU concentration is of the order of 200–400 ng/ml [19, 22, 23]. The area under the concentration×time curve for 5-FU has been reported to range from approximately 200 to 400 ng/ml×h [19, 22]. These pharmacokinetic parameters compare favourably with equimolar doses of infusional 5-FU [22]. In addition, we have demonstrated that co-administration of LV does not alter the bioavailability and pharmacokinetics of tegafur derived from UFT. Likewise, UFT does not affect leucovorin and 5-methyltetrahydrofolate pharmacology [24].

Phase II studies in metastatic colorectal cancer using a 14 or 28 day schedule, in patients previously untreated for metastatic disease, showed response rates of 25–42% (Table 1) [19–21, 25]. These results have led to phase III randomised trials comparing the 28 day regimen of oral UFT/LV with i.v. 5-FU/LV. Two trials in previously untreated (except adjuvant therapy > 1 year earlier) metastatic colorectal cancer are nearing completion. A third, ongoing study undertaken by the National Surgical Adjuvant Breast and Bowel Project (NSABP C-06), compares UFT/LV to 5-FU/LV in the adjuvant setting in patients with resected stage II and III colon cancer. In these studies, a UFT dose of 300 mg/m^2/d is used, as the first cohort in one of the phase II trials had increased gastrointestinal toxicity over that predicted by phase I results [20]. Also, a daily dose of 75–90 mg LV is used in each of these studies, given saturability of LV oral bioavailability [26]. Two phase II studies of daily oral UFT/LV in patients with advanced colorectal cancer who failed previous therapy with bolus 5-FU showed no responses in 36 patients treated [23, 24]. Since protracted venous infusions of 5-FU yield superior results to bolus 5-FU when combined with external beam radiation [27], UFT is also being developed as a radiosensitiser in patients with rectal adenocarcinoma.

Based upon the available data, UFT is currently approved or awaiting approval for marketing in over 40 countries world-wide.

MORE POTENT DPD INHIBITION

As noted above, DPD accounts for rapid clearance of 5-FU. In patients with congenital deficiency of DPD, the half-life of 5-FU is markedly increased and fatal 5-FU toxicity has been reported [28]. 5-FU metabolism occurs predominantly in the liver, but DPD is expressed in many tissues, including the gastrointestinal tract. Gastrointestinal DPD accounts for the unpredictable bioavailability of orally administered 5-FU and wide interpatient variations in extraintestinal DPD contribute to interpatient variability in 5-FU pharmacokinetics. In addition, 5-FU degradation products have been implicated in toxicity [29]. Thus, inhibitors of DPD more potent than uracil are currently being developed to improve the oral bioavailability of 5-FU, alter its pharmacology to facilitate predictable prolonged continuous exposure and improve its therapeutic index.

Ethynyluracil

Ethynyluracil (5-ethynyl-2,4(1H,3H)-pyrimidinedione, GW776, 776C85, EU) is a mechanism-based irreversible inhibitor of DPD [30] (Figure 1). In preclinical models, EU

Table 1. *Phase II studies of UFT plus leucovorin*

Study [Reference]	Patients (*n*)	UFT dose (mg/m^2/d)*	LV dose (mg/d)*	Response rate (CR + PR) (*n* (%))
Meropol and colleagues [19]	8	350	90	2 (25)
Pazdur and colleagues [20]	54	350/300†	90	22 (41)
Saltz and colleagues [21]	20	350	15	5 (25)
Gonzalez-Baron and colleagues [25]	75	390	30	2 (39)

*UFT and leucovorin administered in 2 [25] or 3 [19–21] divided doses for 14 [25] or 28 [19–21] days. In Ref. 25, leucovorin 500 mg/m^2 was also administered i.v. on day 1. †After the initial 15 patients were treated at UFT 350 mg/m^2, the starting dose was reduced because of gastrointestinal toxicity. PR, partial response; CR, complete response.

results in depletion of mononuclear cell DPD activity associated with an increase in endogenous plasma uracil, the normal substrate for DPD [31]. EU does not have single agent antitumour activity. However, in rats bearing colorectal carcinoma, the administration of EU improved the therapeutic index of 5-FU and was superior to other modulators [32]. The addition of 5-FUH$_2$, an early metabolite of 5-FU, abrogates this benefit, suggesting that 5-FU degradation products may interfere with antitumour activity [33]. In dogs, higher plasma levels of 5-FU could be achieved when EU was co-administered, with elimination of dose-limiting neurotoxicity, providing evidence that 5-FU catabolites may also contribute to toxicity [29].

Based upon these animal data, phase I clinical trials with GW776 were undertaken. At non-toxic doses, elimination of DPD activity can be maintained for at least 24 h. When administered after GW776, the half-life of 5-FU is increased to 4–5 h, with renal excretion accounting for clearance [34, 35]. In addition, GW776 permits oral dosing of 5-FU, through elimination of intestinal DPD activity which accounts for the incomplete and erratic bioavailability of 5-FU administered alone. When administered with GW776, the oral bioavailability of 5-FU is 100% [34]. At a daily oral 5-FU dose of 25 mg/m^2 for 5 days (administered with GW776), the plasma area under the curve (AUC) for 5-FU is comparable to that achieved with a continuous intravenous infusion at 1000 mg/m^2/d [34].

Several administration schedules for the oral combination of GW776 and 5-FU are being developed. In one schedule, GW776 is administered once daily for 7 consecutive days and 5-FU is given on days 2–6. With a fixed GW776 dose of 18 mg/m^2/d, the recommended phase II 5-FU dose is 25 mg/m^2/d without leucovorin, or 20 mg/m^2/d with a daily leucovorin dose of 50 mg. The DLTs are neutropenia and diarrhoea [35]. In 24 patients with previously untreated colorectal cancer, 6 partial responses were observed [36]. Larger multicentre phase II studies, both with and without LV, are currently being conducted in the U.S. in patients with advanced colorectal cancer.

In an effort to mimic the pharmacology of continuous infusion 5-FU, a 28 day oral GW776/5-FU regimen is also being explored. Preliminary results of a phase I study show that twice daily oral dosing of 5-FU 1.8 mg/m^2 plus GW776 for 28 consecutive days is tolerated and may achieve biologically active plasma 5-FU levels [37]. A phase II study of this schedule in advanced colorectal cancer is underway.

S1

S1 is a combination of tegafur, 5-chloro-2,4-dihydroxypyridine (CDHP) and oxonic acid in a fixed molar ratio of 1:0.4:1. CDHP is a potent inhibitor of DPD. Oxonic acid is an inhibitor of phosphoribosyl transferase, an initial enzyme in the anabolic pathway that leads to 5-FU interference with RNA function [10]. Gastrointestinal inhibition of phosphoribosyl transferase may be able reduce diarrhoea associated with 5-FU administration. Daily oral administration of S1 to rats bearing advanced colorectal carcinoma showed a greater antitumour effect with less toxicity than an equivalent schedule of tegafur alone [38, 39]. In this model system, synergy with cisplatin was observed [39, 40]. An improved therapeutic index for S1 compared with 5-FU and UFT was also seen in sarcoma-bearing rats [41]. In a phase I study of twice daily oral dosing for 28 days, the DLTs for S1 were diarrhoea and neutropenia [42]. Further clinical development is underway.

CAPECITABINE

Capecitabine (Xeloda™, N4-pentoxycarbonyl-5′-deoxy-5-fluorocytidine) is a new oral fluoropyrimidine carbamate that is converted to 5-FU by three enzymatic steps (Figure 2). It was rationally designed in an effort to achieve tumour selectivity. Capecitabine is absorbed intact in the gastrointestinal tract and initially metabolised in the liver by carboxylesterase to 5′-deoxy-5-fluorocytidine (5′-dFCR). It is subsequently metabolised to 5′-deoxy-5-fluorouridine (5′-dFUR, doxifluridine,

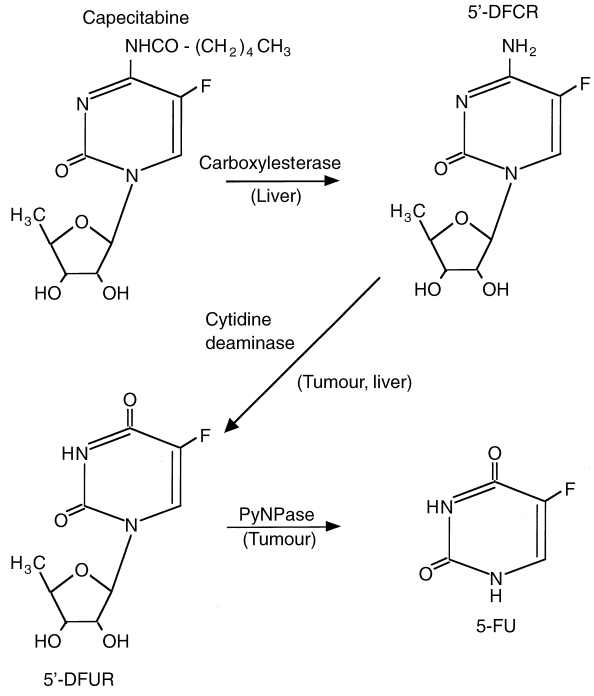

Figure 2. Activation of capecitabine. 5′-DFCR, 5′-deoxy-5-fluorocytidine; 5′-DFUR, 5′-deoxy-5-fluorouridine; PyNPase, pyrimidine nucleoside phosphorylase; 5-FU, 5-fluorouracil.

Fortulon™) by cytidine deaminase, expressed in higher concentrations in liver and tumour than normal tissues. Orally administered doxifluridine itself has shown a 32% response rate in advanced colorectal cancer [43], but with a significant incidence of severe diarrhoea, thought to be secondary to the presence of pyrimidine nucleoside phosphorylase (PyNPase) in small intestine, which converts doxifluridine to 5-FU. However, intratumoral concentrations of PyNPase are higher than normal tissues and, therefore, capecitabine has the potential to result in higher 5-FU concentrations in tumour relative to normal tissue. Since the conversion to doxifluridine does not take place in the gut, the therapeutic index of capecitabine may be improved over that of doxifluridine.

Preclinical models support the tumour selectivity of capecitabine. In human colon cancer xenografts capecitabine was effective against 5-FU-resistant tumours [44, 45]. At the MTDs of each agent, the tumour concentrations of 5-FU were more than 30 times higher with capecitabine than with 5-FU [45]. In addition, tumour concentrations of 5-FU were higher than plasma (127-fold) and muscle (22-fold) [45]. The therapeutic index of capecitabine was also superior to that of UFT [46].

Preliminary results of a clinical trial in patients with colorectal cancer undergoing surgical resection support the tumour selectivity of capecitabine [47]. 13 patients received capecitabine at 1255 mg/m^2 twice daily for 5–7 days preoperatively. At surgery, samples of tumour and adjacent normal tissue were obtained. In this small group of patients, the mean tumour:normal tissue ratio of 5-FU was 2.9:1.

In a phase I clinical trial of continuous daily capecitabine administered as two divided doses each day, the MTD was 1657 mg/m^2/d, with diarrhoea, palmar-plantar erythrodysesthaesia and nausea dose-limiting [48]. Peak plasma concentrations of capecitabine, 5′-dFCR and 5′-dFUR, are achieved at 30–90 min and decline exponentially with half-lives of 0.5–1 h [49]. Low plasma levels of 5-FU with AUC comparable to that achieved with continuous infusions of 5-FU are obtained at the MTD [50]. Pharmacokinetic parameters of capecitabine and metabolites are dose proportional and do not vary over the course of prolonged therapy [49].

A randomised phase II study of three capecitabine schedules has been conducted in patients with previously untreated advanced colorectal cancer [51]. 101 patients were randomised to receive:

(1) Capecitabine 1331 mg/m^2/d in two divided doses continuously;
(2) 2510 mg/m^2/d for 14 days followed by a 1 week rest (intermittent schedule); or
(3) the intermittent schedule with capecitabine 1657 mg/m^2/d plus LV 60 mg/d.

Preliminary results showed complete + partial response rates of 19, 28 and 24% in arms (1), (2) and (3), respectively. Based upon these results, the intermittent schedule of arm (2) is currently being tested in two phase III randomised trials against a 5 day intensive course schedule of i.v. 5-FU plus low-dose leucovorin in patients with previously untreated advanced colorectal cancer.

CONCLUSIONS

Oral administration of fluoropyrimidines may soon replace much of the i.v. use of 5-FU in colorectal cancer. Such a paradigm shift will require the demonstration of therapeutic equivalence in phase III studies comparing oral regimens with i.v. 5-FU in the adjuvant setting, as front-line therapy in advanced disease, and as radiosensitisation. Although oral therapy has intuitive benefits, clinical trials must prospectively include quality of life and pharmacoeconomic endpoints. Only then may i.v. therapy appropriately become a historical footnote.

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