5-Fluorouracil Pharmacokinetics Predicts Disease-free Survival in Patients Administered Adjuvant Chemotherapy for Colorectal Cancer

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Abstract

Purpose: To evaluate 5-fluorouracil (5-FU) and 5-fluoro-5,6-dihydrouracil (5-FDHU) pharmacokinetics and disease-free survival (DFS) in colorectal cancer patients given 5-FU-based adjuvant chemotherapy within a nonrandomized, retrospective, pharmacokinetic study.

Experimental Design: One hundred fifteen patients including 72 men (median age, 63 years; range, 36-79 years) and 43 women (median age, 60 years; range, 36-73 years) received 6 cycles of L-leucovorin 100 mg/m²/day and 5-FU 370 mg/m²/day i.v. boluses (5 days every 4 weeks). Individual plasma concentrations of 5-FU and 5-FDHU were determined on day 1 of the first cycle with a validated high performance liquid chromatography method, and the main pharmacokinetic variables were determined. Follow-up of all patients was extended up to 5 years after the end of adjuvant chemotherapy, and DFS was recorded. Univariate and multivariate analyses were conducted to evaluate any correlation among 5-FU pharmacokinetics, clinical and pathologic variables, and DFS.

Results: The area under the time/concentration curve (AUC) of 5-FU was significantly lower in 58 subjects who recurred (7.5 ± 2.9 h × mg/L) with respect to other patients (9.3 ± 4.1 h × mg/L). Furthermore, AUC values lower than 8.4 h × mg/L together with lymph node involvement and the interruption of treatment or reduction of doses were identified as risk factors at univariate analysis. The completion of 6 cycles of adjuvant treatment without dosage modifications was the only independent risk factor at multivariate analysis, despite a trend toward significance for 5-FU AUC values (cutoff value, 8.4 h × mg/L) was observed (P = 0.06).

Conclusions: Pharmacokinetics of 5-FU should be regarded as an important factor for predicting disease recurrence in colorectal cancers.

Patients affected by colorectal cancer who undergo a radical surgery have a variable probability of disease relapse in the following years, according to pathologic characteristics of surgically excised neoplasms. Tumor-node-metastasis stage represents the best predictive prognostic factor in colon carcinoma (1). Moreover, poorly differentiated and undifferentiated tumors have a worse prognosis than well and moderately differentiated neoplasms (2), whereas the presence of positive lymph nodes is an additional prognostic factor. Of note, ~50% of cancers with the worst prognostic features (American Joint Committee on Cancer/Union Internationale Contra Cancrum stage III) are likely to relapse within the next 5 years after resection (3). Because of the serious problem of disease recurrence, adjuvant treatments have been introduced in clinical settings, and today, adjuvant 5-fluorouracil (5-FU)-based chemotherapy is considered standard of care for patients with node-positive colon and rectal cancer after surgical excision of the tumor (4, 5). More recently, to increase the disease-free and overall survival of colorectal cancer patients, newer agents (i.e., oxaliplatin) have been introduced in the therapeutic armamentarium (6).

It is well-known that 5-FU pharmacokinetics is characterized by a large interpatient variability, despite strict adherence to treatment protocol. Several factors may contribute to this variability, including the activity of dihydropyrimidine dehydrogenase (DPD), which is responsible for drug catabolism to yield the inactive metabolite 5-fluoro-5,6-dihydrouracil (5-FDHU; ref. 7). The interpatient variability in 5-FU pharmacokinetics may in part explain the different tolerability to the drug in subjects who are treated with 5-FU (8), whereas 5-FU exposure [expressed as the area under the time concentration curve (AUC) values] may predict treatment efficacy in advanced/metastatic colorectal cancer patients (9). On the
basis of these premises, the variability of 5-FU disposition could also influence the effectiveness of adjuvant chemotherapy in terms of disease-free survival (DFS).

Therefore, the aims of the present nonrandomized, retrospective, pharmacokinetic study were as follows: (a) to evaluate the possible correlations of 5-FU and 5-FDHU pharmacokinetics [including DPD activity measured in peripheral blood mononuclear cells (PBMC)] with DFS in colorectal cancer patients given 5-FU–based adjuvant chemotherapy, and (b) to identify cutoff values of pharmacokinetic variables related to better prognosis in terms of DFS.

Materials and Methods

Patients. Chemotherapy-naive patients with histologically confirmed, surgically resected colorectal adenocarcinoma were considered eligible for the present study. Enrollment criteria included the following: (a) one month of time interval between surgery and the start of chemotherapy; (b) an Eastern Cooperative Oncology Group performance status of ≤2; (c) normal values of bone marrow, hepatic, and renal functions; and (d) the completion of six cycles of planned adjuvant chemotherapy without changes (reductions) of daily dose of 5-FU. Patients were given adjuvant chemotherapy with 5-FU 370 mg/m² i.v. bolus (≤2 min) plus leucovorin 100 mg/m²/d for 5 consecutive d, every 4 wk for 6 cycles (10). Drugs were administered between 9 and 10 a.m. and they were preceded by metoclopramide 10 mg i.v. bolus to prevent early nausea and vomiting. The provisions of the Helsinki declaration were implemented in this study that was approved by the Ethics Committee of Pisa University Hospital. Investigations on DPD activity and pharmacokinetics of 5-FU/5-FDHU were done after obtaining written informed consent from patients.

Treatment tolerability and follow-up. Chemotherapy-induced toxicities were assessed by physician examination, electrocardiogram, urinalysis, serum biochemistry, and blood cell count with differential before the start of the next cycle of chemotherapy or earlier if indicated by clinical signs or symptoms of toxicity, and scored according to the WHO criteria. Toxicities after the first cycle of chemotherapy and the worst toxicity experienced along the 24-wk treatment period were recorded.

In case of severe toxicities, 5-FU dose was reduced or suspended, and in both cases, the patient was not included in the final analysis. After completion of planned chemotherapy, follow-up visits were done every 6 mo within the first year and then each year thereafter or when needed based on symptoms, signs, and laboratory findings.

Blood sampling and collection of PBMC. 5-FU and 5-FDHU disposition was evaluated in patients on day 1 of the first cycle of therapy. Blood samples were drawn between 9:00 a.m. and 1:00 p.m. from a catheter placed in a peripheral vein of the forearm before the start of the next cycle of chemotherapy or earlier if indicated by symptoms, signs, and laboratory findings. Blood sampling and collection of PBMC. 5-FU and 5-FDHU AUC values was calculated. Peak plasma concentrations (C_{\text{max}}) and time to reach it (T_{\text{max}}) for 5-FU and 5-FDHU were determined from visual inspection of plasma concentration versus time curves. Finally, the ratio between 5-FU i.v. bolus. Blood was collected in heparinized tubes, centrifuged, and then plasma was used to measure 5-FU and 5-FDHU concentrations. Baseline sample was used to isolate PBMC and to determine in vitro DPD activity. Briefly, baseline blood sample was diluted 1:1 with PBS (pH 7.4), layered over Lymphoprep Separation Medium, and centrifuged for 40 min at 1,100 rpm. PBMCs were harvested and washed twice with PBS, whereas contaminating erythrocytes were lysed by diluting the cell suspension 1:8 (v/v) with a hypotonic solution (10 mmol/L KHCO₃, 160 mmol/L NaH₂CO₃, and 0.13 mmol/L EDTA) for 15 min at room temperature. After centrifugation and washing with PBS, PBMCs were resuspended in 35 mmol/L sodium phosphate buffer (pH 7.4) and freeze thawed thrice in liquid nitrogen. Cytoplasmic extracts were obtained by centrifugation at 15,000 rpm for 25 min at 4°C and their concentration was measured by the Protein Assay kit (Sigma). Then the measurement of DPD activity was immediately done, using 5-FU (20 μmol/L) as a substrate after a nonradioactive method (11). Concentrations of 5-FU and 5-FDHU were determined according to the procedure described in the next section.

High performance liquid chromatography analysis. Plasma samples and cytosolic extracts (0.5 mL each) were mixed with 25 μL of sodium acetate 1 mol/L (pH 4.8), 250 μL of sodium sulfate 0.2 g/mL, 5-fluorocytosine as internal standard (10 mg/L), and 7 mL of diethyl ether/n-propyl alcohol (84:16, v/v; ref. 8). Samples were shaken by a rotator for 15 min, then centrifuged at 3,500 rpm for 10 min, and supernatants (6 mL) were transferred in tubes and evaporated in a rotavapor and then lyophilized. Organic extracts were reconstituted with 250 μL of KH₂PO₄, 50 mmol/L (pH 4.0), vortexed, and sonicated for 0.5 min. After centrifugation for 15 min at 15,000 rpm, clear supernatants were transferred to autosampler vials and eluted through Hypersil BDS C18 stationary phase (250 × 4.6 mm; 5 μm; Alltech) with 50 mmol/L KH₂PO₄ (pH 4.0) at flow rate of 1 mL/min. Eluants were monitored at 200 nm and analyzed by the Millennium 2.1 software (Waters). Standard calibration curves were obtained by adding 5-FU and 5-FDHU to 0.5 mL of blank plasma or PBMC cytosolic extracts obtained from healthy donors on each day of analysis, resulting in final concentrations that ranged from 0.08 to 75 μg/mL.

Pharmacokinetic analysis of 5-FU and 5-FDHU. Plasma levels of 5-FU and 5-FDHU from each patient were fit according to a two-compartment open model, using nonlinear least squares regression analysis by means of a computer software (AP02PR; MediWare). Distribution and terminal half-lives (t_{1/2p} and t_{1/2b}, respectively), AUC, t_{1/2}, and apparent volume of distribution were calculated. Peak plasma concentrations (C_{\text{max}}) and time to reach it (T_{\text{max}}) for 5-FU and 5-FDHU were determined from visual inspection of plasma concentration versus time curves. Finally, the ratio between 5-FU and 5-FDHU AUC values was calculated.

Statistical analysis. Results are expressed as mean value ± SD and median. Kolmogorov-Smirnov test to check for normal distribution of pharmacokinetic variables and the unpaired Student’s t test with Welch’s correction were done by Prism vers. 4.0 (GraphPad Software)
5-FU plasma concentrations in 115 patients revealed a wide range of values. Differences in terms of age, stage, and grade between the groups were observed. Among the 115 patients, 58 subjects (37 males and 21 females) experienced disease recurrence at 5 years of follow-up. Notably, at 1 and 3 years, disease recurrence rates were 24.3% and 43.5%, respectively, and there were no significant differences in terms of age, stage, and grade between the groups. The remaining 101 patients, 66 men (median age, 63.0 years; range, 36-79 years) and 35 women (median age, 60 years; range, 36-73 years) completed the adjuvant treatment. Gastrointestinal side effects were observed (diarrhea, stomatitis, nausea, and vomiting), but they were tolerable and easily manageable with pharmacotherapy and supportive care over the entire treatment period, and delays in administration or reductions in drug dosage were not required.

Eleven patients experienced grade 3 WHO diarrhea and/or stomatitis that led to discontinuation of drug administration (number of administered cycles: median 3; range, 2-5), whereas in further three patients, a reduction in 5-FU dose was required. The log-rank test was used to compare difference in survival curves. Cox proportional hazards regression models were done to examine the association of clinical-pathologic risk factors and DFS. Finally, receiver operating curve analysis and positive and negative predictive value calculation were done by using Prism and Excel (Microsoft) to identify optimal cutoff values for pharmacokinetic variables. The level of significance was set at a P value of <0.05.

Results

Demographic data and follow-up of patients. Between January 1997 and December 1999, 115 patients affected by colorectal adenocarcinomas were enrolled in this study (Table 1). Eleven patients experienced grade 3 WHO diarrhea and/or stomatitis that led to discontinuation of drug administration (number of administered cycles: median 3; range, 2-5), whereas in further three patients, a reduction in 5-FU dose was required. The remaining 101 patients, 66 men (median age, 63.0 years; range, 36-79 years) and 35 women (median age, 60 years; range, 36-73 years) completed the adjuvant treatment. Gastrointestinal side effects were observed (diarrhea, stomatitis, nausea, and vomiting), but they were tolerable and easily manageable with pharmacotherapy and supportive care over the entire treatment period, and delays in administration or reductions in drug dosage were not required.

Among the 115 patients, 58 subjects (37 males and 21 females; 50.4%) experienced disease recurrence at 5 years of follow-up. Notably, at 1 and 3 years, disease recurrence rates were 24.3% and 43.5%, respectively, and there were no significant differences in terms of age, stage, and grade between the groups of patients. Pharmacokinetics of 5-FU and 5-FDHU. The analysis of 5-FU plasma concentrations in 115 patients revealed a C\text{max} value of 21.9 ± 14.9 mg/L 5 minutes after administration of 5-FU, with a terminal half-life value of 0.26 ± 0.19 hours (Table 2). The C\text{max} of 5-FDHU was 4.7 ± 1.4 mg/L, whereas T\text{max} accounted for 0.71 ± 0.21 hours (Table 2). Mean AUC values of 5-FU and catabolite were found to be 8.7 ± 4.1 and 11.4 ± 7.6 h × mg/L, respectively.

Pharmacokinetic variables of the drug and its inactive metabolite were normally distributed according to the Shapiro-Wilk test. Data were further analyzed using SPSS/PC+11.5 statistical software. The Kaplan-Meier methodology was used for plots of DFS. All patients (n = 115) Males (n = 72) Females (n = 43)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All patients (n = 115)</th>
<th>Males (n = 72)</th>
<th>Females (n = 43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily dose (mg)</td>
<td>620 ± 88 (606)*</td>
<td>651 ± 84 (660)</td>
<td>566 ± 58 (555)\dagger</td>
</tr>
<tr>
<td>DPD (pmol/min/mg)</td>
<td>187.6 ± 113.1 (163.3)</td>
<td>182.7 ± 112.9 (162.7)</td>
<td>194.7 ± 114.6 (185.3)</td>
</tr>
<tr>
<td>T\text{max} (h)</td>
<td>21.0 ± 14.9 (17.9)</td>
<td>22.0 ± 15.5 (19.9)</td>
<td>19.3 ± 14.0 (16.2)</td>
</tr>
<tr>
<td>AUC (h × mg/L)</td>
<td>11.4 ± 7.6 (10.0)</td>
<td>11.8 ± 8.5 (10.0)</td>
<td>10.6 ± 5.8 (9.3)</td>
</tr>
<tr>
<td>T\text{1/2} (h)</td>
<td>0.97 ± 1.49 (0.55)</td>
<td>0.99 ± 1.59 (0.55)</td>
<td>0.93 ± 1.33 (0.55)</td>
</tr>
<tr>
<td>C\text{max} (mg/L)</td>
<td>4.7 ± 1.4 (4.4)</td>
<td>4.8 ± 1.5 (4.4)</td>
<td>4.6 ± 1.3 (4.5)</td>
</tr>
<tr>
<td>T\text{max} (h)</td>
<td>0.71 ± 0.21 (0.68)</td>
<td>0.68 ± 0.21 (0.67)</td>
<td>0.75 ± 0.21 (0.73)</td>
</tr>
<tr>
<td>AUC ratio</td>
<td>0.90 ± 0.53 (0.76)</td>
<td>0.86 ± 0.47 (0.68)</td>
<td>0.96 ± 0.62 (0.85)</td>
</tr>
</tbody>
</table>

Abbreviations: CL, total body clearance; Vd, volume of distribution; T\text{1/2}, terminal half-life; C\text{max}, maximal plasma concentration; T\text{max}, time to peak; AUC ratio, 5-FU/5-FDHU AUC ratio.

*Numbers within parentheses, median values.
\dagger Significantly different from males (unpaired Student’s t test with Welch’s correction).

Table 2. Pharmacokinetics of 5-FU and 5-FDHU in 115 colorectal cancer patients

Fig. 1. Correlation between AUC of the drug and daily dose of 5-FU (A) or DFS (B) in 115 or 58 colorectal cancer patients, respectively. Statistical analysis gave P and r values of 0.674 and 0.040, respectively (A) and a P value of <0.05 and an r value of 0.487 (B).

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Kolmogorov-Smirnov test, and they did not significantly differ among men and women. However, male subjects received a significantly higher 5-FU dose per day with respect to female patients (651 ± 84 versus 566 ± 65 mg, respectively). That difference was due to a significantly greater body surface area in men with respect to women (1.78 ± 0.22 versus 1.55 ± 0.16 m², respectively; \( P < 0.0001 \)), whereas DPD activity did not differ among men and women. Finally, statistical analysis showed that there was no correlation between total daily dose and AUC values of 5-FU (\( P = 0.23; r = 0.076 \); Fig. 1A).

**DFS and pharmacokinetics.** In 58 of 115 patients who recurred within 5 years of follow-up, 5-FU AUC values were significantly correlated with DFS (\( r < 0.05; r = 0.487 \); Fig. 1B), suggesting that pharmacokinetics of 5-FU may influence treatment efficacy in terms of reducing the risk of disease recurrence.

Moreover, AUC values of 5-FU significantly differed in patients who experienced a disease relapse within 5 years with respect to relapse-free subjects (Table 3), confirming that a higher exposure to the drug was significantly related to a better DFS.

On the basis of these results, receiver operating curve analysis was used to identify cutoff values of 5-FU AUC predictive of chemotherapy outcome in terms of DFS. Receiver operating curve analysis showed that the best cutoff value for 5-FU AUC was 8.4 h × mg/L, corresponding to a sensitivity and specificity of 61.4% and 77.3%, respectively. The performance of these values was confirmed by positive predictive value and negative predictive value, accounting for 0.698 and 0.608, respectively.

**Univariate and multivariate analysis.** Univariate analysis showed that in 115 patients, only 5-FU AUC (cutoff value, 8.4 h × mg/L), lymph node involvement (according to the tumor-node-metastasis staging system), and the completion of adjuvant treatment were significantly associated with DFS (Fig. 2), despite that only the latter retained a statistical significance when evaluated by multivariate analysis (Table 4).

Furthermore, the same analyses were carried out only in those patients who completed the adjuvant treatment, to ascertain the role of 5-FU pharmacokinetics in those subjects who received a homogenous adjuvant treatment (i.e., six cycles of chemotherapy at unmodified standard doses of 5-FU). Univariate analysis carried out in 101 patients strengthened the significant influence of lymph node status and 5-FU AUC on DFS, despite that only the first one was an independent risk factor at multivariate test, whereas a trend (\( P = 0.07 \)) was observed for drug exposure.

### Discussion

The present nonrandomized, retrospective, pharmacokinetic/pharmacodynamic study showed a correlation between 5-FU exposure and DFS in the adjuvant setting. In colorectal cancer patients, the adjuvant administration of 5-FU results in improved overall survival and DFS with respect to surgery alone, especially in high risk subjects (12, 13). Early results have been confirmed by more recent studies, in which the use of newer drugs, including oxaliplatin, has significantly reduced the rate of disease relapse (6, 14). Although these encouraging achievements, the correlation between DFS and 5-FU pharmacokinetics was neglected, and data are still lacking, whereas the majority of clinical studies have focused their attention on the correlation between pharmacokinetics of 5-FU and toxicities (15–18). After these premises, the present study reports original findings concerning the association between 5-FU AUC values and DFS in colorectal cancer patients who received adjuvant chemotherapy.

The present population of patients received a 5-FU–based adjuvant chemotherapy following the Machover’s schedule: during each one of the 6 cycles, patients were treated with daily bolus injections of leucovorin (100 mg/m²) and 5-FU (370 mg/m²) for 5 days every 4 weeks (10). This schedule was well-tolerated, despite 14 of 115 patients required treatment discontinuation or dose reduction for the occurrence of severe toxicities.

### Table 3. Pharmacokinetic parameters of 5-FU in 115 colorectal cancer patients after the first dose of 5-FU in adjuvant chemotherapy

<table>
<thead>
<tr>
<th>Disease recurrence at 5 y of follow-up</th>
<th>No, ( n = 57 ) patients (median)</th>
<th>Yes, ( n = 58 ) patients (median)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily dose (mg)</td>
<td>615 ± 79 (602)</td>
<td>629 ± 94 (614)</td>
</tr>
<tr>
<td>DPD (pmol/min/mg)</td>
<td>196.1 ± 125.9 (163.3)</td>
<td>179.0 ± 105.2 (164.9)</td>
</tr>
<tr>
<td>5-FU</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC (h × mg/L)</td>
<td>9.3 ± 4.1 (8.5)*</td>
<td>7.5 ± 2.9 (6.8)</td>
</tr>
<tr>
<td>CL (L/h/m²)</td>
<td>48.0 ± 22.4 (43.6)</td>
<td>57.5 ± 25.7 (54.1)</td>
</tr>
<tr>
<td>Vd (L/m²)</td>
<td>17.3 ± 15.8 (13.2)</td>
<td>19.4 ± 15.3 (13.8)</td>
</tr>
<tr>
<td>( t_{1/2} ) (h)</td>
<td>0.25 ± 0.20 (0.20)</td>
<td>0.25 ± 0.18 (0.21)</td>
</tr>
<tr>
<td>( C_{max} ) (mg/L)</td>
<td>21.8 ± 16.3 (18.0)</td>
<td>21.0 ± 14.6 (17.6)</td>
</tr>
<tr>
<td>5-FDHU</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC (h × mg/L)</td>
<td>11.0 ± 4.7 (10.8)</td>
<td>11.8 ± 9.9 (9.5)</td>
</tr>
<tr>
<td>( t_{1/2} ) (h)</td>
<td>1.02 ± 1.20 (0.65)</td>
<td>1.07 ± 1.95 (0.52)</td>
</tr>
<tr>
<td>( C_{max} ) (mg/L)</td>
<td>4.7 ± 1.5 (4.4)</td>
<td>4.8 ± 1.3 (4.5)</td>
</tr>
<tr>
<td>( T_{max} ) (h)</td>
<td>0.74 ± 0.22 (0.75)</td>
<td>0.67 ± 0.20 (0.67)</td>
</tr>
<tr>
<td>AUC ratio</td>
<td>0.96 ± 0.57 (0.82)</td>
<td>0.76 ± 0.35 (0.64)</td>
</tr>
</tbody>
</table>

**NOTE:** Patients were divided in two groups according to their 5-y follow-up.

*Significantly different from patients who experienced diseases recurrence (unpaired \( t \)-test with Welch’s correction).
gastrointestinal and hematologic toxicities, and at the end of the 5-year follow-up, the disease recurred in 58 subjects. In the present population, lymph node status (classified according the WHO criteria) was a factor significantly influencing the recurrence rate of the disease, in agreement with recently reported data obtained in a pooled analysis of colon cancer patients (5). On the contrary, there was no a significant correlation or a trend between histologic grade of tumor and the DFS, being the latter worse in high grade carcinomas, as previously described (1, 5).

The major novelty of the present data relies on the association between DFS and 5-FU AUC, and the latter significantly differed among patients according the recurrence of the disease or not, confirming that 5-FU levels have a role in clinical settings. As a matter of fact, univariate analysis showed that 5-FU pharmacokinetics is predictive of the risk of relapse. In particular, a 5-FU AUC value higher than 8.4 h × mg/L was associated to a better DFS, and that cutoff value was predictive in ~70% of subjects. The multivariate analysis, which included the lymph node status and the completion of adjuvant chemotherapy without interruption or dosage reductions, showed that only the administration of the drug for six cycles was an independent factor of DFS. However, a trend for 5-FU AUC was evident (P = 0.06), being the risk of recurrence halved in those patients with the highest AUC values (>8.4 h × mg/L).

To ascertain the possible influence of 5-FU pharmacokinetics in a population of patients who received standard doses of Machover’s schedule for all 6 cycles, the same univariate and multivariate analyses were repeated in those 101 subjects who completed adjuvant chemotherapy without dosage modifications. Results overlapped those obtained in the entire population because a trend toward statistical significance was determined for 5-FU AUC. On the contrary, the lymph node status gained a role as an independent prognostic factor, demonstrating a hierarchy among considered clinical and pathologic variables.

Overall, the present results showed that 5-FU AUC values might be a predictive marker for DFS, and this conclusion should be transferred to clinical settings, where several validated methods are available for 5-FU analysis (19–21), Bayes approaches may be applied (22) and limited sampling models can accurately predict 5-FU AUC values (23).

Because 5-FU pharmacokinetics is characterized by a large interpatient variability and nonlinear behavior (24), the same standard dose of the drug could lead to a wide range of plasma and tissue levels, as shown in the present study. Therefore, to maximize treatment efficacy, dose adjustment in clinical oncology has been adopted and evaluated for many anticancer agents, among which carboplatin, etoposide, and 5-FU (25). In head and neck cancer patients receiving 5-FU, dose adaptation allowed the same objective response rate as the standard protocol (26). In advanced colorectal cancer patients, 5-FU plasma levels were found to be significantly higher in patients who experienced a complete or partial response, independently of the dose administered (27). In prospective studies, dose adjustment with pharmacokinetic monitoring led to higher overall survival and response rates than fixed-dose regimen in colorectal cancer patients (28), being reliable for therapy individualization (29).

Although, these studies strongly differed from the present one because of several issues (i.e., type and stage of cancers, chemotherapy regimens, and primary end-points), dose adaptation based on a patient’s drug pharmacokinetics and not on body surface area could maximize treatment effectiveness. Indeed, statistical analysis of the present results failed to show a correlation between AUC values and daily dose of 5-FU, suggesting that dosage calculation by body surface area is not a reliable strategy for therapy optimization in patients, whereas
5-FU doses should be calculated on metabolic capabilities of every patient. Furthermore, any possible interaction between 5-FU and other administered drugs (i.e., metoclopramide and antifungals) should be excluded because there are no evidences published in the literature and some of those agents known to potently influence hepatic metabolism (i.e., azoles) were administered during the period between two cycles, far away and not concomitantly with 5-FU injections.

Results of the present study suggest to evaluate 5-FU AUC at first cycle of chemotherapy and then adopting dose changes according to the target AUC in the following cycles. Because of the non-linearity of 5-FU pharmacokinetics (24), further studies are warranted to calculate AUC values at several dose levels. Moreover, this strategy of 5-FU optimization retains its value as a useful pharmacokinetic/pharmacodynamic approach in recent protocols of adjuvant chemotherapy that adopt i.v. continuous infusions of 5-FU or oral prodrugs of 5-FU in combination with other drugs, including oxaliplatin and irinotecan (13), although several factors may obscure the use of a dose adaptation strategy (30). Finally, it is conceivable that the evaluation of both 5-FU pharmacokinetics and pharmacogenetic determinants of drug efficacy (i.e., thymidilate synthase and DPD) should significantly increase the benefit offered to patients candidate to receive fluoropyrimidines.

In conclusion, 5-FU AUC was found to be associated with DFS in colorectal cancer patients receiving adjuvant chemotherapy based on i.v. 5-FU boluses, and the findings of the present study encourage dose modification to reach target AUC. The capability to increase treatment effectiveness by dose adaptation on the basis of pharmacokinetic variables should play a pivotal role in patient’s chemotherapeutic protocols.

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References

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