Advances in Brief

Clinical Impact of Pharmacokinetically-guided Dose Adaptation of 5-Fluorouracil: Results from a Multicentric Randomized Trial in Patients with Locally Advanced Head and Neck Carcinomas

Régine Fety, Frédéric Rolland, Muriel Barberi-Heyob, Agnès Hardouin, Loïc Campion, Thierry Conroy, Jean-Louis Merlin, Alain Rivière, Geneviève Perrocheau, Marie-Christine Etienne, and Gérard Milano

Centre René Gauducheau, 44805 Nantes [R. F., F. R., L. C., G. P.]; Centre Alexis Vautrin, 54511 Vandoeuvre-Lès-Nancy [A. H., A. R.]; and Centre Antoine Lacassagne, 06050 Nice [M-C. E., G. M.], France

Abstract

A significant link between 5-fluorouracil (SFU) plasma concentration and its therapeutic activity has been demonstrated in colon and head and neck cancer patients for SFU used as a continuous infusion. Dose adjustment based on pharmacokinetic follow-up has been proposed to decrease hematological and digestive toxicities, but the clinical impact of this approach has not yet been demonstrated. A randomized multicentric study was conducted to evaluate the clinical interest of SFU dose adaptation guided by pharmacokinetics. One hundred twenty-two head and neck cancer patients were randomly assigned to receive induction chemotherapy with cisplatin (100 mg/m², day 1) and SFU (96-h continuous infusion), either at standard dose (St-arm; 4 g/m²) or at a dose adjusted according to the SFU area under the curve (AUC0-t; PK-arm). In total, 106 patients were evaluable for toxicity and response. In the PK-arm (n = 49), SFU doses and area under the curve were significantly reduced during cycle 2 and cycle 3 (P < 0.001) as compared with the St-arm (n = 57). Grade 3–4 neutropenia and thrombopenia were significantly more frequent in the St-arm as compared with the PK-arm (17.5% versus 7.6%, respectively; P = 0.013). No grade 3–4 mucositis occurred in the PK-arm, whereas 5.1% was observed in the St-arm (P < 0.01). The objective response rate was comparable in the two treatment arms: 77.2% in the St-arm versus 81.7% in the PK-arm. The present study is the first to demonstrate, in a randomized design, the clinical interest of an individual 5FU dose adaptation based on pharmacokinetic survey, in terms of therapeutic index improvement.

Introduction

Despite being one of the oldest anticancer drugs, 5FU is still increasingly used in cancer chemotherapy. 5FU is considered not only as the standard drug for the treatment of advanced colorectal cancer, but also as one of the major drugs for the treatment of breast and head and neck carcinomas (1–3). Although SFU is a prodrug, significant relationships have been evidenced between SFU plasma concentrations, drug pharmacodynamics, side effects, and antitumor activity (4, 5). In this context, critical thresholds for 5FU plasma concentrations at risk for toxicity have been demonstrated. Indeed, Au et al. (6) noted that, during a 5-day continuous infusion, steady-state SFU plasma concentrations above 1.5 μM were significantly associated with leukopenia. Most data were obtained from studies conducted in head and neck cancer patients treated by 5FU-based chemotherapy as induction treatment. Thyss et al. (7) showed a significant relationship between elevated 5FU AUC (over 30,000 ng.h/ml) and the frequency of cycles with toxicity (myelosuppression, mucositis, and diarrhea). More recently, Vokes et al. (8) confirmed these observations. The next logical step was to use these pharmacokinetic data to propose individualized 5FU dose adjustment. Santini et al. (9) adopted such a strategy in head and neck cancer patients. They proved that the incidence of 5FU-related side effects could be reduced by individually controlling 5FU AUC at mid-cycle during the 5-day continuous infusion, and, if required, by modifying the 5FU dose using a simple diagram. These data were further confirmed by other authors (10). However, these last studies (9, 10) presented methodological limitations because they were based on historical controls as comparators to 5FU dose-adapted patients. For this reason, it was decided to conduct a multicentric study in which the clinical interest of SFU dose adaptation guided by pharmacokinetics could be evaluated on the basis of a randomized trial. Patients with locally advanced head and neck cancer from three different institutions were enrolled in this study and were randomly assigned to induction chemotherapy by cisplatin and SFU at St-arm or at PK-arm.

Patients and Methods

This prospective study involved 122 patients (114 men and 8 women), with a median age of 55 years (range, 29–72). All...
Table 1  Pretreatment characteristics of patients randomly assigned to St-arm or PK-arm

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>St-arm (n = 61)</th>
<th>PK-arm (n = 61)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of evaluable patients</td>
<td>57</td>
<td>49</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>52</td>
<td>48</td>
</tr>
<tr>
<td>Female</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Median age, yr (range)</td>
<td>54 (29-72)</td>
<td>55 (36-69)</td>
</tr>
<tr>
<td>Performance status (PS)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>16</td>
<td>11</td>
</tr>
<tr>
<td>1</td>
<td>34</td>
<td>35</td>
</tr>
<tr>
<td>2</td>
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<td>Primary site</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oropharynx</td>
<td>21</td>
<td>20</td>
</tr>
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<td>3</td>
</tr>
<tr>
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<tr>
<td>Stage of primary tumor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
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<td>Not determined</td>
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<td>0</td>
</tr>
<tr>
<td>Node stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>13</td>
<td>16</td>
</tr>
<tr>
<td>N1</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>N2</td>
<td>22</td>
<td>14</td>
</tr>
<tr>
<td>N3</td>
<td>11</td>
<td>10</td>
</tr>
</tbody>
</table>

patients had received no previous treatment and had histologically proven locally advanced squamous cell carcinoma of the head and neck. Patients’ characteristics are listed in Table 1. The eligibility criteria included age between 18 and 75 years; performance status grade 0, 1, or 2; measurable disease, life expectancy of at least 3 months; adequate bone marrow function (WBC >4.0 x 10^9/L, neutrophil count >2.0 x 10^9/L, and platelet count >100 x 10^9/L); adequate liver function (< twice upper limit of normal); and renal function (serum creatinine level <130 μmol/L). Ethical committee approval was obtained and all patients gave written informed consent.

**Treatment Regimens.** The treatment consisted of three cycles of 5FU-cisplatin delivered every 2 weeks (11), followed by response assessment and subsequent surgery and/or radiation therapy. All patients were treated with curative intent. Patients were randomly assigned to receive 5FU-cisplatin induction chemotherapy with either 5FU at St-arm or 5FU at PK-arm. In both arms, and at day 1 of each cycle, the treatment consisted of a 6-h prehydration with 2 l of 5% dextrose containing 6 g/L of NaCl, 2 g/L of KCl, followed by cisplatin at a dose of 100 mg/m^2 diluted in 500 ml of 10% mannitol and administered on a 2-h infusion. Therapy with 5FU started immediately after completion of cisplatin. 5FU was infused i.v. during 96 h at a constant rate with a volumetric pump.

In St-arm, 5FU was delivered at a fixed dose of 4 g/m^2 cycle. Doses were modified according to pretreatment blood cell counts and other toxicities. Patients with a WBC count ≥4.0 x 10^9/L, a neutrophil count ≥2.0 x 10^9/L, or a platelet count ≥100 x 10^9/L received 100% of the dose. Patients with a WBC count of 3.0–3.9 x 10^9/L, a neutrophil count of 1.5–1.9 x 10^9/L, or a platelet count of 75–99 x 10^9/L were given a total dose of 4 g/cycle. Patients with a WBC count ≤2.9 x 10^9/L, a neutrophil count ≤1.4 x 10^9/L, or a platelet count ≤74 x 10^9/L had treatment course delayed for 1 week.

In PK-arm, patients received 5FU at a dose defined by the AUC measured individually during treatment (12). During the first cycle, the AUC was calculated from 0–48 h (AUC_0–48h) and during the 96-h infusion (AUC_0–96h) to identify patients who accumulate 5FU. For patients with an AUC_0–96h lower than 3 x AUC_0–48h, the 5FU dose was adapted for cycles 2 and 3 according to diagram 1 (Fig. 1). For patients with an AUC_0–96h higher than 3 x AUC_0–48h, the dose was adapted for cycles 2 and 3 according to diagram 2 (Fig. 1). During this first cycle, 5FU doses were not adapted, except when AUC_0–48h was greater than 20,000 ng/h/ml, because this value has been previously reported to be highly predictive for toxicity (12). In this case, 5FU infusion was stopped at mid-cycle. The 5FU dose administered at the beginning of cycle 2 was determined by using diagrams 1 or 2 according to the AUC_0–48h calculated at cycle 1. The 5FU dose delivered at the beginning of cycle 3 was the dose administered during cycle 2. During cycle 2 and cycle 3, AUC_0–48h was controlled at mid-cycle and modified when necessary. The initial dose was decreased from 15–50% when AUC_0–48h values ranged from 15,600–20,000 ng/h/ml for diagram 1 and from 8,640–16,000 ng/h/ml for diagram 2. The dose was increased (0–50%) when the AUC_0–48h value was low (below 10,400 ng/h/ml for diagram 1 and below 5,760 ng/h/ml for diagram 2). An increase in 5FU dose was possible only if the changes in the WBC count, neutrophil count, or platelet count were lower than 25% as compared with the previous cycle. Without a dose reduction predicted by pharmacokinetics, and in case of a WBC count at 3.0–3.9 x 10^9/L, a neutrophil count at 1.5–1.9 x 10^9/L, or a platelet count of 75–99 x 10^9/L, the 5FU dose administered was a 4 g total dose/cycle. In case of a WBC count ≤2.9 x 10^9/L, a neutrophil count ≤1.4 x 10^9/L, or a platelet count ≤74 x 10^9/L, treatment was delayed for 1 week.

In the both arms, in case of mucositis grade 1, the full dose of 5FU was reduced to a 4 g total dose/cycle, and in case of grade higher than 1, treatment was delayed for 1 week. In case of other toxicities and a serum creatinine level greater than 130 μmol/L, treatment was delayed for 1 week.

**Response and Toxicity Assessments.** Assessments of response and toxicity were performed every 2 weeks during chemotherapy and 2 weeks after the completion of treatment. At each visit, a physical examination was performed, with blood cell counts and measurement of the serum creatinine level. Response was evaluated by the product of the two perpendicular lesion diameters, based on clinical, fibroscopic, ultrasound and or computed tomography scan examination. CR was defined as the disappearance of all lesions. PR was defined as a tumor regression exceeding 50% without occurrence of new lesions. ST was defined as any tumor regression less than 50%. Progression was defined as a tumor increase of more than 25%, or as the occurrence of any new lesion. Hematological and nonhematological toxicities were evaluated 10 days and 14 days after each cycle using the WHO criteria. Nonhematological toxicities included mucositis and digestive tract toxicity (including nausea, vomiting, and diarrhea).
Pharmacokinetic Investigations. Plasma 5FU levels were measured in all patients included in the study. Two blood samples/day were collected from days 1–4. Blood sampling on day 1 was performed before 5FU administration (control prior chemotherapy) and 2 h after 5FU infusion; on the following days, blood sampling was done as follows: on days 2 and 3, at 8 a.m. and 5 p.m.; on day 4, at 8 a.m., and just before the end of 5FU infusion. Venous blood (5 ml) was collected into heparinized tubes. The tubes were immediately centrifuged at 3000 rpm for 10 min at 4°C. Resulting plasma supernatants were transferred to individual 3-ml polypropylene tubes and stored frozen in the hospitalization ward. The frozen tubes were transferred to the laboratory once a day and stored at −20°C. 5FU plasma concentrations were analyzed by high-performance liquid chromatography (13) using UV detection (λ = 262 nm). The limit of sensitivity was 25 ng/ml. Intra- and interassay variations were lower than 10%. The AUC was determined according to the trapezoidal rule. The AUC was calculated over the first part of the cycle (AUC\textsubscript{0–48h}) and during the whole pharmacokinetic follow-up (AUC\textsubscript{0–\text{to-
obreakdash-end}}). For each patient, the pharmacokinetic parameters representative of 5FU exposure during the treatment were the average AUC\textsubscript{0–48h} (sum of AUC\textsubscript{0–48h} for each cycle divided by the number of cycles) and the AUC\textsubscript{0–\text{to-
obreakdash-end}} intensity (sum of AUC\textsubscript{0–\text{to-
obreakdash-end}} for each cycle divided by the number of weeks of treatment). Likewise, the average 5FU dose/cycle (sum of 5FU dose for each cycle divided by the number of cycles) and the 5FU dose intensity (sum of 5FU dose for each cycle divided by the number of weeks of treatment) were calculated for each patient.

Statistical Considerations and Analysis. The primary end point of the study was the incidence of hematological toxicity. The procedure tested a null hypothesis (H0) that the occurrence of grade 3–4 hematological toxicity was similar in both treatment groups versus the alternative hypothesis (H1) that occurrences were different between patients in the St-arm and the PK-arm. A sample size of 61 patients/arm afforded approximately 80% power to detect a 20% difference in grade 3–4 hematological toxicity between the two arms. Randomization was stratified by center (3 centers). Categorical data were analyzed using the χ² test. Continuous data were analyzed using Student’s t or Mann-Whitney U two-sided tests.

The secondary end point was the equivalence of tumoral response. The second procedure tested a null hypothesis (K0) that the occurrence of objective response rate was different in the two treatment arms (difference higher than 10%), versus the alternative hypothesis (K1) that the occurrence was identical in the St-arm and the PK-arm. Objective response rates were compared with the Dunnett and Gent one-sided test (14).

The statistical significance was considered at P < 0.05.

Results

Patient Characteristics. Among the 122 patients randomly assigned to one of the two treatment arms, 16 patients (13%) were subsequently found invaluable for response and toxicity (4 patients in the St-arm, and 12 patients in the PK-arm). One patient had concomitant treatment with an alkylating agent due to altered blood marrow function (polyglobulia), and 15 patients had major protocol violations: 3 patients had concomitant cisplatin dose reduction; 1 patient was adapted using the diagram 1 instead of the diagram 2; 4 patients had an incorrect dose increase; 5 patients had an incorrect dose increase and dose reduction; 2 patients had both incorrect 5FU dose increase and dose reduction. Incorrect dose was considered as a percentage of deviation from the recommended protocol dose higher than 20%. Of the remaining 106 evaluable patients, 57 were randomized to the St-arm, and 49 were randomized to the PK-arm. The gender and age distribution between the two arms was not significantly different. The distribution of patients within each
stratification variable (performance status, tumor site, tumor
stage, and node stage) was also comparable (Table 1).

**Cisplatin and 5FU Doses.** The initial cisplatin dose
received/cycle was not significantly different between the
two treatment arms (Table 2).

Considering 5FU, the percentage of the 5FU initial planned
dose was significantly different in the two groups of treatment
during cycle 2 and cycle 3 ($P < 0.001$). In PK-arm, the changes
were more pronounced (72.6% for cycle 2 and 68.9% for cycle
3) as compared with the St-arm (98.1% for cycle 2 and 91.6%
for cycle 3). In the St-arm, changes corresponded to reductions
in 5FU delivered dose according to pretreatment toxicity (3.9%
and 20.9% of the cycles had 5FU dose reductions during cycle
2 and cycle 3, respectively). In PK-arm, changes were due either
to a decrease or to an increase in 5FU doses according to the
pharmacokinetic protocol for dose adaptation, or to reductions
in 5FU-delivered doses according to pretreatment toxicity. Dur-
ing cycle 2, 5FU dose reductions occurred in 66.6% of the
cycles and dose increases occurred in 8.8% of the cycles. Dur-
ing cycle 3, the changes occurred in 78.0% of the cycles (dose
reduction) and in 4.8% of the cycles (dose increase).

When dose modifications were performed, reductions ranged
from $-40\%$ to $-50\%$ in the St-arm and from $-40\%$ to
$-48\%$ in the PK-arm. The percentages of dose increases in the
PK-arm were low: 6% and 7% for cycle 2 and cycle 3, respec-
tively.

**5FU AUC/Cycle.** 5FU AUC$_{0-96h}$ were available for pa-
patients in the St-arm and the PK-arm (Table 3). During cycle 1,
there was no significant difference between the two treatment
arms (AUC$_{0-96h}$ = 31,220 ± 12,414 ng/h/ml and 29,525 ±
10,673 ng/h/ml for the St-arm and the PK-arm, respectively).
During cycle 2 and cycle 3, AUC$_{0-96h}$ were significantly lower
in the PK-arm as compared with the St-arm ($P < 0.01$). There
was less interpatient variability for AUC values in the PK-
guided arm in comparison with the ST-arm (coefficient of
variation: 31\% versus 40\%, $P < 0.001$, cycle 3).

**Toxicity.** Hematological and mucosal toxicities attribut-
able to 5FU were significantly reduced in the PK-arm as com-
pared with the St-arm (Fig. 2). Grade 3–4 neutropenia and
thrombocytopenia were observed in 17.5% of the cycles in the
St-arm as compared with only 7.6% in the PK-arm ($P = 0.013$).
A complete absence of mucositis was observed in the PK-arm,
whereas 5.1% of the cycles in the St-arm experienced grade 3–4
toxicity ($P < 0.01$). There was no significant difference in
digestive tract toxicity between the two treatment arms.

Due to 5FU-related toxicity, three patients (5.2%) in the
St-arm left the study before completing chemotherapy: two pa-
tients after cycle 1 and one patient after cycle 2. In the
PK-arm, three patients (6.1%) left the study before completing
chemotherapy: one patient after cycle 1 and two patients after
cycle 2. As for cycle delay, the incidence was lower in the
PK-arm (14.9% of cycles, corresponding to 165 days) as com-
pared with the St-arm (21.2% of cycles, corresponding to 213
days), but the difference was not significant ($P = 0.269$).

**Response.** Patients (77.2%) in the St-arm (19 of 57 or
33.3% CR; 25 of 57 or 43.9% PR) and 81.7% of patients in the
PK-arm (14 of 49 or 28.6% CR; 26 of 49 or 53.0% PR) responded
to treatment. The objective response rates were signifi-
cantly equivalent (Dunnett and Gent, $P = 0.03$), with upper
90\% confidence limit equal to 8.7\% (Fig. 3).

**Link between Clinical Events and Pharmacological Data.**
Table 4 illustrates the link between hematological tox-
icities and mucositis with average AUC$_{0-96h}$/cycle and 5FU
doses. The analysis was performed on the whole study group
($n = 106$ patients). All patients received one, two, or three
cycles. The mean value for the average AUC$_{0-96h}$ was signifi-
cantly related to the severity of hematological toxicity (grade
3–4; $P = 0.035$). No significant relationship was found with

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**Table 2** Doses and mean percentage of initial planned dose received/cycle for patients with St-arm or PK-arm

<table>
<thead>
<tr>
<th></th>
<th>Cycle 1</th>
<th>Cycle 2</th>
<th>Cycle 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$n$</td>
<td>Dose (mg) $\pm$ SD (%)</td>
<td>$n$</td>
</tr>
<tr>
<td>Cisplatin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>St-arm</td>
<td>57</td>
<td>171 $\pm$ 17 (100)</td>
<td>52</td>
</tr>
<tr>
<td>PK-arm</td>
<td>49</td>
<td>174 $\pm$ 17 (99.8)</td>
<td>45</td>
</tr>
<tr>
<td>$\text{SRi}$</td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5FU</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>St-arm</td>
<td>57</td>
<td>6798 $\pm$ 801 (99.1)</td>
<td>52</td>
</tr>
<tr>
<td>PK-arm</td>
<td>49</td>
<td>6683 $\pm$ 1219 (96.0)</td>
<td>45</td>
</tr>
</tbody>
</table>

$^a$ The percentage of cisplatin dose was 99.8% for the three cycles because one obese patient received at each cycle 95\% of the initial dose.
$^b$ NS, not significant.

**Table 3** 5FU AUC$_{0-96h}$ (ng $\cdot$ h/ml) received/cycle

<table>
<thead>
<tr>
<th></th>
<th>Cycle 1</th>
<th>Cycle 2</th>
<th>Cycle 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$n$</td>
<td>Dose (mg) $\pm$ SD (%)</td>
<td>$n$</td>
</tr>
<tr>
<td>St-arm</td>
<td>53</td>
<td>31,220 $\pm$ 12,414 (n = 53)</td>
<td>50</td>
</tr>
<tr>
<td>PK-arm</td>
<td>45</td>
<td>29,525 $\pm$ 10,673 (n = 45)</td>
<td>42</td>
</tr>
<tr>
<td>$P$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>NS</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$^a$ Due to analytical problem, AUC$_{0-96h}$ was not evaluable for all patients.
$^b$ NS, not significant.
5FU dose. For mucositis, average $AUC_{0-96h}$ was higher in patients with severe toxicities (grade 3–4), but the difference was not significant as compared with patients with no or moderate toxicity (grade 0–2).

Regarding objective response (Table 5), no significant association was observed with available pharmacokinetic parameters (average, $AUC_{0-96h}$ and $AUC_{0-96h}$ intensity) and 5FU doses (average dose/cycle and dose intensity).

**Discussion**

The current role of chemotherapy in head and neck carcinomas is presently focused on the treatment of locally advanced stages, for which continuous infusion 5FU and cisplatin chemotherapy is considered as a reference protocol (15). This protocol has demonstrated a high response rate (80%), but severe toxicities have been reported. Several investigators have shown that interindividual variability in 5FU clearance and AUC are linked to the risk of severe toxicities (7, 16–18). These pharmacokinetic parameters have also been reported to be correlated with response and survival in patients receiving 5FU-cisplatin induction chemotherapy (8, 19). In the present study, it was possible to confirm the relationship between 5FU pharmacokinetics and pharmacodynamics. Cycles with grade 3–4 hematological toxicity had significantly higher 5FU systemic exposure than cycles with grade 0–2 hematological toxicity. This observation is consistent with a study by Vokes et al. (8) who noted...

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**Table 4** Analysis of clinical toxicity as a function of 5FU pharmacological parameters (all patients)

<table>
<thead>
<tr>
<th></th>
<th>Average $AUC_{0-96h}$/cycle (ng · h/ml)</th>
<th>Average dose/cycle (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hematologic Toxicity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 0–2</td>
<td>$27,622 \pm 7,752 (65)^a$</td>
<td>$6,104 \pm 1,339 (75)$</td>
</tr>
<tr>
<td>Grade 3–4</td>
<td>$31,451 \pm 6,924 (26)^a$</td>
<td>$6,070 \pm 980 (31)$</td>
</tr>
<tr>
<td></td>
<td>$P = 0.035$</td>
<td>NS</td>
</tr>
<tr>
<td>Mucositis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 0–2</td>
<td>$28,866 \pm 8,066 (86)^b$</td>
<td>$6,098 \pm 1,248 (100)$</td>
</tr>
<tr>
<td>Grade 3–4</td>
<td>$34,285 \pm 6,814 (5)^b$</td>
<td>$6,225 \pm 962 (6)$</td>
</tr>
</tbody>
</table>

$^a$ Values are given as mean ± SD (number of patients).

$^b$ Average $AUC_{0-96h}$/cycle in 15 patients was not evaluable.

$^c$ NS, not significant.
a significant inverse correlation between neutrophil nadir values and 5FU plasma concentration, and only a poor correlation between 5FU pharmacokinetics and mucositis. In the present study, no link was found between 5FU pharmacokinetics and mucositis. As for tumoral response, no difference in average AUCO_96h and AUCO_%h intensity was observed between patients who achieved a CR or PR and patients who had stable disease or progression. This result is not consistent with previous studies (8, 19) that demonstrated that response and survival were significantly related to high 5FU plasma concentrations in patients with head and neck cancer. This discrepancy can be explained by the fact that in these previous studies, the patient-to-patient variability may have been larger than in the present one. Therefore, a closer relationship between tumor response and 5FU systemic exposure could be evidenced.

5FU therapeutic monitoring with 5FU dose adjustment was previously performed, and comparisons with historical groups suggested that the 5FU therapeutic index could be improved with 5FU dose adaptation based on pharmacokinetics (9). To our knowledge, the present study is the first randomized trial to investigate the clinical impact of pharmacokinetically-guided dose adaptation. This work was centered on 5FU clinical pharmacology only, despite the potential role played by cisplatin in the pharmacodynamics data analyzed herein. In fact, cisplatin exhibits antitumor activity against head and neck tumors (17% response rate; Ref. 20), and experimental data strongly suggest that cisplatin enhances 5FU cytotoxicity by indirectly increasing the intracellular levels of reduced folates (21, 22). In the present study, the impact of individual 5FU dose adaptation based on pharmacokinetics on clinical outcome is striking. The present randomized trial clearly demonstrates that patients with individually adapted 5FU dose rate develop significantly lesser toxic manifestations than patients receiving a fixed 5FU dose. In the PK-arm, grade 3–4 neutropenia and thrombocytopenia were reduced by more than 50%, and no grade 3–4 mucositis was observed. These results reflect the dose reduction applied in the PK-arm and the subsequent reduction in AUC values (Table 3). 5FU dose modifications were mainly dose reductions (66% and 78% of cycles 2 and cycles 3, respectively) and with few dose increases (8.8% of cycles 2 and 4.8% of cycles 3), thus indicating that the target AUC in this protocol is very close to the maximal tolerated dose.

The overall response rate remained within the range of those usually observed in these tumors (15). It should be noticed that the 5FU dose modifications performed did not alter the response rate. In a retrospective study, Santinini et al. (1989) reported similar results in monitored patients (9). Previous work (9) shows that for the 5-day continuous infusion of 5FU combined with cisplatin, the AUC predictive for toxicity is 30,000 ng·h/ml. Our results (Table 4) for the 4-day 5FU infusion confirm that high-grade hematological toxicity is associated to 5FU AUC higher than 30,000 ng·h/ml (average AUCO_96h = 31,451 ± 6,954 ng·h/ml). Taken together, these data demonstrate that for 5- and/or 4-day continuous infusion of 5FU, the target 5FU AUC for an optimal dose is 30,000 ng·h/ml. An alternative approach based on pretreatment determination of biological parameters instead of pharmacokinetics should be investigated to anticipate individual 5FU clearance and 5FU AUC. Such a strategy has already been applied successfully to carboplatin with individual dosage calculation based on pretreatment glomerular clearance determined directly (23) or indirectly (24). As for 5FU clearance, correlations have been demonstrated between this parameter and pretreatment hepatic function test (serum alkaline phosphatase level), age, and the activity of dihydorpyrimidine dehydrogenase (25, 26, 27), the main enzyme involved in the catabolism of 5FU. However, these correlations were too weak for a reliable prediction of 5FU clearance.4 Interestingly, the development of new dihydropyrimidine dehydrogenase inhibitors (such as etinylurylacil), when combined with 5FU, lead to the elimination of 5FU mainly by kidney route and to a decrease of the interindividual variability in 5FU clearance. In this case, it would be possible to predict 5FU clearance based on creatinine clearance and thus to evaluate the optimal individual 5FU dose before starting treatment (28).

For other drugs than anticancer agents like aminoglycosides, the cost-saving benefit of therapeutic drug monitoring has been demonstrated (29). In the present study, a pharmacoeconomic analysis was undertaken in a subgroup of 82 patients (41 patients in each arm; data not shown). The medical cost included three management groups. The first group included hospitalization and patient care required to manage toxic events. The second group included costs linked to 5FU plasma concentration monitoring. The third group included cost linked to calculation of 5FU dose adjustment. Overall, our analysis demonstrated a reduction of 14.6% in the medical cost in the PK-arm. More precisely, the respective costs (U.S. dollars) for the ST-arm and the PK-arm were, $21,758 and $16,835 for toxicity management; $0 and $13,798 for 5FU monitoring; and $16,835 and $12,325 for 5FU dose adjustment. This information

Table 5: Analysis of clinical response as a function of 5FU pharmacological parameters

<table>
<thead>
<tr>
<th>Respondersa</th>
<th>Nonresponders</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>29,065 ± 8,174 (75)c</td>
<td>28,180 ± 5,636 (16)c</td>
<td>NSd</td>
</tr>
<tr>
<td>15,766 ± 4,774 (75)c</td>
<td>16,401 ± 3,348 (16)c</td>
<td>NSd</td>
</tr>
<tr>
<td>6,133 ± 1,138 (87)</td>
<td>5,887 ± 1,651 (19)</td>
<td>NSd</td>
</tr>
<tr>
<td>3,378 ± 860 (87)</td>
<td>3,425 ± 1,049 (19)</td>
<td>NSd</td>
</tr>
</tbody>
</table>

Values are given as mean ± SD (number of patients).

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indicates that economic approach should be included as an end point in clinical pharmacokinetic studies.

In conclusion, this prospective study strongly suggests that the exploitation of 5FU pharmacokinetic-pharmacodynamic relationships could improve cancer chemotherapy of locally advanced head and neck carcinomas. We hope that the present study would show the interest, for other anticancer drugs, of prospective studies conducted on the basis of randomized trials, to establish the clinical value of individual drug dosage based on real time pharmacokinetic follow-up.

References
Clinical impact of pharmacokinetically-guided dose adaptation of 5-fluorouracil: results from a multicentric randomized trial in patients with locally advanced head and neck carcinomas.


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