

# Tegafur/Uracil + Calcium Folinate in Colorectal Cancer

## Double Modulation of Fluorouracil

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### Abstract

The oral chemotherapeutic agent tegafur/uracil (UFT®) is the first of a new class of anticancer drugs called dihydropyrimidine dehydrogenase inhibitory fluoropyrimidines. Tegafur/uracil combines uracil with the fluorouracil prodrug tegafur in a 4 : 1 molar ratio. Uracil competitively inhibits the degradation of fluorouracil, which results in the concentration of fluorouracil remaining at sustained levels in both plasma and tumour. Tegafur/uracil has been commercially available in Japan since 1983 and examined extensively in various tumours. Trials conducted in the US have focused on the combination of tegafur/uracil plus calcium folinate (calcium leucovorin) [ORZEL®]. Several phase I and II trials have evaluated the maximum tolerated dose, pharmacokinetics, efficacy, and safety of this combination in the treatment of colorectal cancer. Results have shown that tegafur/uracil at 300 mg/m<sup>2</sup>/day in divided doses given every 8 hours for 28 days provides prolonged exposure to fluorouracil. Furthermore, tegafur/uracil + calcium folinate is well tolerated, with dose-limiting toxicity manifesting as diarrhoea. Compared with intravenous fluorouracil plus folinic acid (leucovorin) regimens, tegafur/uracil + calcium folinate has similar efficacy with less toxicity and is more convenient because it is an oral regimen. Early studies have also shown potential cost savings because of fewer complications.

Colorectal cancer is the third leading cause of cancer mortality in males and females in the US, with an estimated 131 600 new cases and 55 500 deaths in 1998.<sup>[1]</sup> Even though the majority of tumours are surgically resectable at the time of diagnosis, disease in more than 50% of these patients will recur and require further treatment.

Fluorouracil is the most widely prescribed anti-neoplastic drug for the treatment of advanced colorectal cancer and is currently the only recommended agent for use as adjuvant chemotherapy in stage II and III disease.<sup>[2]</sup> It is primarily given as an intravenous infusion and frequently combined

with folinic acid (leucovorin), which acts as a biochemical modulator of fluorouracil. Some studies have suggested that a prolonged fluorouracil infusion results in superior response rates and may even increase median survival compared with that produced by bolus fluorouracil regimens.<sup>[3-5]</sup> However, protracted intravenous infusions may be expensive because they require the insertion of central intravenous catheters and the use of portable infusion pumps. In addition, catheter-related complications of venous thrombosis, catheter slippage, and infection can be noted in 30% of patients, requiring catheter replacement in 11% of

all patients.<sup>[6]</sup> An oral regimen that provides continuous fluorouracil exposure for prolonged periods of time without such complications would be an improvement over existing treatments.

## 1. History of Tegafur/Uracil

Synthesised more than 30 years ago by Hiller et al.,<sup>[7]</sup> tegafur is a prodrug of fluorouracil. Initial trials of tegafur in the US evaluated short-duration intravenous dosages, which resulted in high peak plasma concentrations of tegafur and fluorouracil but unacceptable toxicity. Toxic reactions consisted of myelosuppression, diarrhoea, and central nervous system toxicity. This unfavourable toxicity profile led to the abandonment of tegafur development in the US for more than 2 decades.<sup>[8-10]</sup>

In contrast to the US experience, Japanese investigators used low dose oral schedules of tegafur over prolonged periods and obtained moderate efficacy in gastric, colon, and breast cancers, with minimal neutropenia and oral mucositis observed.<sup>[11,12]</sup> Tegafur/uracil (UFT®) is an oral antineoplastic drug that combines uracil and tegafur in a 4 : 1 molar ratio.<sup>[13,14]</sup> Fluorouracil is generated from tegafur and is subsequently modulated by uracil, which *in vitro* competitively inhibits the enzyme dihydropyrimidine dehydrogenase (DPD).<sup>[15,16]</sup> Tegafur/uracil is therefore the first in a new class of anticancer agents called DPD inhibitory fluoropyrimidines. Since early 1980, tegafur/uracil has been largely studied in, and used to treat, solid tumours in Japan,<sup>[17]</sup> where it was approved in 1983 for use in a variety of solid tumours. In 1990 US investigators initiated phase I trials of single agent tegafur/uracil,<sup>[18]</sup> with subsequent phase I trials combining tegafur/uracil with oral calcium folinate (calcium leucovorin) [ORZEL®] in attempts to biochemically modulate the fluorouracil generated from tegafur/uracil by calcium folinate.<sup>[19]</sup> Treatment with tegafur/uracil + calcium folinate therefore provides dual-modulated fluoropyrimidine therapy, i.e. modulation by both uracil and calcium folinate.

## 2. Pharmacology

Tegafur is slowly metabolised to fluorouracil, primarily by the hepatic microsomal cytochrome P450 pathway.<sup>[20]</sup> The resultant agent has the same metabolism and cytotoxic activity as intravenous fluorouracil. *In vivo*, fluorouracil is metabolised to 2 active nucleotides: fluorodeoxyuridine monophosphate, which forms a complex with thymidylate synthase that affects DNA synthesis, and fluorouridine triphosphate, which is integrated into cellular RNA and may alter its processing and function.<sup>[12,21,22]</sup> As hypothesised, tegafur/uracil produced higher concentrations of fluorouracil in breast and gastric tumours than did single agent tegafur.<sup>[23,24]</sup> In addition, increased antitumour activity, characterised by increased response rates, was also demonstrated.<sup>[25,26]</sup>

The modulation of fluorouracil by calcium folinate is characterised by the stabilisation of the fluorodeoxyuridylate-thymidylate synthase covalent ternary complex in the presence of 5,10-methylene tetrahydrofolate. This modulation increases inhibition of the enzyme thymidylate synthase in the DNA synthetic pathway, which enhances the cytotoxic activity of fluorouracil.<sup>[21,27-29]</sup> Uracil and calcium folinate provide a double modulation of the fluorouracil generated from tegafur. This combination has been demonstrated to be superior to tegafur/uracil alone in rats bearing subcutaneous advanced colorectal tumours,<sup>[27]</sup> and to increase the degree of thymidylate synthase inhibition in patients with gastric cancer.<sup>[30]</sup>

## 3. Pharmacokinetics

Initial phase I studies evaluated the pharmacokinetics of tegafur, uracil, and fluorouracil after administration of tegafur/uracil to 21 patients with solid tumours (Dr D.H. Ho, University of Texas M.D. Anderson Cancer Center, personal communication). Two schedules were studied: a 5-day course with doses starting at 360 mg/m<sup>2</sup>/day and escalating to 900 mg/m<sup>2</sup>/day, and a 28-day course with doses starting at 180 mg/m<sup>2</sup>/day and escalating to 450 mg/m<sup>2</sup>/day. The total daily dose was

divided into 3 doses, with one dose given every 8 hours. Plasma concentrations were highest for tegafur, followed by uracil and fluorouracil. Peak plasma concentrations of fluorouracil were achieved between 0.5 and 2 hours after the dose.

The pharmacokinetics of intravenous fluorouracil were compared with those of oral tegafur/uracil administered in an equimolar dosage in 10 patients.<sup>[31]</sup> Patients first received a continuous intravenous infusion of fluorouracil at 250 mg/m<sup>2</sup>/day over 5 days, followed by a washout period of 1 week, and tegafur/uracil at 370 mg/m<sup>2</sup>/day. Following the initiation of the intravenous fluorouracil, plasma levels rapidly achieved a steady-state concentration of 0.08 mg/L, which was maintained for the 5 days. After the administration of tegafur/uracil, the mean peak plasma concentration of fluorouracil ranged from 0.3 to 0.35 mg/L in the first 5 days and reached 0.44 mg/L by day 25. Although the fluorouracil area under the plasma concentration-time curve (AUC) was greater for the intravenous infusion on day 1, by day 5, it was similar for both regimens. These studies indicate that tegafur/uracil delivers higher peak plasma concentrations of fluorouracil and similar systemic exposure compared with an equimolar dosage of continuously infused fluorouracil.

#### 4. Dose-Ranging Trials

##### 4.1 Single Agent Tegafur/Uracil

Initial phase I trials of single agent tegafur/uracil included 2 schedules: 5 days of drug administration repeated every 21 days, and 28 days of drug

administration repeated every 35 days.<sup>[18]</sup> The daily dose of tegafur/uracil was given in 3 doses every 8 hours. In the 5-day schedule, doses ranging from 360 to 900 mg/m<sup>2</sup>/day were evaluated. Dose-limiting toxicity (DLT) was seen at 900 mg/m<sup>2</sup>/day, manifesting as grade 4 granulocytopenia in 4 of 5 patients. Grade 4 granulocytopenia developed in only 1 of 8 patients treated at 800 mg/m<sup>2</sup>/day (recommended phase II dose). In the 28-day schedule, doses from 180 to 450 mg/m<sup>2</sup>/day were evaluated. A steep dose-toxicity relationship was seen, with DLT occurring at doses above 360 mg/m<sup>2</sup>/day and manifesting as grades 3 and 4 diarrhoea. Because the DLT occurred above but not at 360 mg/m<sup>2</sup>/day, this dose was selected for future phase II trials.

##### 4.2 Tegafur/Uracil + Calcium Folinate

Although initial phase I studies have evaluated tegafur/uracil as a single agent, further studies have concentrated on tegafur/uracil + calcium folinate. Four large institutions in the US conducted similar phase I trials of tegafur/uracil + calcium folinate, given in 3 daily doses at 8-hour intervals (table I).<sup>[19,32-35]</sup> As in the single agent tegafur/uracil trials, the DLT manifested as diarrhoea and occurred at doses between 350 and 400 mg/m<sup>2</sup>/day. Attempts at reducing the duration of treatment by using a 14-day schedule did not allow a substantially higher dose of tegafur/uracil.<sup>[32,36]</sup>

#### 5. Phase II Trials in Colorectal Cancer

In 1993 a phase II trial of tegafur/uracil + calcium folinate was initiated at M.D. Anderson Cancer

**Table I.** Phase I trials of tegafur/uracil + calcium folinate (calcium leucovorin) [ORZEL®] in the US

Institution	MTD of tegafur/uracil (mg/m <sup>2</sup> /day)	Length of each course (days)	Calcium folinate dose (mg/day)	No. of patients
MDACC <sup>[18]</sup>	300	28	150	38
MDACC <sup>[32]</sup>	350	14	150	14
RPCI <sup>[33]</sup>	350	28	150	18
USC <sup>[34]</sup>	350	28	15	15
MSKCC <sup>[35]</sup>	250	28	15	21

**MDACC** = University of Texas M.D. Anderson Cancer Center (Houston, TX); **MSKCC** = Memorial Sloan-Kettering Cancer Center (New York City, NY); **MTD** = maximum tolerated dose; **RPCI** = Roswell Park Cancer Institute (Buffalo, NY); **USC** = University of Southern California (Los Angeles, CA).

**Table II.** Comparison of grade 3/4 adverse effects in patients treated with tegafur/uracil + calcium folinate (calcium leucovorin) [ORZEL®]<sup>a</sup>

Grade 3/4 adverse effects	Tegafur/uracil dose	
	350 mg/m <sup>2</sup> /day	300 mg/m <sup>2</sup> /day
	[n = 7]	[n = 38]
	(% of patients)	
Diarrhoea	71	11
Nausea	14	0
Vomiting	14	5
Abdominal cramping	0	3
Anorexia	14	0
Fatigue	14	5

<sup>a</sup> This phase II trial was conducted at University of Texas M.D. Anderson Cancer Center, Houston, Texas. The calcium folinate dose was 150 mg/day. Daily doses of tegafur/uracil and calcium folinate were divided and administered every 8 hours.

Center.<sup>[19]</sup> 45 patients were enrolled in this trial; all had measurable disease and no prior chemotherapy for metastatic colorectal cancer. The first 7 patients received tegafur/uracil 350 mg/m<sup>2</sup>/day + calcium folinate 150 mg/day for 28 days. However, prolonged grade 3 diarrhoea developed in 5 of these patients. Subsequent patients were treated with tegafur/uracil at 300 mg/m<sup>2</sup>/day + calcium folinate 150 mg/day. The toxic effects of the 2 doses are compared in table II. The lower dose was associated with less grade 3 diarrhoea, which occurred in only 11% of patients compared with 71% observed at the higher dose. No significant neutropenia, thrombocytopenia, hand-foot syndrome, mucositis, or alopecia was seen.

Treatment delays in the group given tegafur/uracil 300 mg/m<sup>2</sup>/day were insignificant, with only 11 of 127 courses being interrupted for 5 to 10 days and only one being interrupted for more than 10 days. This was in contrast to patients treated with tegafur/uracil 350 mg/m<sup>2</sup>/day, in whom 20% of courses were delayed for more than 10 days.

Among the 38 patients treated with 300 mg/m<sup>2</sup>/day, there were 15 partial responses (39%) and one complete response (3%).<sup>[19]</sup> Among the 7 patients treated with 350 mg/m<sup>2</sup>/day, there were 3 partial responses. The overall response rate for the combined group was 42% (95% confidence interval: 28 to 58%). Responses were seen in liver, lung, and bones. Median survival of patients entered in

this trial was 16 months. Subsequent trials of tegafur/uracil + calcium folinate have used a calcium folinate dosage of 75 or 90 mg/day (25 to 30mg every 8 hours), because of the saturable oral absorption of calcium folinate when the dose exceeds 25mg.<sup>[37]</sup>

An additional phase II trial included 21 patients with advanced colorectal cancer who received tegafur/uracil at 350 mg/m<sup>2</sup>/day plus calcium folinate at 15 mg/day, with each drug given in 3 daily doses every 8 hours for 28 days followed by a 1-week rest.<sup>[35]</sup> Of 20 assessable patients, a complete response was seen in one patient and partial responses in 4, giving an overall response rate of 25%. The most commonly observed adverse effect was diarrhoea (grade 3 in 3 patients and grade 4 in one patient).

Several international phase II trials using different regimens have been conducted in patients with colorectal cancer.<sup>[38,39]</sup> Subsequent trials of tegafur/uracil + calcium folinate have used a calcium folinate dose of 75 or 90 mg/day (25 to 30mg every 8 hours), because of the saturable oral absorption of calcium folinate when the dose exceeds 25mg.<sup>[37]</sup> These regimens have focused on administering tegafur/uracil and calcium folinate over 14 days, with each drug given twice daily. Objective response rates ranged from 25 to 40%, corroborating the response rates observed in the US studies.

The Oncopaz clinical trial group in Spain evaluated tegafur/uracil + calcium folinate in elderly patients (aged more than 70 years; median age, 74 years) with advanced colorectal cancer.<sup>[40]</sup> They observed an overall response rate of 29%, with diarrhoea as the major toxicity (10% grade 3 or 4). Tegafur/uracil + calcium folinate was found to be well tolerated and feasible as outpatient treatment for elderly patients.

The treatment of localised rectal cancer has conventionally combined the use of protracted intravenous fluorouracil with radiotherapy.<sup>[41]</sup> Investigators at M.D. Anderson are currently conducting a phase I trial in which tegafur/uracil + calcium folinate will be administered concurrently with pelvic irradiation. Four to 6 weeks after the completion of

pelvic irradiation, patients will undergo definitive surgery followed by 4 more courses of tegafur/uracil + calcium folinate.<sup>[42]</sup>

## 6. Phase III Trials in Colorectal Cancer

The results obtained in phase II trials led to the initiation of two large phase III trials of tegafur/uracil + calcium folinate as first-line treatment for metastatic colorectal cancer in North America and Europe. These trials compare tegafur/uracil + calcium folinate versus a 5-day intravenous bolus fluorouracil and folinic acid regimen. The trials are using tegafur/uracil at 300 mg/m<sup>2</sup>/day plus calcium folinate at 75 to 90 mg/day, with both drugs given in 3 daily doses at 8-hour intervals for 28 days, with a 1-week rest between courses. These doses were selected because of their favourable toxicity profiles and response rates, as observed in phase II trials.<sup>[19]</sup> A phase III trial which has enrolled 816 patients has survival as the primary end-point. In addition to evaluating efficacy (survival, response rates, time to progression) and toxicity, this trial also will compare quality of life, control of disease symptoms, and pharmacoeconomics of the 2 treatments. An additional phase III trial has completed patient accrual. The National Surgical Adjuvant Breast and Bowel Project (NSABP) [NSABP C-06] is comparing tegafur/uracil + calcium folinate with weekly infusions of fluorouracil and folinic acid in the adjuvant treatment of patients with surgically resected stage II and III colon cancer. A total of 1500 patients have been enrolled, and 5-year disease-free survival and overall survival are the primary end-points.

## 7. Pharmacoeconomics

Tegafur/uracil + calcium folinate may have the potential to reduce the overall treatment costs, through reductions in both toxicity and hospitalisation, for the management of toxicities. Administration costs are also reduced.

Investigators in Brazil and Argentina recently compared the pharmacoeconomics of tegafur/uracil versus intravenous fluorouracil in the treat-

ment of metastatic colorectal cancer.<sup>[43]</sup> A panel of experts from each country developed a model identifying clinical practices associated with chemotherapy administration and adverse effects management. These models were then evaluated for resource utilisation trends. Cost data were derived from a survey of local healthcare institutions. These data were used to calculate the average cost per patient receiving 6 cycles of intravenous fluorouracil with levamisole and/or folinic acid versus the cost per patient receiving an oral regimen of tegafur/uracil + calcium folinate. In both countries cost savings are noted for the use of tegafur/uracil + calcium folinate compared with intravenous fluorouracil plus levamisole and/or folinic acid. The differences were attributed to lower costs for managing adverse effects and drug administration.

## 8. Summary

Tegafur/uracil + calcium folinate has been shown to be a convenient, well tolerated, and effective treatment regimen for advanced colorectal cancer.<sup>[19,35]</sup> Tegafur/uracil + calcium folinate produces a higher concentration of fluorouracil in plasma compared with equimolar doses of protracted intravenous fluorouracil and produces similar total drug exposure as measured by the AUC.

The recommended tegafur/uracil + calcium folinate dose (300mg tegafur/uracil per m<sup>2</sup>/day divided into 3 doses given every 8 hours for 28 days, combined with calcium folinate, 25 to 30mg every 8 hours) is well tolerated. The primary toxic effect is diarrhoea (generally grade 2), which can be managed by eliminating several doses with subsequent toxicity resolution. In addition, unlike toxic effects produced by intravenous fluorouracil regimens, neutropenia is uncommon in patients treated with tegafur/uracil + calcium folinate. Potential advantages of this oral regimen compared with intravenous bolus fluorouracil plus folinic acid are summarised below:

- Convenience
- Fewer office visits
- Fewer venous punctures
- Reduced neutropenia

- Fewer hospitalisations for toxicity management
- Reduced oral mucositis
- Reduced frequency of laboratory tests.

Tegafur/uracil + calcium folinate can be easily administered in the outpatient setting, resulting in potential cost savings, convenience for patients and, possibly, improved quality of life.

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