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ORIGINAL ARTICLE

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Dihydropyrimidine dehydrogenase inactivation and 5-fluorouracil pharmacokinetics: allometric scaling of animal data, pharmacokinetics and toxicodynamics of 5-fluorouracil in humans

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Abstract The pharmacokinetics of 5-fluorouracil (5-FU) in different animal species treated with the dihydropyrimidine dehydrogenase (DPD) inactivator, 5-ethynyluracil (776C85) were related through allometric scaling. Estimates of 5-FU dose in combination with 776C85 were determined from pharmacokinetic and toxicodynamic analysis. *Method*: The pharmacokinetics of 5-FU in the DPD-deficient state were obtained from mice, rats and dogs treated with 776C85 followed by 5-FU. The pharmacokinetics of 5-FU in humans were then estimated using interspecies allometric scaling. Data related to the clinical toxicity for 5-FU were obtained from the literature. The predicted pharmacokinetics of 5-FU and the clinical toxicity data were then used to estimate the appropriate dose of 5-FU in combination with 776C85 in clinical trials. *Results*: The allometric equation relating total body clearance (CL) of 5-FU to the body weight (B) ($CL = 0.47B^{0.74}$) indicates that clearance increased disproportionately with body weight. In contrast, the apparent volume of distribution (V_c) increased proportionately with body weight ($V_c = 0.58\ B^{0.99}$). Based on allometric analysis, the estimated clearance of 5-FU (10.9 l/h) in humans with DPD deficiency was comparable to the observed values in humans lacking DPD activity due to genetic predisposition (10.1 l/h), or treatment with 776C85 (7.0 l/h) or (E)-5-(2-bromovinyl)-2′-deoxyuridine (BVdUrd, 6.6 l/h). The maximum tolerated dose (MTD) of 5-FU in combination with 776C85 was predicted from literature data relating toxicity and plasma 5-FU area under the concentration-time curve (AUC). Based on allometric analysis, the estimated values for the MTD in humans treated with 776C85 and receiving 5-FU as a single i.v. bolus dose, and 5-day and 12-day continuous infusions were about 110, 50 and 30 mg/m^2 of 5-FU, respectively. *Discussion*: The pharmacokinetics of 5-FU in the DPD-deficient state in humans can be predicted from animal data. A much smaller dose of 5-FU is needed in patients treated with 776C85.

Key words 5-Fluorouracil · 5-Ethynyluracil · Dihydropyrimidine, Dehydrogenase inactivation · Pharmacokinetics · Allometric scaling

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Introduction

5-Fluorouracil (5-FU) is widely used as a single agent and in combination with other chemotherapeutic agents to treat various solid tumors. However, it has not produced the desired tumor responses [4]. Alternative approaches to increase the therapeutic efficacy of 5-FU include variations in the mode of administration such as bolus intravenous (i.v.) administration for 5 days or continuous intravenous infusion for 4 weeks or more [20].

The limited efficacy of 5-FU is probably due in part to its pharmacokinetics [18]. 5-FU is rapidly and extensively catabolized by dihydropyrimidine dehydrogenase (DPD) [7]. DPD is the enzyme that catabolizes 5-FU to dihydro-5-fluorouracil which undergoes further catabolism to form α-fluoro-β-alanine. In humans, 60 to 90% of 5-FU is catabolized while 10 to 20% is excreted unchanged in the urine. The plasma half-life of 5-FU is short (10 min) [5]. Since the antitumor activity of 5-FU is S-phase specific, the short plasma half-life results in the unavailability of 5-FU during the cell division phase [14]. Moreover, in most adult tumors the percentage of cells that are actively dividing at a given time is small. DPD activity in peripheral blood

lymphocytes in patients differs by as much as sixfold and correlates directly with plasma clearance of 5-FU [11]. In addition, high variability in DPD activity in the intestinal mucosa [24] may cause the low and variable bioavailability of 5-FU absorption after oral dosing. In an individual patient, DPD activity also fluctuates in a circadian rhythm resulting in mirror image oscillations of plasma 5-FU concentrations during constant i.v. infusion [15]. A patient has been reported to have experienced severe 5-FU-related toxicity after a conventional dose of 5-FU (300 mg/m^2) and was found to be genetically deficient in DPD activity [9]. The pharmacokinetics of 5-FU were determined in this patient at a lower dose (25 mg/m^2), and the half-life of 5-FU was 159 min and about 90% of the 5-FU dose was excreted unchanged in the urine. These results indicate a reduction in the elimination of 5-FU through the catabolic pathway. Therefore, a modulator that effectively inactivates DPD in vivo may potentially increase the bioavailability and prolong the mean residence time of 5-FU in the body, thus improving the therapeutic profile of 5-FU in cancer therapy.

5-Ethynyluracil (776C85) is a potent inactivator of DPD in vitro [22] and in vivo [24]. The pharmacokinetics of 5-FU in different animal species lacking DPD activity due to inactivation by 776C85 have been reported [1]. Here we present an allometric scaling analysis of the 5-FU pharmacokinetics in animal species treated with 776C85. The allometric equations describing the animal data were then used to estimate 5-FU pharmacokinetics in DPD-deficient humans. We also compare the estimated 5-FU pharmacokinetic parameters with results from clinical trials.

Another goal of this analysis was to estimate safe doses of 5-FU in combination with a DPD inhibitor in clinical trials. When coadministered with a DPD inhibitor, 5-FU clearance is decreased because the enzymatic breakdown of 5-FU normally accounts for as much as 90% of the elimination. Therefore, the 5-FU dose typically given in monotherapy produces severe toxicity in patients with reduced or no DPD activity [9]. Hence a lower 5-FU dose is needed to avoid toxicity. Suitable 5-FU doses were estimated from the clearance of 5-FU and previously published data on the relationship between area under the concentration-time curve (AUC) and toxicity [13, 23, 25, 26]. The probability of toxicity increases if plasma 5-FU AUC values exceed a threshold value [23], which is dependent upon the schedule of 5-FU administration.

Although it is an obvious choice to directly relate the pharmacodynamic results with plasma AUC of 5-FU, toxicity may also be influenced by the presence of 5-FU catabolites. Hence, the relationship between toxicity and 5-FU AUC may be different in combination treatments with a DPD inhibitor because 5-FU catabolites will not be formed. Nonetheless, the relationship between AUC and toxicity without a DPD inhibitor may be a good starting point to estimate the maximum tolerated dose (MTD) for the combination therapy.

Methods

Pharmacokinetics

Pharmacokinetics of 5-FU in the DPD-deficient state were obtained in three animal species treated with 776C85. These results were from the literature [1] and from the data presented here. Pharmacokinetics of 5-FU in the DPD-deficient state in humans were from published data from a patient genetically deficient in DPD [9], or following treatment with the DPD inhibitors 776C85 [19] or BVdUrd [18].

Animal dosing and sample collection

Data for mice and rats were those reproted by Baccanari et al. [1]. In that study, animals were fasted 24 h prior to drug administration. Mice were given 5-FU (50 mg/kg) via the intraperitoneal (i.p.) route, whereas the rats were dosed intravenously at 10 mg/kg. 776C85 (2 mg/kg) was dissolved in alkaline saline (pH 10) and was dosed 30 min before 5-FU in mice, and 1 h before 5-FU in rats.

Beagle dogs received oral doses of 776C85 at 3 mg/kg followed by i.v. doses of 5-FU (0.5 mg/kg) for 5 days. 776C85 was synthesized at the Burroughs Wellcome Research Laboratories. On days 1 and 5, plasma samples were collected prior to the 776C85 dose and at 0.17, 0.33, 0.5, 0.67, 1, 2, 4, 6, and 24 h after the 5-FU dose. Data collected on day 1 were used in the 5-FU allometric scaling analysis. Samples were stored at $-70\,^{\circ}$C before analysis. A validated reversed-phase HPLC assay was used to measure plasma 5-FU. 5-FU was eluted from a reversed-phase C_{18} analytical column with 50 m*M* ammonium acetate buffer, pH 4.8, at a flow rate of 0.4 ml/min. The eluate was monitored at 265 nm with a UV detector.

Pharmacokinetics and toxicity

Clinical pharmacokinetic (5-FU AUC) and pharmacodynamic (toxicity) data of 5-FU (given alone) were obtained from the literature. The AUC value (18 000 ng/ml h) associated with increased risk of toxicity (WHO classification, hematological and/or non-hematological) after a single i.v. bolus dosing at 500 mg/m^2 is that reported by Groeningen et al. [13]. The AUC value (7500 ng/ml h) associated with hematological and digestive tract toxicities after 5 days continuous i.v. infusion at 1000 mg/m^2 per day is that reported by Santini et al. [23]. Lastly, the AUC value (4800 ng/ml h) associated with mucocitis and diarrhea in patients treated for 28 days with a continuous i.v. infusion at a dose of 300 mg/m^2 per day was estimated from the published pharmacokinetics of 5-FU [5] as well as from the results reported by Spicer et al. [25].

Pharmacokinetic analysis

The plasma concentration-time data were analyzed using a nonlinear regression algorithm [21]. Absorption in mice after i.p. administration was assumed to be rapid and complete. A biexponential equation was used to fit the data obtained from each individual animal for mice, rats and dogs. Pharmacokinetic parameters were calculated using the coefficients and exponents of the fitted biexponential equation [12].

Allometric analysis

The allometric expression:

$$Y_i = \alpha_i \cdot B^{\phi_i}, \quad (1)$$

for i = c, vβ, vc, vs was used to relate pharmacokinetic parameters (Y_i) of 5-FU with animal body weight (B). The subscripts c, vβ, vc and vs refer to clearance (CL), volume of distribution associated with the terminal phase of the concentration-time profile (V_β), apparent volume of distribution (V_c) and steady-state volume of distribution (V_{ss}), respectively. The values of α and φ were estimated by transforming the allometric expression into:

$$\log Y_i = \log\alpha_i + \phi_i \log B \quad (2)$$

The slope and intercept of a linear least-squares analysis of log Y_i versus logB gave the values of ϕ_i and $\log\alpha_i$, respectively. The half-life value in humans was estimated using the equation:

$$t_{1/2} = \frac{0.693 \ V_\beta}{CL} \quad (3)$$

A complex Dedrick plot for 5-FU in animals treated with 776C85 was generated [2]. The following equation was used to determine the total 5-FU dose needed to achieve a target AUC in humans treated with 776C85:

$$\text{Dose} = \alpha_c \ B^{\phi_c} \ \text{AUC} \quad (4)$$

where $\alpha_c \ B^{\phi_c}$ represents clearance in terms of the body weight (B = 70 kg). Dose per square meter surface area was calculated by dividing the total estimated dose by 1.73 m^2 (average body surface area in humans).

The effect of 776C85 on the pharmacokinetics of 5-FU was also investigated by comparison of the allometric equations for animals treated with 5-FU alone. In mice, a single dose of 5-FU (50 mg/kg) produces an AUC of 70 μ*M* h [1] and an estimated clearance value of 0.12 l/h. When a similar dose is given to rats, the AUC value is 90 μ*M* h and the estimated clearance is 0.73 l/h. The reported clearance for humans treated with 15.8 mg/kg of 5-FU alone is 4.8 l/h [6]. Equation 2 was then used to estimate the coefficient and the exponent for the relationship between animal body weight and 5-FU clearance when given alone.

Results

Pharmacokinetics and allometry

The dose-adjusted concentrations of 5-FU in animals treated with 776C85 versus chronological time are shown in Fig. 1. Literature data are also plotted for the concentration-time profile of 5-FU in a cancer patient with a genetic deficiency in DPD [9]. The dose-adjusted concentrations for humans are largest at all time points followed by that for dogs, rats and mice. The rank order in the concentrations indicates that 5-FU clearance per kilogram animal weight is lower in larger animals under a DPD-deficient state.

The pharmacokinetic parameters of 5-FU in 776C85-treated animals are summarized in Table 1. The results of allometric analyses are also included in Table 1. The total body clearances of 5-FU in dogs, rats and mice were 2.3, 0.18 and 0.02 l/h, respectively.

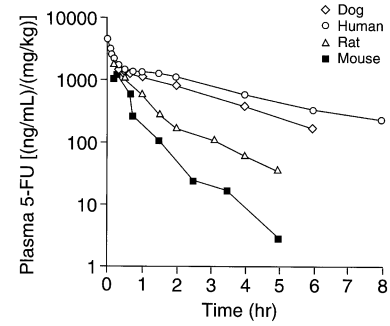

Fig. 1 Dose-normalized plasma 5-FU concentrations in humans and animals lacking dihydropyrimidine dehydrogenase activity. The human data were obtained from a patient who was genetically deficient in DPD. The animals were treated with 776C85 to induce the DPD-deficient state

The allometric correlation between the clearances (l/h) and the animal body weight (kg) is:

$$CL = 0.47 \ B^{0.74}, \quad r^2 = 0.98 \quad (5)$$

The exponent 0.74 is less than one, indicating that clearance increases disproportionately as a function of body weight. The estimated clearance using Eq. 5 for a 70-kg human is 10.9 l/h. This estimated value is comparable to the observed values in humans who are deficient in DPD (10.1 l/h), treated with BVdUrd (6.6 l/h), or treated with 776C85 (7.0 l/h) (Fig. 2). The values of the clearance from humans are very close to the lines generated from Eq. 5.

The allometric equation correlating V_β and body weight is:

$$V_\beta = 1.28 \ B^{0.76}, \quad r^2 = 0.96 \quad (6)$$

while the corresponding equation for V_c is:

$$V_c = 0.59 \ B^{0.99}, \quad r^2 = 0.99 \quad (7)$$

Values for V_c are not available from the literature for humans treated with 776C85 or BVdUrd. The allometric equation for V_{ss} is:

$$V_{ss} = 0.84 \ B^{0.96}, \quad r^2 = 0.97 \quad (8)$$

The exponents for V_c and V_{ss} were close to unity indicating that these volume terms are directly proportional to body weight.

The results from Eq. 5, 7 and 8 were used to generate complex Dedrick plots (Fig. 3). The complex Dedrick plots of 5-FU concentrations in the three animal species and in humans with genetic deficiency in DPD activity were superimpozable. Thus, Eq. 5, 6 and 7 are predictive of the pharmacokinetics of 5-FU. The exponent of the allometric equation for 5-FU clearance in animals treated with 5-FU alone was 0.84 ($r^2 = 0.99$). This exponent was slightly higher than that in Eq. 5.

The relationship between AUC and toxicity depends on the dosing schedule for 5-FU. The threshold AUCs

Table 1 Observed pharmacokinetic parameters of 5-FU in animals pretreated with 776C85 and the predicted pharmacokinetic parameters in humans pretreated with 776C85 (*na* not applicable, V_c volume of distribution of the central compartment, V_β volume of distribution associated with the terminal phase, V_{ss} volume of distribution at steady state, $t_{1/2}$ terminal phase half-life)

	Experimental results			Allometric equation ($Y_i = \alpha_i B^{\phi_i}$)[a]		Human predicted	Human observed
	Mouse	Rat	Dog	α	ϕ		
Weight (kg)	0.02	0.17	10	na	na	70	70
5-FU (mg/kg)	50	10	0.5	na	na	na	na
Route	i.p.	i.v.	i.v.				
776C85 (mg/kg)	2	2	3	na	na	na	na
Route	oral	oral	oral				
Clearance (l/h)	0.02	0.18	2.28	0.47	0.74	10.9	10.1
V_c (l)	0.0093	0.15	5.05	0.59	0.99	39.6	12.5
V_β (l)	0.046	0.58	6.09	1.28	0.76	32.3	38.2
V_{ss} (l)	0.013	0.29	6.11	0.84	0.96	49.6	37.2
$t_{1/2}$ (h)	1.65	2.21	1.94			2.4	2.8

[a]Allometric expression relating pharmacokinetic parameters (Y_i) with body weight (B) with coefficient α_i and exponent ϕ_i

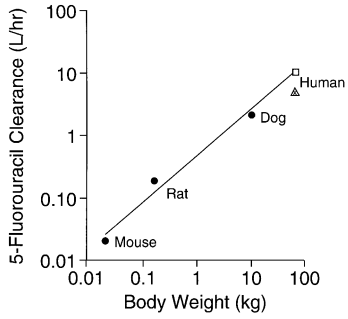

Fig. 2 Interspecies allometric scaling of 5-FU clearance in animals treated with 776C85. Comparison of the estimated and observed 5-FU clearance in humans with genetic deficiency in DPD activity (□), treated with BVdUrd (△) and 776C85 (X), respectively. Three points (●) were used to obtain the line of best fit

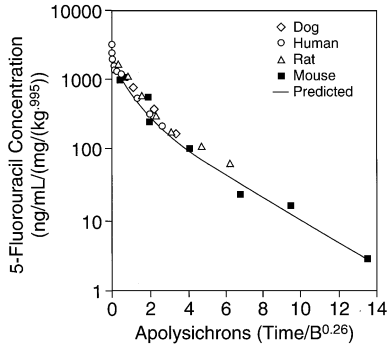

Fig. 3 Complex Dedrick plot of 5-FU in humans and different animal species with DPD deficiency. The human data were obtained from a patient who was gentically deficient in DPD. The animals were treated with 776C85 to induce the DPD-deficient state

associated with clinical toxicity from the literature are shown in Table 2. Also included in Table 2 are the predicted 5-FU doses needed in combination with 776C85 to produce the AUCs associated with each dosing schedule in the monotherapy. With i.v. bolus

Table 2 5-FU AUC after monotheraphy and the predicted doses of 5-FU in combination with DPD inactivator in humans

5-FU Dose[a] (mg/m^2)	5-FU dosing (route, schedule)	5-FU AUC[b] (ng/ml h)	Predicted 5-FU dose[c] (mg/m^2)
500	i.v. bolus, weekly	18000[d]	113.4
1000	i.v. constant inf. daily × 5	7500[e]	47.3
300	i.v. constant inf.	4800[f]	30.2

[a]5-FU dose given as monotherapy
[b]Estimated 5-FU AUC after the first dose of the scheduled doses
[c]Dose of 5-FU needed in humans lacking DPD activity to produce AUC in column 3
[d]AUC associated with hematological and/or nonhematological toxicity
[e]AUC associated with hematological and digestive tract toxicities including stomatitis
[f]AUC associated with mucositis and diarrhea

dosing of 5-FU alone at 500 mg/m^2, the threshold AUC is 18 000 ng/ml h [13]. The above AUC value was associated with the first dose of the weekly schedule. The i.v. bolus dose needed to produce equivalent plasma AUC in humans treated with 776C85 was estimated to be 113 mg/m^2 which is about one-fifth of the dose when 5-FU was given alone.

For 5-day continuous infusion at 1000 mg/m^2 per day, the threshold AUC that is predictive of toxicity is 15 000 ng/ml h over a 48-h period. This is equivalent to an AUC value of 7500 ng/ml h over a 24-h period. The daily dose of 5-FU that would produce an equivalent AUC in humans treated with 776C85 was estimated (Eq. 4) to be about 47 mg/m^2.

The current dosing schedule of 5-FU given alone that provides an acceptable therapeutic profile is protracted i.v. infusion at 300 mg/m^2 per day for 3–4 weeks. Unlike most other compounds that reach a steady-state concentration when administered by

constant i.v. infusion, a sinusoidal concentration profile over a 24-h period is observed where 5-FU is infused alone [15]. This oscillating 5-FU concentration profile is the result of a circadian rhythm in the DPD activity, and it is very similar to the concentration-time profile of a compound after twice a day oral dosing. When 5-FU is administered at 350 mg/m^2 per day through continuous i.v. infusion in a 28-day schedule, the mean onset time for toxicity (diarrhea) is 12 days. The exposure to 5-FU up to the onset of toxicity is 4.2 g/m^2. Using a clearance value of 1800 ml/h per kg for 5-FU [5], the estimated AUC over a 24 h period is 4800 ng/ml h. The 5-FU dose that would produce a similar AUC over 24 h in humans pretreated with 776C85 was estimated to be 30 mg/m^2.

Discussion

776C85 alters the pharmacokinetics of 5-FU in animals by inactivating DPD. The resulting 5-FU pharmacokinetics from different species were related through allometric equations. An exponent of 0.74 was obtained for the allometric equation relating total body clearance to the animal body weight (Eq. 4). 5-FU clearance in humans lacking DPD activity can be estimated from the allometric equation obtained solely from animal data. The estimated 5-FU clearance in humans was 10.9 l/h. In patients treated with 776C85 and BVdUrd, the 5-FU clearances are 7.0 [19] and 6.6 l/h [18], respectively. The clearance in a patient with a genetic deficiency in DPD activity was estimated to be 10.1 l/h. Although the underlying causes of the DPD deficient state related to these clearance values in humans are different, the allometric equation obtained from animal data alone gives estimates that are comparable with the values in humans.

The exponent of 0.74 in Eq. 5 is close to the exponent (0.79) of the allometric equation relating glomerular filtration rate (GFR) to body weight in several animal species [17]. This is consistent with renal elimination becoming the prominent route of 5-FU elimination when DPD activity is completely inactivated. However, GFR constitutes only a fraction of the total body clearance of 5-FU in mice and rats. Using the estimated GFR (l/h) from the following equation [17]:

$$GFR = 1.95\ B^{0.79}$$

the percentage ratios of GFR to the total body clearance were 29, 16, 32 and 51% in mice, rats, dogs and humans, respectively. However, the recoveries of unchanged 5-FU from urine in mice and rats exceeded the ratios of GFR to total clearance. The 24-h urinary recovery of unchanged 5-FU in mice and rats treated with 5-FU and 776C85 were 50 and 80%, respectively. The urine samples in both cases were collected over a period of more than five half-lives. Since these urinary recoveries of 5-FU are higher than the percentages of the total clearance that can be attributed to GFR, other renal elimination processes such as secretion may occur in mice and rats in addition to passive diffusion through the glomerulus. In contrast, in humans treated with BVdUrd, the urinary recovery of unchanged 5-FU (45%) is comparable with the percentage of the GFR to the total body clearance of 5-FU (51%). This indicates that 5-FU is mainly excreted by glomerular filtration in humans treated with BVdUrd.

The elimination of 5-FU in a DPD-deficient state may also involve other routes in addition to the renal pathway. Despite the increase in the urinary recovery of unchanged 5-FU, a substantial amount (more than 50% in humans) of 5-FU is not accounted for. Since small amounts of unchanged 5-FU can be detected in human bile after dosing with 5-FU alone [16], biliary excretion could be a source of 5-FU elimination when hepatic DPD is inactivated. The elimination of hepatic DPD activity may increase the availability of 5-FU for biliary excretion in the liver. 5-FU may also be sequestered in various body tissues through anabolism and incorporation into RNA and DNA [8].

The effect of 776C85 on 5-FU pharmacokinetics was also evaluated by comparing the allometric equations for animals treated with 5-FU alone and those following treatment with 776C85/5-FU. The allometric analysis of the 5-FU clearance values in mice, rats, and humans produced an exponent of 0.84 ($r^2 = 0.99$). This exponent is greater than that determined for 5-FU in combination with 776C85. Thus, in the presence of extensive catabolism, there is a more direct relationship between 5-FU clearance and body weight, and 776C85 decreases the clearance of 5-FU to a greater extent in the larger animal species.

The estimated 5-FU pharmacokinetics in humans, along with published data on AUC and toxicity, provides a means of estimating safe 5-FU doses for clinical trials combining 5-FU and 776C85 in cancer patients. The predicted MTD for a 5-day dosing schedule was 47 mg/m^2. In a phase I clinical trial combining 5-FU with 776C85 in a 5-day schedule, the starting dose was 10 mg/m^2, which was well tolerated by the patients [19].

A single-dose schedule was used in a study of 5-FU combined with BVdUrd [18]. Bolus doses of 5-FU at 110–400 mg were given intravenously to the patients. In the present analysis the predicted dose likely to produce toxicity for a single bolus dose schedule is 113 mg/m^2. Thus the dose for a patient with an average body surface area (1.73 m^2) would be about 195 mg and is within the range of the doses used in the study with BVdUrd. However, 5-FU-related toxicity for 5-FU/BVdUrd has not been reported.

The cumulative 5-FU doses to the onset of toxicity for a single i.v. bolus administration, 5-day i.v. infusion schedule and protracted i.v. infusion are different and are not linearly proportional. The results of the present

study show that a single bolus 5-FU dose of 113 mg/m^2 with 776C85 will produce a risk of toxicity. On the other hand, for a 5-day schedule, the dose that is likely to produce toxicity is 47 mg/m^2 per day for a total dose of 235 mg/m^2 over 5 days. The dose from the 5-day schedule is about twice that from a single i.v. bolus dose. In continuous i.v. infusion of 5-FU alone at 350 mg/m^2, the onset of toxicity is 12 days. The equivalent exposure to 5-FU in the combination treatment of 5-FU and 776C85 is 30 mg/m^2 per day. The total dose over the 12-day period is 360 mg/m^2. However, Caballero et al. [3] have reported that there is no relationship between the time on therapy and the appearance of toxicity in patients after continuous infusions of 5-FU, although the duration of infusions in that study was long and varied widely from 54 to 324 days.

In summary we have shown that the extrapolation from animal data for 5-FU pharmacokinetics to humans in the DPD-deficient state is consistent with the results from clinical trials. The values of the clearance of 5-FU in patients lacking DPD activity due to genetic predisposition or treatment with 776C85 or BVdUrd are comparable. In mice and rats, other renal elimination processes such as secretion, in addition to passive diffusion through the glomerulus, may be present. The predicted values for the MTD in humans treated with 776C85 and receiving 5-FU as a single i.v. bolus dose, or 5-day and 12-day continuous infusions are approximately 110, 50 and 30 mg/m^2, respectively.

After this report was submitted for publication, a phase I clinical trial has determined that 25 mg/m^2 of 5-FU is a suitable dose for a 5-day dosing schedule in phase II trials combining 5-FU and 776C85.

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