

5-Ethynyluracil (776C85): Effects on the Antitumor Activity and Pharmacokinetics of Tegafur, a Prodrug of 5-Fluorouracil¹

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ABSTRACT

We studied the effects of 5-ethynyluracil (776C85 and 776C), a potent mechanism-based inactivator of dihydropyrimidine dehydrogenase, on the antitumor efficacy and pharmacokinetics of tegafur (FT), a prodrug of 5-fluorouracil (5-FU), in rats with large s.c. colon carcinoma. Rats were dosed p.o. once daily for 7 days with either FT, FT and uracil in a 1:4 molar ratio (UFT), FT 1 h after 776C (776C/FT), or UFT 1 h after 776C (776C/UFT). 776C, which was dosed at 1 mg/kg, had neither intrinsic antitumor activity nor toxicity. The rank order in antitumor efficacy at the maximal tolerated dose of the FT (mg/kg/day) component was 776C/FT (5 mg/kg/day) \geq UFT (80 mg/kg/day) = 776C/UFT (5 mg/kg/day) \gg FT (200 mg/kg/day). One-hundred % of rats treated with 776C/FT had complete and sustained tumor regression with no severe toxicity. The area under the plasma 5-FU concentration *versus* the time curve generated from UFT, FT, and 776C/FT at their maximum tolerated dose was 140, 50, and 27 $\mu\text{M} \cdot \text{h}$, respectively. The area under the concentration in plasma *versus* time curve did not correlate with the rank order of antitumor efficacy. The vast majority of 5-FU derived from FT (alone) appeared to be rapidly catabolized. Furthermore, plasma exposure of 5-FU derived from UFT was more variable than that from 776C/FT. Each therapy also produced different levels of plasma uracil. Endogenous plasma uracil levels (1–3 μM) were not affected by FT but increased to 100 μM after dosing with 776C. Plasma uracil from UFT was 800 μM 1 h after dosing. These results suggest that moderately elevated uracil (776C/FT) may be beneficial, whereas uracil that is greatly elevated during the first 5 h (UFT) and 5-FU catabolites (FT alone) may interfere with antitumor efficacy. 776C, coadministered with FT, could provide once-a-day oral therapy for cancer patients.

INTRODUCTION

FT³ is an oral prodrug of 5-FU that is used widely in Asian countries. The tetrahydrofuryl group is slowly hydrolyzed to generate low levels of 5-FU (1, 2). Uracil in a 4:1 molar ratio with FT is usually coadministered with FT (UFT) to competitively inhibit the degradation of 5-FU by DPD (EC 1.3.1.2; uracil reductase) (3, 4). However, because uracil is rapidly catabolized by DPD and because DPD levels vary greatly among individuals (5) and fluctuate with time within individuals (6), uracil provides only limited and unpredictable preservation of 5-FU (7). Therefore, we initiated studies with 5-ethynyluracil (776C85 and 776C), a potent mechanism-based *in vitro* (8) and *in vivo* (9) inactivator of DPD. Because new DPD is synthesized with a half-time of 63 h (9), 776C temporarily produces an enzyme-deficient state in treated animals. By eliminating DPD, 776C was expected to

provide prolonged and uniform preservation of 5-FU. Furthermore, based on earlier studies with 5-FU, we also anticipated that 776C could enhance the therapeutic benefits of FT by preventing the formation of 5-FU catabolites and/or preserving uracil and thymine (reviewed in Refs. 10, 11).

These secondary effects probably account for the findings that (a) 776C increases the therapeutic index of 5-FU by 2- to 4-fold in two tumor-bearing mouse models (12); and (b) 776C increases the therapeutic index of 5-FU by 6-fold and markedly improves the absolute efficacy in rats with advanced colon carcinoma (13). Presently, we chose the tumor-bearing rat model to study the effects of 776C on the antitumor efficacy and the pharmacokinetics of FT. Preliminary findings have been presented elsewhere (14, 15).

MATERIALS AND METHODS

Materials. 776C was synthesized at the Wellcome Research Laboratories (Research Triangle Park, NC). 5-FU, uracil, and FT were purchased from Sigma Chemical Co. (St. Louis, MO). UFT was generously provided by Taiho Pharmaceuticals (Tokyo, Japan). Methyl cellulose (400 centipoise) was obtained from Fisher Scientific Co. (Fair Lawn, NJ).

Antitumor Therapy. Ward colorectal carcinoma tumor fragments were transplanted s.c. into 150–200 g rats, and treatment was initiated 14–16 days later when tumor weights were approximately 2.5–3.0 g as described previously (13). Each group had four rats/experiment, and each experiment was repeated four to six times. Tumor regression was expressed as PR when tumor weight was reduced by at least 50% and as CR when tumors were completely resolved and were not detectable for 90 days.

Drug Dosing. FT and UFT were dosed in 1% methyl cellulose suspensions by gavage. The dose indicated for UFT refers to the FT content. 776C was dissolved in sterile saline adjusted to pH 10 with NaOH and was dosed at 1 mg/kg 1 h before FT or UFT.

Pharmacokinetic Samples and Analyses. Male CD rats with jugular vein cannulas were obtained from Charles River Breeding Laboratories. Whole blood samples (0.3 ml) were collected via the cannula, which was then flushed with 0.3 ml saline. Blood samples were treated with 50 μl of 5% EDTA, and plasma was isolated by centrifugation (3000 $\times g$ for 10 min) and was stored at -20°C . Plasma samples were thawed, extracted with 85% ice-cold ACN, evaporated to dryness, and dissolved in water for high-performance liquid chromatography analyses on a reverse-phase Microsorb C₁₈ column (250 \times 4.6-mm, inner diameter; Rainin, Woburn, MA) with a Dynamax axial compression guard column. A Waters model 712 WISP automated sample injector was used for sample injection, and microcomputer-controlled LDC Analytical constaMetric 4100 high-performance liquid chromatography pumps delivered the mobile phases: 50 mM ammonium acetate buffer (pH 5.6) and 0.5% ACN (buffer A) and 50 mM ammonium acetate buffer (pH 5.6) and 25% ACN (buffer B). A three-part elution program was used: (a) a 4-min isocratic elution in buffer A at 1 ml/min; (b) a 26-min isocratic elution in buffer A at 0.1 ml/min; and (c) a 20-min linear gradient to 100% buffer B at 1 ml/min. The flow rate adjustments after segments one and two were made over 1 min. The effluent was monitored by UV absorption at 265 nm by using a LDC Analytical spectroMonitor 4100 variable wavelength detector. Uracil, 5-FU, and FT had retention times of 13, 22, and 45 min, respectively.

Pharmacokinetic Data Analysis. The elimination portion of semilogarithmic plasma concentration *versus* time plots was analyzed by linear regression. AUC values were determined by the linear trapezoidal method for measured values. The residual portion of the AUC was calculated by adding the quotient of the final measured plasma concentration divided by the terminal elimination

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³ The abbreviations used are: FT, tegafur or Florafur [1-(2-tetrahydrofuryl)-5-fluorouracil]; 5-FU, 5-fluorouracil; 776C, 5-ethynyluracil; UFT, FT and uracil dosed in a 1:4 molar ratio; 776C/FT, FT dosed 1 h after 1 mg/kg 776C; 776C/UFT, UFT dosed 1 h after 1 mg/kg 776C; DPD, dihydropyrimidine dehydrogenase; PR, transitory (at least 50%) tumor regression; CR, complete tumor regression that is sustained for 90 days posttherapy; MTD, maximal tolerated dose; AUC, area under the concentration in plasma *versus* time curve; ACN, acetonitrile.

rate constant. The UV peak areas and retention times in plasma samples were compared to those of a standard curve prepared from known concentrations of uracil, 5-FU, and FT added to plasma or water. Recoveries were 88–98%, and plots of UV peak area versus concentration were linear between ~0.5 and 300 μM .

RESULTS

Antitumor Activity. Rats with large s.c. colon tumors were dosed p.o. once-a-day for 7 days with either FT, UFT, 776C/FT, or 776C/UFT, and their tumor weights were measured. The results for the therapies at their MTD (FT content), 200 mg/kg/day FT, 80 mg/kg/day UFT, and 5 mg/kg/day 776C/FT, are shown in Fig. 1. The modest antitumor activity of FT was significantly improved by adding uracil in a 4:1 molar ratio (UFT), and was markedly improved by low doses of 776C (776C/FT). The three regimens produced CR in 19, 75, and 100% of the rats, respectively. Moreover, a single dose of 776C in FT-treated rats was as efficacious as seven daily doses of UFT (Table 1). Interestingly, in 776C-treated rats, 5 and 2.5 mg/kg/day of FT was more effective than the same doses of FT administered with uracil as UFT (Table 1). Furthermore, the antitumor activity of UFT was also variable among experiments. For example, 80 mg/kg/day UFT produced CR in 25% of the animals in one experiment, in 75% of the animals in two experiments, and in 100% of the animals in two experiments. In contrast, 776C/FT produced 100% CR in all six experiments.

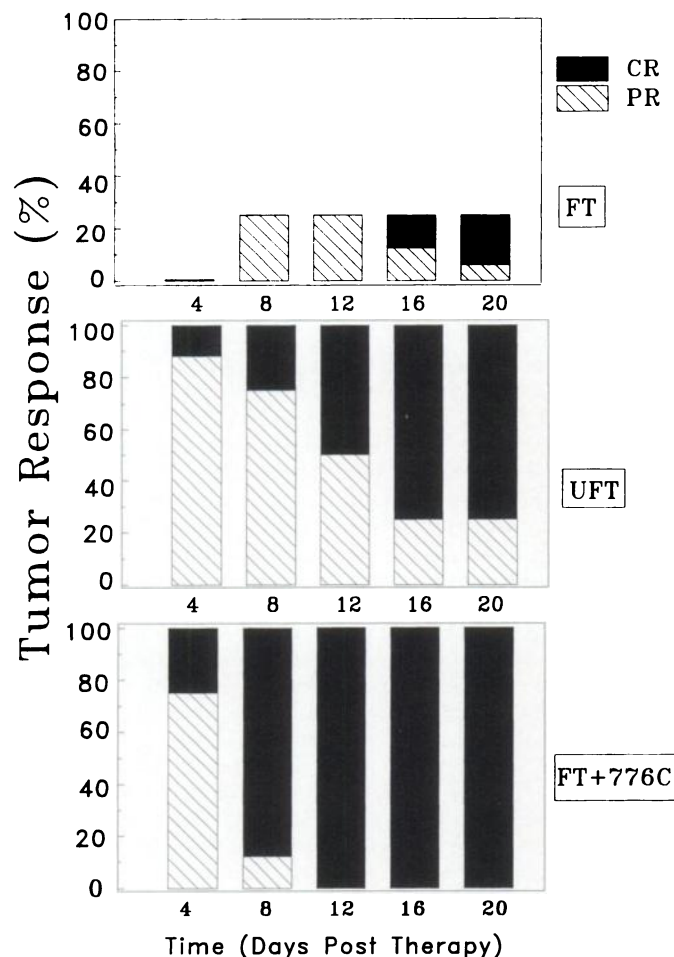


Fig. 1. Antitumor efficacy of the indicated oral therapies in rats dosed daily on days 1–7 at the corresponding MTDs (FT content); 200 mg/kg FT, 80 mg/kg UFT, or 5 mg/kg 776C/FT. The data are the average of four to six experiments.

Table 1. Antitumor efficacy of FT regimens

Drug ^a (mg/kg/day)	Modulator (days dosed)	Antitumor activity	
		PR (%)	CR (%)
FT (200)	None	6	19
FT (100)	None	13	0
FT (5)	776C (day 1)	25	75
FT (5)	776C (days 1, 4)	12	88
FT (5)	776C (days 1–7)	0	100
FT (2.5)	776C (days 1–7)	40	60
UFT (80)	None	25	75
UFT (40)	None	25	13
UFT (5)	776C (days 1–7)	25	75
UFT (2.5)	776C (days 1–7)	75	0

^a Dosed daily for 7 days.

Table 2. Toxicity of FT regimens

Drugs ^a (mg/kg/day)	MWL ^b (%)	Incidence (%)		
		Diarrhea	Stomatitis	Death
FT (250)	26 ± 3	50	25	75
FT (200) ^c	12 ± 2	0	0	0
FT (10) + 776C (1)	24 ± 4	50	75	100
FT (6) + 776C (1)	20 ± 5	13	38	38
FT (5) + 776C (1) ^c	13 ± 1	0	0	0
FT (5) + 776C (1) (day 1) ^d	4 ± 1	0	0	0
FT (5) + 776C (1) (day 1 & 4) ^d	5 ± 2	0	0	0
UFT (100)	22 ± 7	50	25	75
UFT (80) ^c	12 ± 2	0	13	0
UFT (10) + 776C (1)	22 ± 2	25	50	75
UFT (5) + 776C (1) ^c	12 ± 2	0	0	0

^a Dosed daily for 7 days except where indicated for 776C.

^b Maximal transitory weight loss.

^c MTD.

^d for 776C.

Toxicity. At the MTD, FT, 776C/FT, and 776C/UFT caused only 12–13% transitory weight loss, and UFT caused similar weight loss plus stomatitis in 13% of the rats (Table 2). At doses above the MTD, all regimens produced diarrhea, stomatitis, and death.

Therapeutic Window. 776C/FT produced CR over a wider dosing range than either UFT or FT (Table 1). At one-half of the MTD, 776C/FT still produced CR in 60% and PR in 40% of the animals. UFT was less effective at one-half of the MTD, producing CR in only 13% and PR in 25% of the animals.

Pharmacokinetics of FT, UFT, and 776C/FT at the MTD. The pharmacokinetic profiles of FT, uracil, and 5-FU in rats treated with the MTD of FT, UFT, or 776C/FT are shown in Fig. 2. AUC values and plasma terminal half-lives are presented in Table 3. FT dosed at 200 mg/kg and UFT at 80 mg/kg resulted in large plasma levels of FT. 776C/FT (5 mg/kg) produced a FT concentration time profile that was much smaller but parallel to the other curves (Fig. 2A). The terminal $t_{1/2}$ values of FT were similar (2.9–3.1 h) for the three dosing regimens.

Endogenous plasma uracil levels (1–3 μM) were not affected by FT alone but increased to approximately 100 μM after dosing with 1 mg/kg 776C and remained >70 μM for at least 15 h (Fig. 2B). Plasma uracil derived from UFT was 800 μM 1 h after dosing and returned to basal levels by 6 h.

The 5-FU concentration time profiles are compared in Fig. 2C. UFT provided the largest plasma exposure to 5-FU with an AUC of 140 $\mu\text{M} \cdot \text{h}$. As expected, the plasma profiles of 5-FU and uracil were parallel in UFT-treated animals. The AUC of 5-FU generated from 776C/FT, 27 $\mu\text{M} \cdot \text{h}$, was much smaller and was even less than that from FT alone, 50 $\mu\text{M} \cdot \text{h}$. After approximately 8 h, plasma 5-FU and FT from these three dosing regimens decreased in parallel with terminal $t_{1/2}$ values of approximately 3 h.

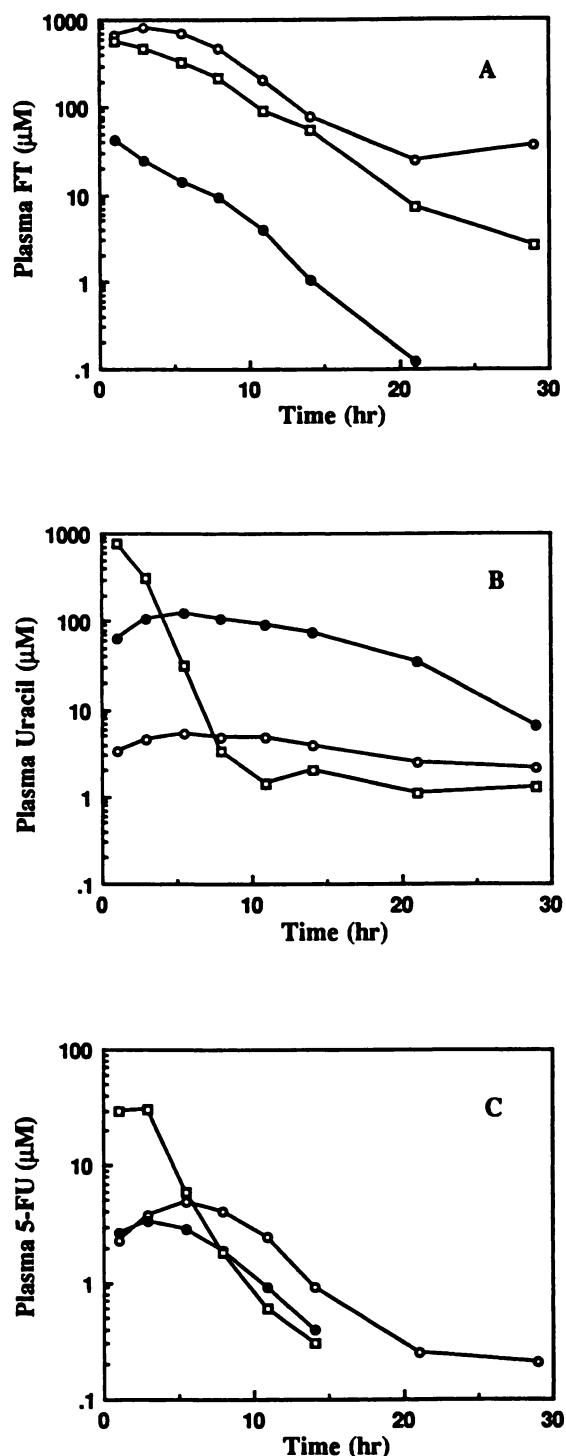


Fig. 2. Plasma concentration *versus* time profiles of FT (A), uracil (B), and 5-FU (C) in rats dosed p.o. with the following therapies at the corresponding MTDs: 200 mg/kg FT (○), 80 mg/kg UFT (□), or 5 mg/kg 776C/FT (●). Points, mean values from 3 to 5 rats.

Interestingly, when the pharmacokinetics of UFT were repeated on different days, the plasma half-life and AUC of FT were fairly reproducible, but the AUC and half-life for 5-FU were variable. The AUC of uracil from UFT also varied among experiments (data not shown). Thus, these data support the earlier study showing that the level of rat DPD varies considerably on different days (9) and suggest that 776C may decrease the variability of 5-FU in plasma.

Effect of 776C on the Variability of 5-FU Derived from FT. The plasma 5-FU concentration *versus* time profiles were measured in

different rats treated with UFT or 776C/FT at the same dose of FT (20 mg/kg) on different days over several months. As noted above, the plasma profile of 5-FU derived from UFT was quite variable. Plasma 5-FU reached peaks varying from 1 to 10 μM and was approximately 1 μM by 3.5 h in all animals. The AUC was $12 \pm 9 \mu\text{M} \cdot \text{h}$. In contrast, the plasma 5-FU profiles in rats dosed with 776C/FT were fairly uniform and more prolonged. Plasma 5-FU levels peaked at 10–17 μM and were still approximately 5 μM 9 h after dosing. The AUC was $100 \pm 20 \mu\text{M} \cdot \text{h}$.

DISCUSSION

776C very effectively enhanced the antitumor activity of FT. All rats with large s.c. tumors that were treated daily for 7 days with 1 mg/kg 776C plus 5 mg/kg/day FT had sustained CR with no severe toxicity. Although uracil also improved the modest antitumor activity of FT, it was not as consistently effective as 776C as a modulator. The increased efficacy with 776C may be due in part to its reproducible ability to block 5-FU catabolism.

Because uracil and 5-FU are equally efficient substrates of DPD (16, 17), they compete for catabolism by DPD. Therefore, 5-FU protection by uracil is lost as uracil is catabolized. Furthermore, because DPD levels vary widely in cancer patients (5, 6), 5-FU levels derived from UFT also vary widely (7, 18). Six patients receiving 300 mg/m² UFT (FT content) had plasma AUC values for 5-FU that varied 12-fold and corresponded to a 13-fold difference in uracil AUC values, whereas FT AUC values varied <2-fold (7). Our data show that the AUC of 5-FU generated from UFT also varies greatly among individual rats. On the other hand, 776C, an irreversible inactivator of DPD (8) that eliminates DPD (9), provided prolonged and uniform preservation of 5-FU generated from FT. Phase 1 clinical studies indicate that a daily oral dose of 0.1 mg/kg 776C maintains DPD inactivated in cancer patients (19). Thus, in light of the 7- to 10- h half-life of FT in humans (18, 20, 21), 776C and FT could be coadministered once-a-day in a single dosage form.

The pharmacokinetic data provide clues to the other mechanisms by which 776C improves the antitumor efficacy of FT and 5-FU. Although 776C/FT produced the best antitumor therapy most consistently, it generated the smallest plasma exposure of 5-FU. In fact, the 5-FU plasma AUC generated from the three regimens at their MTD was 140, 50, and 27 $\mu\text{M} \cdot \text{h}$ for UFT, FT, and 776C/FT, respectively, and did not correlate with the rank order of antitumor efficacy, which was 776C/FT \geq UFT \gg FT. Previously, we found in the same tumor model that 776C plus 5-FU was considerably more efficacious than 5-FU alone even when the latter was dosed at the MTD by continuous infusion. Therefore, we concluded that 776C must be conferring benefits that were in addition to those resulting from improved systemic exposure to 5-FU (13). We hypothesized that the lack of 5-FU catabolites and/or the elevation of endogenous uracil and/or thymine, which result from DPD inactivation, improve antitumor efficacy and/or decrease host toxicity (12, 13). However, because UFT produced a 5-fold greater plasma 5-FU AUC than 776C/FT produced, but

Table 3. AUC and terminal $t_{1/2}$ values^a of FT and 5-FU after dosing with FT, UFT, or 776C/FT

Treatment (mg/kg)	FT		5-FU	
	$t_{1/2}$ (h)	AUC ($\mu\text{M} \cdot \text{h}$)	$t_{1/2}$ (h)	AUC ($\mu\text{M} \cdot \text{h}$)
FT (200)	$3.0^b \pm 0.6$	7300 ± 700	$3.2^b \pm 0.4$	50 ± 8
UFT (80)	3.2 ± 0.4	4000 ± 600	3 ± 2	140 ± 60
776C/FT (5)	2.9 ± 0.4	260 ± 50	2.5 ± 0.7	27 ± 4

^a Mean \pm SD of 3–5 determinations.

^b The $t_{1/2}$ value of FT and 5-FU was estimated from the 8–21 h time points of Fig. 2.

was less consistently efficacious, it appeared that the large concomitant exposure to uracil from UFT may have decreased the antitumor efficacy of 5-FU. This conclusion is supported by our finding that 776C/UFT was less efficacious than 776C/FT. The exogenous uracil of the former constitutes the only difference between these two regimens.

Although large exposures to uracil appear to decrease 5-FU efficacy, moderate exposures may still be beneficial. Thus, 776C/FT, which elevated endogenous uracil from approximately 2–100 μM , was markedly more efficacious than FT alone, which does not affect uracil levels. Although thymine levels were not measured in the present study, inactivation of DPD by 776C also increases the level of this pyrimidine.⁴ Therefore, thymine, another physiological substrate of DPD, may also contribute to the beneficial effects of 776C. It is noteworthy that (E)-5-(2-bromovinyl)uracil, another inactivator of DPD, also improves the therapeutic index and the efficacy of FT in a tumor-bearing mouse model (22).

776C/FT and FT also differ greatly with respect to the amount of 5-FU catabolites produced. Because rats treated with 776C do not catabolize 5-FU (12), very low doses of 5-FU (12, 13, 23) or FT were required to establish therapeutic plasma levels of 5-FU. In contrast, compared to 776C/FT, the MTD of FT alone was 40-fold larger but produced only a 2-fold larger plasma AUC of 5-FU and was considerably less efficacious. Furthermore, the 5-FU AUC from 200 mg/kg/day FT was one-third of the AUC of 5-FU from 80 mg/kg/day UFT. Therefore, the vast majority (~95%) of 5-FU released from FT must have been catabolized rapidly. Similar extensive catabolism occurs in human patients (18). Thus, it appears that dihydrofluorouracil and/or one or more of the other downstream catabolites interfere with the antitumor activity of 5-FU. This hypothesis has been confirmed recently with studies of dihydrofluorouracil in a similar tumor-bearing rat model (24).

Interestingly, FT accumulates in human cerebral spinal fluid, reaching levels that are higher than those in plasma, whereas the levels of 5-FU in cerebral spinal fluid are similar to or lower than those in plasma (18, 25). Therefore, the central nervous system toxicity (25) in patients treated with large doses of FT appeared to be caused by FT itself (18, 25). Because very low doses of FT are used in combination with 776C, this regimen may circumvent FT-related central nervous system toxicity.

In conclusion, low doses of 776C/FT produced sustained CR without severe toxicity in 100% of rats with large s.c. tumors. 776C and FT could be coadministered and may provide an attractive once-a-day oral therapy for cancer patients.

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⁴ D. J. Nelson, L. W. Frick, M. A. De La Mata, and M. T. Paff, unpublished data.

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