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Plasma 5-fluorouracil and α-fluoro-β-alanin accumulation in lung cancer patients treated with continuous infusion of cisplatin and 5-fluorouracil

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Abstract This study was undertaken to investigate the day-to-day pharmacokinetic variability of 5-fluorouracil (5FU) given as a continuous i.v. infusion concomitantly with cisplatin. Ten lung cancer patients were investigated during the first course of chemotherapy. All patients had advanced, previously untreated, inoperable non-small-cell lung cancer. They received continuous infusions of cisplatin given at 100 mg/m^2 over 5 days and of 5FU given at 1 g/m^2 daily from day 2 to day 5. Both drugs were infused i.v. for 24 h/day at a constant rate with a volumetric pump. Blood samples were drawn from day 2 to day 5, every 4 h from 8 a.m. to 8 p.m. and every 2 h during the night (8 p.m. to 8 a.m.). Plasma 5FU and FBAL concentrations were determined simultaneously by gas chromatography-mass spectrometry. Plasma 5FU concentrations varied widely over the 4-day treatment course for each patient. Despite continuous constant-rate 5FU administration, plasma 5FU concentrations were significantly lower between 8 a.m. and 8 p.m. than during the night. Mean plasma concentrations of 5FU and FBAL increased significantly from the 1st day (0.42 and 1.19 μg/ml for 5FU and FBAL, respectively) to the 4th day of 5FU infusion (0.67 and 1.78 μg/ml for 5FU and FBAL, respectively). Further study is warranted to elucidate the mechanisms of the observed increase in plasma 5FU concentrations as well as its relationship with cisplatin coadministration and to assess the clinical relevance of this plasma 5FU accumulation.

Key words 5FU · FBAL · Cisplatin · Continuous infusion · Lung cancer · Pharmacokinetics

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Introduction

Cisplatin and 5-fluorouracil (5FU) are among the most efficient cytostatic agents in the treatment of classically chemoresistant cancers of the gastrointestinal tract [2], head and neck [8, 18, 19], and lung [22, 33]. Whereas experimental [32] and clinical [18] data have suggested a synergistic effect of these drugs, the best sequence of administration and schedule have not yet been determined [3]. Among several schedule possibilities, the simultaneous administration of both drugs by continuous i.v. infusion offers many advantages. Although they involve a higher total dose, 5FU infusions lasting for 8 hours or more are less hematotoxic than bolus administration [3]. Moreover, increased antitumoral efficacy for prolonged continuous 5FU infusion as compared with bolus administration has been demonstrated in metastatic colon carcinomas [3] and head and neck carcinomas [19]. In the same way, cisplatin given as a continuous i.v. infusion for 5 days allows a 1.5- to 2-fold increase in total exposure to the filterable platinum species [12] along with a decrease in the incidence of nausea and vomiting and of renal toxicity [22, 29]. In lung cancer patients, the antitumoral activity of both drugs given simultaneously by continuous infusion is at least identical to that produced by Weiden's cisplatin-5FU schedule using a cisplatin bolus on the 1st day of chemotherapy [22, 33, 37]. Moreover, the recent availability of ambulatory chemotherapy infusion pumps allows their administration on a safe and economical outpatient schedule [35].

The pharmacokinetics of 5FU following continuous i.v. administration has been widely studied [7, 15, 28, 34]. These studies have shown significant intraindividual vari-

Table 1 Patients' characteristics and 5FU pharmacokinetics

Patient number	Sex	Age (years)	Body surface area (m^2)	5FU (μg/ml) 24 h mean (SD)*	5FU total body clearance (ml min^{-1})*
1	M	52	1.75	0.64 (0.18)	1120
2	M	63	1.6	0.39 (0.26)	1910
3	M	57	1.97	0.15 (0.06)	4815
4	M	48	1.8	0.40 (0.25)	2000
5	M	49	1.6	0.55 (0.46)	1460
6	M	72	1.8	0.93 (0.64)	820
7	M	75	1.36	0.49 (0.42)	1420
8	M	48	1.65	0.25 (0.18)	3000
9	M	56	1.63	0.22 (0.18)	3300
10	M	62	1.42	0.38 (0.28)	1750

*$P < 0.01$, intersubject comparison (ANOVA)

ations in plasma 5FU concentrations with a circadian rhythm following continuous infusion at a constant rate [15, 28]. They have also shown wide interpatient variations in both the systemic clearance and the area under the curve (AUC) of 5FU [7, 10, 28, 34]. Apart from exceptional cases of enzymatic deficiency in the catabolic 5FU pathway [6, 16], these interindividual pharmacokinetic variations appear highly unpredictable [10, 23].

Because a significant relationship between 5FU pharmacokinetics and toxicity has been shown [31, 34, 38], some authors have proposed that 5FU doses given after the 48th h of treatment be adjusted on the basis of midcycle AUC estimation [10, 31, 34, 38]. Whereas this adjustment clearly leads to a decrease in the incidence of toxicity without producing a change in the response rate as compared with historic controls [31, 38], this attitude supposes that both the systemic clearance and the distribution volume of 5FU remain unchanged throughout the chemotherapy cycle. This point has not yet been investigated in the case of concomitant administration of cisplatin and 5FU by continuous infusion.

Therefore, we conducted a pharmacokinetic evaluation of 5FU and its metabolite α-fluoro-β-alanin (FBAL) in the plasma of ten patients suffering from lung cancer following treatment with continuous i.v. infusions of 5FU and cisplatin. The specific purpose of this study was to evaluate the time-related variations in 5FU pharmacokinetic parameters during the chemotherapy.

Patients and methods

Study design

To study the putative interday variability of 5FU pharmacokinetic parameters, we performed serial determinations of plasma FBAL and 5FU concentrations from the 1st to the last day of 5FU administration in lung cancer patients treated with continuous-infusion cisplatin and 5FU. For each patient, blood sampling was performed repetitively at fixed intervals from the 1st to the last day of 5FU infusion. Sampling was carried out more frequently between 8 p.m. and 8 a.m. so as to take into account the possible occurrence of an acrophase in plasma 5FU concentration during the nighttime period as described by Petit et al. [28]. Both drugs were given at a controlled constant rate using volumetric pumps. To avoid any intercycle intraindividual variations in 5FU parameters [11] possibly related to significant changes in the tumor mass or metabolism, this study was conducted during the first cycle of chemotherapy in each patient. From January 1990 to June 1991, ten patients entered the study and completed the entire pharmacokinetic analysis. Plasma 5FU determination was performed in ten patients and plasma FBAL levels were measured in eight subjects. Details of the patient's characteristics are listed in Table 1.

Selection of the patients

To be eligible for this study, patients had to have advanced, previously untreated, inoperable, histologically proven non-small-cell lung cancer requiring chemotherapy. They had to be more than 18 years old and to have given written informed consent. Patients with an altered performance status (>2, WHO classification), a serum creatinine level of >130 μmol/l, an abnormal blood-liver test or abnormal liver echography, known coronary heart disease, or cardiac failure and patients treated with drugs known to interfere with 5FU metabolism [methotrexate, thymidine, folinic acid, uridine, allopurinol, *N*-(phosphonacetyl)-L-asparate, dypiridamole] were not included [26].

Chemotherapy protocol

All patients received cisplatin (Cisplatyl, Roger Bellon Laboratories, France) given at 20 mg/m^2 daily from day 1 to day 5 (100 mg/m^2 per cycle) in a 120-h continuous infusion and 5FU (Roche Laboratories, France) given at 1000 mg/m^2 daily (4000 mg/m^2 per cycle) in a 96-h continuous infusion starting at 8 a.m. on the 2nd day of chemotherapy. Patients were hydrated by continuous daily infusions of 3000 ml 5% dextrose containing 3 g NaCl/l, 1 g KCl/l, and 0.5 g $MgCl_2$/l. 5FU and cisplatin were separately diluted in 250 ml saline (9‰) and given simultaneously in a peripheral vein at a constant rate (500 ml/day) as two separate infusions connected to a volumetric pump (Pharmacia Deltec, model CADD plus). The infusion lines and the patient's arm were protected from direct light. The infusion systems allowed the patient to move freely within the Department of Respiratory Diseases. Methylprednisolone (80 mg/day) and alizapride (200–400 mg/day) were given as antiemetics.

Pharmacokinetics study

The pharmacokinetics study was performed during the first chemotherapy course in each case. A total of 36 samples were taken from each patient. Blood sampling (5 ml) was performed before the start of the 5FU infusion, every 4 h during the day (8 a.m. to 8 p.m., hereafter referred to as daytime), and every 2 h during the night (8 p.m. to 8 a.m., hereafter referred to as nighttime) over the 5 days of infusion. A small heparinized catheter was introduced into a vein of the arm opposite the infusion arm and was left in place throughout the 5FU infusion such that blood samples could be drawn with minimal discomfort and disturbance during sampling. After 3 ml of blood had been discarded, 5 ml was collected into ethylenediaminetetraacetic acid (EDTA)-containing tubes immediately kept at 4 °C and centrifuged (3000 *g*, 5 min) by the ward nurses. Plasma was collected and kept at –80 °C until analysis. The therapeutic protocol as well as the pharmacokinetics study were approved by the Rouen Ethics Committee.

Table 2 Mean plasma 5FU and FBAL concentrations detected during the 4 days of 5FU infusion

Infusion day	Mean plasma 5FU (± SE) (μg/ml, 10 patients)		Mean plasma FBAL (± SE) (μg/ml, 8 patients)	
	Day	Night*1	Day	Night*3
1	0.42 (0.19)	0.42 (0.11)	1.01 (0.23)	1.19 (0.24)
2	0.32 (0.06)	0.44 (0.10)	0.93 (0.19)	1.30 (0.29)
3	0.32 (0.04)	0.47 (0.08)	1.08 (0.23)	1.73 (0.43)
4	0.41 (0.06)	0.67 (0.14)*2	1.61 (0.56)*4	1.78 (0.52)*4

*1 $P < 0.01$, diurnal versus nocturnal 5FU values (two-way ANOVA); *2 $P < 0.05$, 4th versus preceding 5FU infusion nights (two-way ANOVA); *3 $P < 0.05$, diurnal versus nocturnal FBAL values (two-way ANOVA); *4 $P < 0.01$, 4th day and night versus preceding day/night periods (ANOVA)

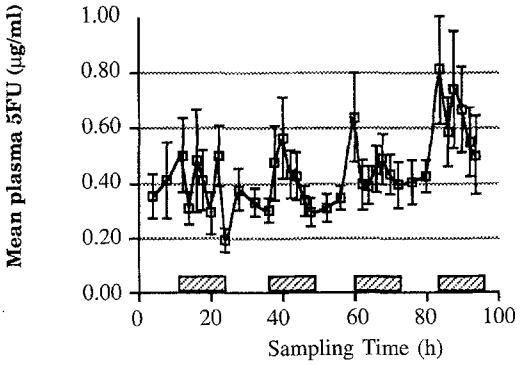

Fig. 1 Mean plasma 5FU concentrations versus time as measured from the start of the 5FU infusion (*Bars* # SEM). ▨, night

Evaluation of toxicity and response

Toxicity was evaluated according to WHO criteria during the first chemotherapy cycle and after each subsequent chemotherapy course. The tumor response was evaluated 3 weeks after the second and fourth chemotherapy cycles according to Miller et al. [24].

Determination of 5FU and FBAL plasma concentrations

Plasma 5FU and FBAL determinations were performed using a coupled gas chromatography-mass spectrometry method (GC-MS) as described elsewhere [20]. Briefly, after the addition of 0.5 μg chlorouracil (ClUr) as an internal standard and acidification to pH 5 with 0.1 *N* HCl, plasma proteins were precipitated with cold acetonitrile (0.5:4 ratio) and centrifuged for 15 min at 3000 *g*. The liquid phase was evaporated with liquid nitrogen. The residue was dissolved in 100 μl acetonitrile and 200 μl terbutyl-dimethyl-silyl-trifluoroacetamide (TBDMS) was added. The samples were heated for 15 min at 80 °C. A 2-μl aliquot of the solution was injected into the chromatograph in the vapor phase after the column (HP5, Hewlett-Packard) had been heated at 220 °C. Signals of 5FU, FBAL, and chlorouracil were recorded by single ion monitoring at m/z = 301, 278, and 315, respectively. Plasma 5FU and FBAL values were determined by comparison with a reference scale repeated daily. The limit of quantification for 5FU, dihydrofluorouracil (5FUH2), FBAL, and ClUr was 2, 50, 100, and 10 ng/ml, respectively. The extraction rate was 75% for 5FU, ClUr, and 5FUH2 and 55% for FBAL. The day-to-day reproducibility was over 95% for all compounds. The derivatization rate by TBDMS was more than 90%. Derivatized samples were injected into the GC-MS system as soon as possible, in all cases by less than 24 h after preparation, to avoid degradation.

Pharmacokinetic analysis

Plasma values for 5FU and FBAL are expressed in micrograms per milliliter of plasma. AUC values were calculated using the trapezoidal method between time zero (start of the 5FU infusion, 24th h of the chemotherapy course) and 96 h (end of the 5FU infusion). 5FU clearance was determined by dividing the 5FU dose by the $AUC_{0-96\,h}$.

Statistical analysis

Inter- and intrapatient variations in plasma 5FU and FBAL values were studied using two-way analysis of variance (ANOVA) with repeated measures. Intrapatient 5FU and FBAL variations were studied between each day of 5FU infusion as well as for each day between daytime and nighttime periods. For each sampling time, mean plasma 5FU and FBAL concentrations were calculated and a concentration-versus-time regression test was performed. The a priori significant *P* value was set at 0.05.

Results

Patients' characteristics

The patients' characteristics, the mean plasma 5FU concentrations determined for the whole 5FU administration period, and the total body clearance of 5FU for each patient are given in Table 1. These data confirm the wide interindividual differences observed in plasma 5FU concentrations and clearance values ($P < 0.01$, ANOVA). These interindividual differences were also found for FBAL ($P < 0.01$, ANOVA; data not shown).

Plasma 5FU concentration-versus-time variations

Plasma 5FU concentration-versus-time analysis found two kinds of variation: (1) a significant difference in *daytime versus nighttime* plasma 5FU concentrations, with the highest values occurring during the night (ANOVA, $P < 0.01$; Table 2), and (2) *interday differences* in plasma 5FU concentrations, with a significant increase occurring during the last night as compared with the previous periods (ANOVA, $P < 0.05$; Table 2, Fig. 1).

Plasma FBAL concentration-versus-time variations

The curves generated for plasma FBAL concentration showed the same variations as those generated for plasma 5FU levels. Mean plasma FBAL concentrations were also significantly higher both during the nighttime periods as compared with the daytime periods (ANOVA, $P < 0.05$) and during the last day and night of 5FU infusion as compared with the preceding daytime and nighttime periods (ANOVA, $P < 0.01$; Table 2, Fig. 2). Figures 1 and 2 show the mean plasma 5FU and FBAL values obtained. Linear regression showed a significant increase in 5FU and FBAL concentrations over time from the start of the 5FU infusion ($n = 36$; $R = 0.59$, $P < 0.05$ and $R = 0.72$, $P < 0.01$ for 5FU and FBAL, respectively).

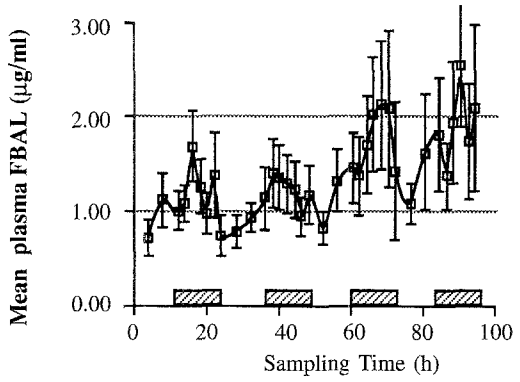

Fig. 2 Mean plasma FBAL concentrations versus time as measured from the start of the 5FU infusion (*Bars* # SEM). ▨, night

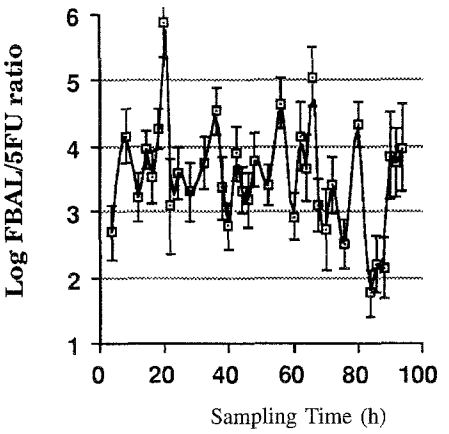

Fig. 3 Plasma FBAL/5FU ratio versus time as determined in 8 patients (*Bars* # SD)

Although significant 5FU and FBAL daytime/nighttime variations occurred, Cosinor analysis failed to find any regular circadian rhythm in the 5FU or FBAL plasma concentrations.

Plasma FBAL/5FU ratio

We found a significant correlation between paired plasma 5FU and FBAL values ($P < 0.001$, data not shown). We did not observe any day-to-day or day-to-night variation in the plasma FBAL/5FU ratio (Fig. 3).

Tumor response and toxicity

Four patients displayed toxicity of WHO grade ≥II during the first chemotherapy cycle (Table 3). Severe cardiac toxicity occurred in two of these patients; patient 7 experienced a transient pulmonary subedema with minor EKG modifications, requiring the administration of 40 mg furosemide and a 2-h interruption of 5FU administration. The 5FU concentration dropped from 354 ng/ml before the 5FU interruption to undetectable levels immediately before its readministration. Although 5FU levels subsequently increased to 2000 ng/ml during the night following the 5FU reintroduction, no subsequent cardiac toxicity was noted in this patient. Patient 2 died 4 h after the completion of the chemotherapy. No postmortem examination was performed. The last plasma 5FU level determined for this patient was 420 ng/ml. The 5FU $AUC_{0-96\,h}$ values determined for these patients are indicated in Table 3.

Discussion

This study shows that plasma concentrations of 5FU and its metabolite FBAL increase from the 1st day to the last day of treatment when high-dose 5FU is associated with cisplatin, both drugs being given simultaneously at a constant

Table 3 Toxicity of the first and following chemotherapy cycles, response rate, and survival of the ten patients (*CT* Chemotherapy, *NC* no change, *PR* partial response)

Patient number	$AUC_{0-96\,h}$ (µg ml^{-1} h)	Number of CT courses	Toxicity (grade ≥II)		Tumor response	Survival (months)
			1st course	All courses		
1	6.25	5	Diarrhoea (grade II)	Hematological (grade III)	PR	10
2	3.35	1	Death (day 5)	–	–	0
3	1.64	4	–	–	PR	8
4	3.6	2	–	Cardiac (grade IV)	NC	14
5	4.38	4	–	–	PR	5
6	8.78	2	Hematological (grade II)	–	PR	4
7	3.83	1	Cardiac (grade III, day 3)	–	–	23
8	2.2	4	–	Hematological (grade III)	PR	16
9	1.95	4	–	–	PR	14
10	3.25	4	–	–	PR	12

rate in continuous infusions. These 1.6- and 1.5-fold increases in plasma levels of 5FU and FBAL, respectively, are superimposed on significant day-night variations. The highest plasma 5FU and FBAL values were obtained during the last night of the 5FU infusion. Although these nocturnal increases occurred repetitively from the 1st day to the last day of 5FU infusion, the Cosinor analysis that we performed failed to demonstrate the circadian rhythmicity in plasma 5FU levels found by other investigators [15, 28]. This discrepancy can easily be explained by the day-to-day increase of the basal 5FU values observed during the chemotherapy cycle. However, our data are consistent with Petit et al.'s study in which the highest plasma 5FU concentrations were found at night between 10 p.m. and 3 a.m. [28], whereas the peak values for plasma 5FU concentration occurred at 11 a.m. in Harris et al.'s study (15U. Such a difference may be related to the coadministration of cisplatin and 5FU in our study as well as in Petit et al.'s study as compared with Harris et al.'s study in which 5FU was given alone.

The increase in plasma 5FU and FBAL levels that we observed cannot be explained by fluctuations in the infusion rate. In this study, 5FU was infused via ambulatory volumetric pumps after dilution of the cytostatics in two separte 250-ml 9‰ NaCl infusion bags, which were protected from direct light and changed every day at the same hour. Mechanically related fluctuations in the infusion rate do not exceed 2% with the device used (Pharmacia Deltec) and therefore cannot account for the 50% variation observed in this study.

An increase in the AUC value has been observed during the second part of the chemotherapy course following continuous 5FU infusions given via the hepatic artery [2]. This increase was attributed to a saturation of hepatic 5FU metabolism occurring after the first 48 h of 5FU infusion. Using short infusions of methotrexate and cisplatin followed by a 5-day continuous i.v. infusion of 5FU, Vokes et al. [35] noticed that the first 24-h 5FU level appeared lower than the 96-h level. Whereas the differences they found were not significant, they suggested an accumulation of 5FU in plasma at the end of prolonged high-dose 5FU infusions [35]. Conversely, using a cisplatin bolus on the 1st day of chemotherapy, Petit and co-workers [28] did not observe any day-to-day variation in the pharmacokinetics of 5FU given as a continuous 5-day systemic i.v. infusion. Two other studies of the pharmacokinetics of very-high-dose 5FU (>2 g/m^2 daily) given by continuous infusion with allopurinol also failed to demonstrate any day-to-day variation in plasma 5FU concentrations [7, 17].

The high total-body 5FU clearance values obtained by us as well as other investigators [2, 7, 23], which sometimes exceed the cardiac output, suggest that in this administration modality, the upper capacity limit of the 5FU catabolic pathway may be reached. Indeed, the initial step of 5FU catabolism involves a saturable enzymatic process, depending on the dihydropyrimidine dehydrogenase (DPD) activity that transforms 5FU into dihydrofluorouracil (5FUH2) [5, 25]. Fleming et al. [11] have recently shown a significant correlation between the total 5FU clearance and the DPD activity from peripheral blood lymphocytes in cancer patients treated with continuous 5FU infusions. This first suggested that a decrease in DPD activity occurring during the second part of the chemotherapy course might account for the increase in 5FU concentration seen in the present study. However, the plasma FBAL kinetics observed in our study argues against such a mechanism. FBAL is the final product of the 5FU catabolic pathway [25]; its kinetics depend directly on its production from 5FUH2 [4]. The plasma half-life of FBAL has recently been estimated at 10–20 min, which is similar to that of 5FU but significantly shorter than that of 5FUH2 [4, 27]. A decrease in DPD activity should theoretically lead to an increase in plasma 5FU concentrations along with a significant decrease in plasma levels of 5FU catabolites (5FUH2, α-fluoro-β-propionic acid, FBAL), as can be observed in familial DPD deficiency [4, 6, 16]. In contrast, our study shows that the FBAL concentration curves display approximately the same kinds of variation as do the plasma 5FU curves and that the FBAL/5FU ratio remains stable throughout the chemotherapy cycle.

Two mechanisms may explain the plasmatic 5FU and FBAL accumulation found in this study: (1) a decrease in FBAL clearance, whose urinary components have been estimated to account for 95% of its clearance [4], and/or (2) an inhibition of the anabolic 5FU pathway, which may account for 40% of its metabolic clearance [4].

A *drug interaction* may account for a modification of the 5FU pharmacokinetic parameters. Several drugs or biomodulators are capable of modifying 5FU pharmacokinetics [12]. In this study, we avoided all drugs known to interfere with 5FU metabolism other than cisplatin. Our study differs from previous pharmacokinetics studies of the cisplatin-5FU association, because cisplatin was given by continuous infusion along with 5FU instead of by bolus administration on the 1st day of chemotherapy. It is therefore possible that the association of continuous-infusion 5FU and cisplatin may be the cause of the observed day-to-day increase in FBAL and 5FU concentrations. Three levels of cisplatin-5FU interaction can be suggested:

1. One interaction may involve an inhibition of the urinary elimination of 5FU metabolites related to the exposure of renal cells to cisplatin [9]. Due to the lack of urinary FBAL or 5FU determination in our study, this possibility cannot be verified.
2. A decrease in 5FU anabolic clearance may occur when the drug is given in association with cisplatin, as has been suggested by experimental data [1]. This could account for the 30%–40% decrease found in the rate of 5FU metabolism when isolated liver preparations are preincubated with cisplatin [21].
3. A decrease in DPD activity related to the inhibition of an enzyme cofactor by cisplatin has been suggested [21]. Such an interaction appears improbable in our study because of the FBAL kinetics as described above. Moreover, the cisplatin concentration required in vitro for this interaction is significantly greater than that obtained in patients using the standard dose of 100 mg/m^2 [21].

Clearly, a cisplatin-5FU interaction cannot be definitely demonstrated in our study because we did not include a control arm of patients treated with 5FU alone. Owing to the lack of activity of 5FU monotherapy in non-small-cell lung carcinoma, such a study would have raised ethical concerns.

An *organ failure* modifying the metabolism of 5FU could have occurred specifically in our group of patients. To date, no correlation has been found between 5FU pharmacokinetics and the delivered dose or the sex, nutritional status, or hepatic function of patients [10, 23]. All patients included in this study had normal renal and hepatic biological tests before the start of chemotherapy. However, they had advanced non-small-cell carcinomas that were considered inoperable because of the thoracic extension of the tumor or because of respiratory failure. This point needs to be clarified since a pulmonary metabolism of 5FU is probable, accounting for the possibility of a 5FU clearance exceeding the cardiac output [25]. In this context, a decrease in 5FU pulmonary metabolism may explain in part the plasma accumulation of 5FU and FBAL.

To date, studies have failed to demonstrate any dose-effect relationship for continuous 5FU infusions [17, 30]. This has recently been highlighted by the study of Peters and colleagues [27], showing that plasma 5FU values are not related to the intratumoral 5FU concentrations. The clinical significance of plasma 5FU monitoring has therefore been demonstrated only in terms of toxicity reduction [34, 38]. In particular, 5FU toxicity is clearly increased by the inhibition of the drug's catabolic pathway, whether drug-induced such as by thymidine [26] or due to a hereditary DPD deficiency [6, 16]. This suggests that plasma 5FU accumulation occurring during the last days of infusion may increase the toxicity of the chemotherapy cycle. Most studies that have shown a significant relationship between 5FU pharmacokinetics and toxicity have examined only the first part of the chemotherapy cycle [31, 34]. Obviously, this does not allow the analysis of a putative day-to-day increase in plasma 5FU concentrations and its consequences in terms of toxicity.

Although it was 20% lower than the dose usually given to previously untreated patients [18, 19], the dose we gave (4 g/m^2 per cycle) corresponded to both the maximum tolerated dose found by Vokes et al. [35] using 5FU biomodulation by folinic acid and that suggested by Saltz and Kelsen [30] in a 5-day continuous-infusion schedule of 5FU given in association with high-dose cisplatin (daily bolus, 35 mg/m^2).

The analysis of the 5FU concentration curves shows that the mean plasma 5FU concentrations measured during the last 24 h of our study always exceeded 300 ng/ml (2.5 μM). This value is higher than the 5FU levels found by Fraile et al. [13] to be associated with significant 5FU toxicity following the continuous i.v. infusion of 5FU (1.1 g/m^2 per day). In our series, we observed a case of gastrointestinal toxicity, a case of hematological toxicity, a case of severe cardiac toxicity (on the 3rd day of 5FU infusion), and a sudden death that occurred just after the completion of the chemotherapy and was suggestive of a cardiac event. These data are in agreement with the results of a recent study showing a significant relationship between 5FU-related cardiac toxicity, 5FU pharmacokinetics, and the prescription of cisplatin [14].

Although it is difficult to determine due to the delayed nature of cytostatic-related toxicity, our data suggest that most of the 5FU-related toxicity occurs during the last day(s) of 5FU-cisplatin infusion and may thus warrant a decrease in either the dose or the rate of administration of 5FU during the last day(s) of infusion. Further study is needed to elucidate the mechanism of the observed increase in plasma 5FU/FBAL concentrations as well as its relationship with cisplatin coadministration and to assess the clinical relevance of this plasma 5FU accumulation.

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