original article

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Pharmacokinetic and demographic markers of 5-fluorouracil toxicity in 181 patients on adjuvant therapy for colorectal cancer

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Background: The relationship between 5-fluorouracil (5-FU) pharmacokinetics and toxicity following i.v. bolus administration has not been extensively studied.

Patients and methods: One hundred and eighty-one patients on adjuvant therapy with 5-FU plus leucovorin for colorectal cancer were the study population. 5-FU pharmacokinetics was determined on day 2 of the first, third, and fifth cycles; type and the grade of adverse reactions were recorded on the next cycle.

Results: The 5-FU area under the curve (AUC) measured at the first cycle ranged between 146 and 1236 mg × min/l and was significantly correlated with drug dose, patients' body weight (BW) and gender, females having higher AUCs. These covariates explained only 23% of AUC variability. AUC and age were the only covariates which discriminated between toxic (grade ≥2) and nontoxic cycles (grade <2), with an optimal AUC cut-off value of 596 mg × min/l. Such a correlation was lost during the next cycles following dose reduction because of toxicity in 80 patients.

Conclusions: A method for calculating the initial 5-FU dose is proposed which takes into account patient BW, gender and a target AUC of 596 mg × min/l. Nevertheless, it appears that a substantial part of 5-FU toxicity is not linked to pharmacokinetic factors and dose adjustments must still be on the basis of careful clinical surveillance.

Key words: area under the curve, colorectal cancer, toxicity, 5-fluorouracil

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introduction

5-Fluorouracil (5-FU) in combination with leucovorin is still widely used for both metastatic colorectal cancer treatment and postsurgical adjuvant therapy. So far, various administration regimens have been tested and, in general, continuous i.v. infusion is considered a better regimen than bolus injection for advanced colorectal cancer in view of a higher response rate and a lower toxicity [1–4]. Furthermore, using an 8-h continuous infusion schedule, Gamelin et al. [5] found a link between toxicity/objective response and 5-FU plasma levels and a 2- to 3-mg/l plasma concentration range, which was successfully used for dose adaptation in a subsequent prospective study [6].

On the contrary, a clear superiority of continuous infusion over bolus administration has not yet been demonstrated in the postsurgical adjuvant setting [7, 8], where bolus administration schedule continues to be an acceptable option in view of its greater simplicity (no need for central venous catheter and portable pump). Moreover, at present only few, small-sized studies [9–12] have tried to establish a relationship between 5-FU plasma concentrations and toxicity following bolus schedule (Mayo Clinic regimen), so that an optimal plasma concentration range has not yet been identified.

The aim of this study is to verify whether demographic characteristics and 5-FU area under the curve (AUC) monitoring may help in predicting the occurrence of toxicity in patients on 5-FU adjuvant therapy with the Mayo regimen for colorectal cancer.

methods

patients and treatment

One hundred and eighty-one Caucasian patients on adjuvant therapy for colorectal cancer were the study population. The study was approved by the Ethics Committee of the General Hospital of Rovigo, and all patients gave their written informed consent. Chemotherapy consisted of the 5-FU + leucovorin combination, according to the Mayo administration schedule (2 min i.v. bolus administration of 425 mg/m^2 + 20 mg/m^2 daily for 5 days, for six consecutive cycles every 4 weeks). In patients of advanced age, the initial 5-FU dose could be reduced according to the doctors' judgment.

study protocol

5-FU pharmacokinetics was determined on day 2 of the first, third and fifth therapy cycles, using a limited previously validated sampling method [13]. Two blood samples (3 ml) were collected in EDTA-spiked tubes, 2.5 and

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20 min after the end of the i.v. bolus. Plasma was obtained by centrifugation (10 minutes at 1200 g) and frozen at −20°C until assayed. The type and severity of adverse reactions were recorded on the next cycle by means of patient interview, medical examination and standard laboratory tests. Toxicity was graded according to World Health Organization (WHO) criteria. The 5-FU dose could be reduced by 25%–50% or completely withdrawn, depending on the severity of the adverse reaction.

5-FU HPLC assay and pharmacokinetic analysis

5-FU was assayed using a high-performance liquid chromatography (HPLC) method described in detail elsewhere [13]. The lowest detection limit was 20 ng/ml and intraday and interday coefficients of variations were 4.5% and 6.1%, respectively. Plasma concentration decay was analyzed by a monoexponential function, so that intercept (Co) and slope (k) were obtained and used to calculate the main pharmacokinetic variables as follows:

- area under the plasma concentration–time curve: AUC = Co/k;
- plasma half-life: $t_{½}$ = 0.693/k;
- plasma clearance: CL = Dose/AUC;
- volume of distribution: Vd = CL/k.

With the limited sampling method used, the bias and accuracy for AUC estimate were 3.4% and 5.1%, respectively.

statistical analysis

Data are presented as means ± standard deviation, if not differently stated. Student's t-test for unpaired data was used to compare pharmacokinetic variables in males and females. One-way analyses of variance (ANOVA) (followed by the linearity trend test or the Newman–Keuls post hoc test, as required) were used to compare demographic and pharmacokinetic parameters in different toxicity grade groups. The chi-square test was used for analysis of categorical data. Independent variables correlated with AUC and toxicity grade were identified by means of multiple linear regression and logistic analysis, respectively. The receiver operating characteristic (ROC) curve was used to identify the AUC cut-off value separating patients with low- and high-toxicity grade, with the highest sensitivity and specificity. The acceptable significance level was set at $P < 0.05$.

results

At the first therapy cycle, pharmacokinetic and toxicity data were collected from 181 patients (124 males and 57 females), aged between 34 and 87 years and weighing 43–103 kg. Some patients did not compete the study protocol due to unwillingness to continue, 5-FU-related toxicity or 5-FU-unrelated events (relapses, concurrent radiotherapy toxicity), so that the number of cases valuable at the third and fifth therapy cycles was 93 and 76, respectively.

The mean 5-FU dose at the first cycle was 717 ± 96 mg. Eighty patients (44%) underwent a dose reduction during the next cycles due to toxicity, so that the average 5-FU doses at the third and fifth cycles were lower than those at the first one (642 ± 131 and 649 ± 133 mg/m^2, respectively). Seven patients stopped the treatment due to severe toxicity. The most frequent adverse reactions were mucositis, diarrhea and/or vomit and neutropenia. Incidence, type and severity of adverse reactions recorded at the first, third and fifth cycles are shown in Table 1. The percentage of patients with toxicity of any grade was 80% at the first cycle, 68% at the third and 64% at the fifth (chi-square test: $P < 0.02$).

pharmacokinetic data

The mean values of the main pharmacokinetic 5-FU variables measured at cycles 1 are shown in Table 2. Although 5-FU dose/m^2 was similar in males and females (391 ± 44 and 398 ± 34 mg/m^2, respectively), significant sex-related differences were noted: CL, CL/kg and dose were lower, whereas $t_{½}$ and AUC were higher, in females than in males. On the contrary, Vd, Vd/kg, Co and dose/kg did not differ significantly between sexes. AUC measured at cycle 1 ranged between 146 and 1236 mg × min/l. To explain such variability, multiple linear regression analysis was carried out using age, sex, body weight (BW), body surface area (BSA), body mass index (BMI) and dose (D) as independent variables. The results indicate that AUC was significantly related only with dose ($P < 0.0001$), BW ($P < 0.0001$) and sex ($P < 0.0001$), according to the following equations:

$$\text{Males}: \text{AUC} = 252.6 + 1.15 \times \text{D} - 7.14 \times \text{BW}; \quad (1)$$

$$\text{Females}: \text{AUC} = 379.1 + 1.15 \times \text{D} - 7.14 \times \text{BW}. \quad (2)$$

Although significant, multiple regression explained only ~23% of AUC variability ($r^2 = 0.23$).

The mean AUCs measured at third and fifth cycles (511 ± 137 and 505 ± 164 mg × min/l, respectively) were significantly lower than those at the first cycle (613 ± 194 mg × min/l), due to dose reduction in 80 patients (see above).

determinants of 5-FU toxicity

The relationship between demographic/pharmacokinetic variables and WHO toxicity grade was first analyzed using the first-cycle data, which included the largest number of patients ($n = 181$) and were not influenced by previous drug exposure. One-way ANOVA followed by the linearity trend test revealed that toxicity grade was significantly correlated with 5-FU AUC ($P < 0.0001$), $t_{½}$ ($P < 0.0001$) and Co ($P < 0.05$), whereas

Table 1. Incidence and severity of specific and overall toxicity in three cycles

Toxicity grade	Cycle 1 (n = 181)		Cycle 3 (n = 93)		Cycle 5 (n = 76)	
	1–2	3–4	1–2	3–4	1–2	3–4
Mucositis	84 (46%)	47 (26%)	41 (44%)	3 (3.2%)	23 (30%)	4 (5.3%)
Diarrhea/vomit	78 (43%)	15 (8.3%)	39 (42%)	0 (0%)	33 (43%)	5 (6.6%)
Neutropenia	45 (25%)	13 (7.2%)	13 (14%)	4 (4.3%)	9 (12%)	1 (1.3%)
Overall	84 (46%)	61 (34%)	57 (61%)	6 (6.5%)	39 (51%)	10 (13%)

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Table 2. Sex dependence of pharmacokinetic variables (cycle 1)

	Units	All (n = 181)	Males (n = 124)	Females (n = 57)	P value
Plasma clearance	l/min	1.32 ± 0.59	1.42 ± 0.57	1.08 ± 0.58	<0.001
	l/min/kg	0.019 ± 0.008	0.020 ± 0.008	0.017 ± 0.008	<0.05
Distribution volume	l	18.2 ± 6.3	18.7 ± 6.0	17.1 ± 6.7	NS
	l/kg	0.26 ± 0.09	0.26 ± 0.09	0.27 ± 0.10	NS
$t_{½}$	min	10.3 ± 3.8	9.6 ± 3.1	11.7 ± 4.7	<0.001
Co	mg/l	43.5 ± 14.3	43.6 ± 14.1	43.3 ± 14.7	NS
AUC	mg × min/l	612.8 ± 193.9	581.6 ± 184.4	680.6 ± 198.3	<0.005
Dose	mg	718 ± 96	744 ± 87	660 ± 89	<0.0001
	mg/kg	10.3 ± 1.4	10.3 ± 1.3	10.5 ± 1.6	NS

NS, not significant; AUC, area under the curve.

Table 3. Distribution of pharmacokinetic and demographic variables in different toxicity groups

	Toxicity grade				
	0	1	2	3	4
Number of patients	31	38	51	48	13
Dose (mg)	704 ± 118	735 ± 96	709 ± 96	717 ± 87	734 ± 65
Co (mg/ml)[a]	37.1 ± 12.0	41.2 ± 12.6	43.9 ± 15.5	47.6 ± 13.8	48.8 ± 15.5
$t_{½}$ (min)[b]	8.4 ± 2.3	8.9 ± 1.7	10.9 ± 4.1	11.1 ± 3.5	13.5 ± 6.7
AUC (mg × min/l)[b]	441 ± 155	506 ± 129	630 ± 159	723 ± 142	859 ± 198
Age	66.4 ± 10.5	61.2 ± 10.0	65.8 ± 9.9	66.0 ± 7.8	62.5 ± 11.8
BW (kg)	73.4 ± 12.7	73.2 ± 12.1	79.8 ± 13.6	67.7 ± 12.5	69.0 ± 10.6
BSA (m^2)	1.87 ± 0.20	1.86 ± 0.18	1.80 ± 0.21	1.77 ± 0.21	1.79 ± 0.17
BMI	25.4 ± 3.4	25.9 ± 4.2	25.5 ± 4.2	24.7 ± 3.5	25.0 ± 3.7
Males/females	26/5	30/8	29/22	30/18	9/4

[a]Analysis of variance (ANOVA): $P < 0.01$; linearity trend test: $P < 0.005$.

[b]ANOVA: $P < 0.0001$; linearity trend test: $P < 0.0001$.

AUC, area under the curve; BMI, body mass index; BSA, body surface area; BW, body weight.

dose, age, BW, BSA and BMI were not (Table 3). Female patients were more frequent in the groups with toxicity grade ≥2 than in those with toxicity grade <2 (39% versus 19%; χ^2 test: $P < 0.005$). When specific toxic effects were analyzed, only the severity of gastrointestinal toxicity (mucositis, nausea, vomit, diarrhea) was significantly related to the AUC, whereas neutropenia was not.

In order to confirm the relationship between AUC and severity of adverse reactions by means of a complementary approach, first-cycle AUCs were grouped according to the clinical decision to maintain or decrease/stop the 5-FU dose on the next cycles because of toxicity. The mean AUC was significantly higher in patients who needed drug withdrawal (846 ± 241 mg × min/l; n = 7) than in those whose doses were decreased (721 ± 155 mg × min/l; n = 80) and, likewise, the AUC was higher in the latter group than in the group who maintained the same 5-FU dose (503 ± 150 mg × min/l; n = 94). Mean dose and age did not differ between groups.

Multivariate logistic regression analysis was also carried out including AUC, Co, $t_{½}$, dose, age, sex (female = 0, male = 1), BW, BSA and BMI as independent variables. Two toxicity grade thresholds were separately used to identify 'toxic' cycles: grade ≥2 and grade ≥3. The first threshold is relevant to the clinical decision to reduce the dose, and the second is an indicator of severe or potentially life-threatening toxicity. The only covariates which significantly discriminated between toxic and nontoxic cycles were AUC (with both thresholds) and age (only with toxicity grade ≥2).

The corresponding logistic regression equations were the following:

$$\text{For } \geq 2 \text{ grade threshold: Logit}\,(p) = -9.32 + 0.0105 \times \text{AUC} + 0.0575 \times \text{age}; \quad \chi^2 = 76.1; P < 0.00001. \qquad (3)$$

$$\text{For } \geq 3 \text{ grade threshold: Logit}\,(p) = -5.61 + 0.0077 \times \text{AUC}; \quad \chi^2 = 55.2; P < 0.00001. \qquad (4)$$

The same results were obtained when gastrointestinal toxicity was separately considered, whereas no covariate predicted hematological toxicity (data not shown).

The AUC cut-off value (ROC analysis) which best identifies patients with toxicity grade ≥2 was >596 mg × min/l, with 75% specificity and 79% sensitivity. When toxicity was defined by a grade ≥3, the AUC cut-off was only slightly higher than the previous one (615 mg × min/l, with 79% specificity and 70% sensitivity).

Surprisingly, on the next two cycles (third and fifth) no significant difference in AUC was found between patients with

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different toxicity degrees. Since the mean AUCs measured at cycles 3 and 5 were under the toxicity thresholds established at cycle 1, the residual toxicity may be ascribed to pharmacodynamic factors.

discussion

As the data presented above pertain to various aspects of 5-FU pharmacology, they will be discussed separately.

pharmacokinetic data

5-FU pharmacokinetics strongly depend on dose and administration rate (bolus or slow infusion) [14, 15] due to saturation of its systemic and, possibly, first-pass pulmonary metabolism [16]. The values of the 5-FU pharmacokinetic parameters found by us using a previously validated limited sampling method [13] are comparable with those reported by others following a similar administration schedule [14], thus confirming method reliability. The inter-subject variability in AUC was quite wide (146–1236 mg × min/l) and only partially explained by differences in 5-FU dose, BW and gender. On the contrary, BSA, BMI and age bore no significant relationship with AUC.

Females had a slightly but significantly lower CL (0.017 versus 0.020 l/min/kg) and a longer plasma half-life (11.7 versus 9.6 min). Accordingly, mean AUC was higher in females than in males (681 versus 582 mg × min/l). Although these findings are in line with previous reports [17, 18], conflicting data are also available in the literature. Indeed, one study could not demonstrate any sex-related differences in 5-FU kinetics [19, 20], whereas another found that dihydropyrimidine dehydrogenase liver activity responsible for 5-FU catabolism was higher in females than in males [21], and our group reported that 5-FU CL, normalized by lean body mass instead of BW, was higher in females than in males [22]. These apparent discrepancies may be reconciled by considering that 5-FU metabolism takes place not only in the liver but also in most metabolically active tissues [23] and that lean body mass is less abundant in women than in men. Thus, when dose is adjusted by BSA or BW, women receive a slightly higher dose per lean mass unit than men.

Contradictory results have also been reported with regard to the influence of advanced age on 5-FU kinetics. Milano et al. [17] studied a large patient population aged between 25 and 91 years and found no effect of age on drug CL. A few years later, the same group reported a significant (though weak) correlation ($r^2 = 0.136$) between age and 5-FU CL [20].

On the whole, it should be stressed that in the studies so far carried out (included the present one), all the covariates significantly related with 5-FU pharmacokinetics accounted for just a small portion of total variability, indicating that the best option to determine drug exposure in the individual patient remains the direct measure of AUC.

In addition, it seems important to note that BSA in our study was not a determinant of 5-FU AUC. These findings confirm previous ones which indicate that the routine use of BSA to individualize the dose of anticancer drugs is inadequate [24].

determinants of 5-FU toxicity

A substantial body of literature exists to indicate that 5-FU toxicity is influenced by AUC [15], advanced age [25, 26] and sex [25–27]. In the present study, the determinants of 5-FU toxicity were sought by means of multiple logistic regression analysis using various demographic and pharmacokinetic covariates and two different toxicity thresholds (≥2 grade and ≥3 grade). The only variable highly related with toxicity incidence (for both thresholds), in the 181 patients who completed the first chemotherapy cycle, was AUC. In addition, a fair linear trend between AUC and toxicity grade was confirmed by means of ANOVA. Such a correlation, already found following a continuous infusion schedule [5], is remarkable also because 5-FU is not directly active but needs intracellular transformation into active metabolites. Age was a significant but less important covariate only for the lower toxicity threshold (≥2 grade). In seeming contrast with published data, sex was not an independent determinant in our multivariate analysis. However, a straightforward explanation is that sex influence was already included in AUC, which was significantly higher in females than in males. Indeed, when sex without AUC was considered, female prevalence was higher in the ≥2 toxicity grade group.

The AUC cut-off value which best discriminated between toxic and nontoxic patients was 596 mg × min/l for a toxicity grade ≥2 and 615 mg × min/l for a toxicity grade ≥3. This minimal difference indicates that AUC is not a very sensitive marker for predicting severe to life-threatening toxicity. Indeed, other observations indicate that non-pharmacokinetic factors must prevalently contribute to 5-FU toxicity. First, substantial AUC overlapping is noted in patients with close toxicity grades. Second, the mean AUCs measured at cycles 3 and 5, i.e. after dose reduction in toxic cycles, were not significantly different between patients with different toxicity grade. It follows, as a practical consequence, that pharmacokinetic monitoring may be useful in preventing 5-FU toxicity at the beginning of 5-FU treatment but, afterward, dose adjustments must still be on the basis of careful clinical surveillance. Third, when different toxicity types were analyzed, only gastrointestinal toxicity grade was clearly correlated with AUC, whereas neutropenia severity was not. Such a result may depend on the low number of patients who developed hematological toxicity but may be well due to different pharmacodynamic sensitivity of bone marrow and intestinal mucosa cells. Finally, it is known that tissue levels of thymidylate synthase (TS), the main molecular 5-FU target, are under genetic control and that a tandem repeat polymorphism in the promoter enhancer region of the TS gene is implicated in modulating TS messenger RNA expression and translational efficiency [28, 29]. Actually, Pullarkat et al. [30] reported a significant inverse association between the number of tandem repeats in the TS enhancer region and severity of toxicity.

conclusions

Our data show that 5-FU AUC is the best predictor of gastrointestinal toxicity of grade ≥2 occurring at the first cycle, in patients on adjuvant therapy with 5-FU + leuvocorin according to Mayo Clinic regimen. AUC, in turn, is related to drug dose, BW and gender. Advanced age appears to be another, but less important, independent risk factor. AUC predicting

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value is completely lost on next cycles, following routine dose reduction in patients with unwarranted toxicity. On the basis of these findings, the following approach to dose individualization may be proposed. The initial 5-FU bolus dose may be calculated a priori by introducing individual BW in equations (1) (for males) and (2) (for females) and by setting as target AUC the threshold value of 596 mg × min/l, which best identify toxicity grade ≥2. Rearranging equations (1) and (2) yields the following equations:

$$\text{Males} : \text{Dose} = \frac{343 + 7.14 \times \text{BW}}{1.15}; \quad (5)$$

$$\text{Females} : \text{Dose} = \frac{217 + 7.14 \times \text{BW}}{1.15}. \quad (6)$$

On day 1 of the first cycle, AUC should be monitored and next doses tailored to approach the target value of 596 mg × min/l. If toxicity occurs despite dose reduction in patients with high AUC, dose should be further reduced according to standard clinical criteria. No specific suggestion can be made for patients with low AUC who, following dose increase, develop no or mild toxicity, in that our data provide no information about possible therapeutic benefit of further dose escalation. Needless to say, our approach needs to be validated in a prospective study and, possibly, integrated with pharmacogenetic data. In this respect, studies are ongoing in our laboratory to explore any additional role of TS genetic polymorphisms in development of AUC-independent 5-FU toxicity.

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