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Clinical pharmacokinetic study of 5-FU in continuous 5-day infusions for head and neck cancer

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Summary. Twenty-nine previously untreated patients with head and neck carcinoma received a total of 63 cycles of an initial chemotherapy protocol combining *cis*-platinum (100 mg/m^2 on day 1) and continuous 5-day infusion of 5-FU (1000 mg/m^2/24 h) from day 2 to day 6. This protocol was repeated on day 16 and day 31. Two daily blood samples obtained from all patients every day during 5-FU administration were analyzed by HPLC to determine the 5-FU concentrations. In the majority of cases a constant elevation was observed in total 5-FU cycle exposure (C × T) from cycle to cycle. A close relationship was demonstrated between elevated 5-FU C × T values (over 30 000 ng h ml^{-1}) and the frequency of cycles in which signs of toxicity (myelosuppression, mucositis, diarrhea) were observed. By contrast, no obvious association was noted between response to treatment and systemic 5-FU exposure.

Introduction

The comprehensive pharmacokinetics data available on 5-fluorouracil (5-FU) in humans have recently been reviewed [2, 10]. By contrast, only limited information has been published on 5-FU blood monitoring during treatment, and the only clinical pharmacokinetics observations indicate that 5-FU blood concentrations may reflect toxicity [1, 8] as well as tumor response [7, 12]. The low number of patients covered by these studies [7, 8, 12] and their heterogeneity in terms of both pretreatment status [1] and the treatment itself [8, 12] may restrict the significance of these findings. The study described in this paper involved routine 5-FU blood measurements in all patients during every cycle of a 5-FU plus *cis*-platinum (CDDP) induction chemotherapy trial for head and neck cancer [9]. To date, 29 patients who had received no previous treatment have been evaluated. Data on patient response and toxicity for a total of 63 cycles were compared with individual total 5-FU exposure (C × T) during each cycle.

Materials and methods

Patients. Twenty-nine patients (27 male, 2 female) with a mean age of 61 years (range 37–84) and with histologically proven head and neck carcinoma were entered on a first-intention chemotherapy study with a protocol [9] combining: (a) On day 1: 6h hydration with 2 l 5% dextrose NaCl 6 g/l and KCl 3 g/l, followed by 100 mg/m^2 CDDP 1 mg/min IV in 0.5 l normal saline with 0.25 l 2% mannitol and then 1 l 5% dextrose NaCl 6 g/l and KCl 3 g/l; and (b) on days 2–6: 5-FU 1000 mg/m^2/24 h by continuous 5-day IV infusion. This protocol was repeated on day 16 and day 31 in each patient whose clinical and biological tolerance allowed it. A total of 63 cycles were evaluated in the pharmacokinetics study: 14 patients were evaluated for all three cycles, 6 patients for 2 cycles, and 9 patients for the first cycle only. Tumor staging for the 29 patients was as follows: 9 T2, 16 T3, 4 T4. Nodal involvement was 14 NO and 15 N+.

Criteria for inclusion in the study were: advanced head and neck tumors, no previous treatment, no metastases, serum creatinine level below 120 μmol/l, WBC 4000/mm^3, platelet count 100 000/mm^3. There was no criterion for exclusion over a given age limit, but elderly patients were given lower CDDP doses.

Study data were obtained as follows:
Direct questioning concerning abdominal pain, diarrhea, difficulty with oral feeding;
Clinical examination for weight, oral mucositis;
Biological tests for RBC and WBC, platelet counts, serum creatinine measurements, and blood and urinary ionograms.

Response to treatment was evaluated as follows: Endoscopy with biopsy (under local anesthesia for oral cavity tumors and under general anesthesia for laryngeal and pharyngeal lesions) was performed before and 8–12 days after the last cycle. Sinus lesions were evaluated by scanography. Complete response was defined as total disappearance of all measurable disease and negative findings in all biopsy checks; partial response was defined as greater than or equal to 50% but less than 100% reduction in all measurable lesions in the absence of any new lesions; and no response was defined as less than 50% reduction, no change or disease progression.

Toxic effects attributable to 5-FU (mucositis, diarrhea, hematologic disorders) were carefully evaluated after each cycle according to the WHO classification.

5-FU blood monitoring. Two blood samples were collected every day (8 a.m., 5 p.m.) during 5-FU administration, i.e., from day 2 to day 6 of the cycle. EDTA tubes were used to obtain 5 ml venous blood and were immediately

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brought to the laboratory and centrifuged (10 min, 4 °C, 2500 rpm). Plasma was collected and stored at −20 °C until analyzed. A previously described HPLC technique [3] was used for 5-FU measurements; the limit of sensitivity was 5 ng/ml. The parameter used for interpretation: area under the curve (C × T), representing total drug exposure during each cycle, was calculated by the trapezoidal rule.

Results

C × T evolution from cycle to cycle

Figure 1 shows 5-FU C × T values for the 14 patients who received three consecutive cycles. Interindividual value dispersion was observed in all cycles, but analysis of individual C × T profiles from one cycle to the next revealed a global increase in systemic drug exposure.

C × T values and toxicity

A total of 26 cycles (41%) were associated with toxic manifestations: digestive disorders (mucositis, diarrhea) after 14 cycles, hematological disorders (leukopenia, thrombopenia, or both) after 16 cycles, and both digestive and hematological problems after 3 cycles. In the majority of cases toxicity was moderate. Figure 2 presents the distribution of total individual 5-FU exposure during each cycle for toxic and nontoxic cycles. While the two groups of values overlap, there was a statistically significant difference in distribution ($P<0.01$). A C × T threshold level of 30 000 ng h ml^{-1} was highly predictive of toxicity ($P<0.001$).

C × T and response

Response to treatment was assessed for 25 patients; 12 exhibited a complete response, 12 a partial response, and 1 patient no response. No apparent association was observed between systemic patient 5-FU exposure (C × T) and the degree of response to treatment.

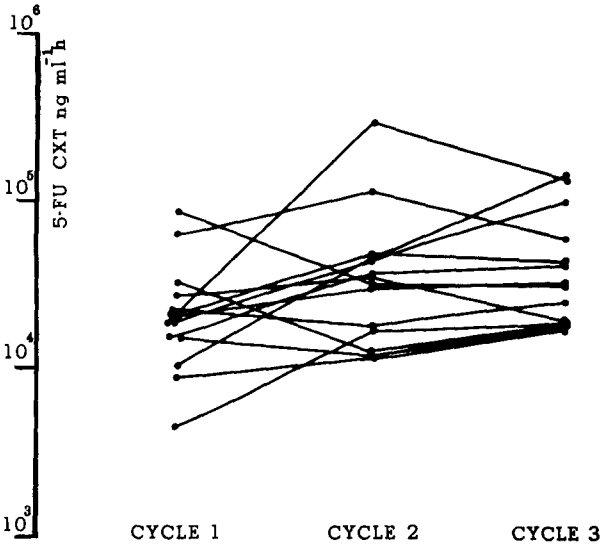

Fig. 1. Evolution of 5-FU exposure from cycle to cycle for 14 patients who received three consecutive chemotherapy cycles

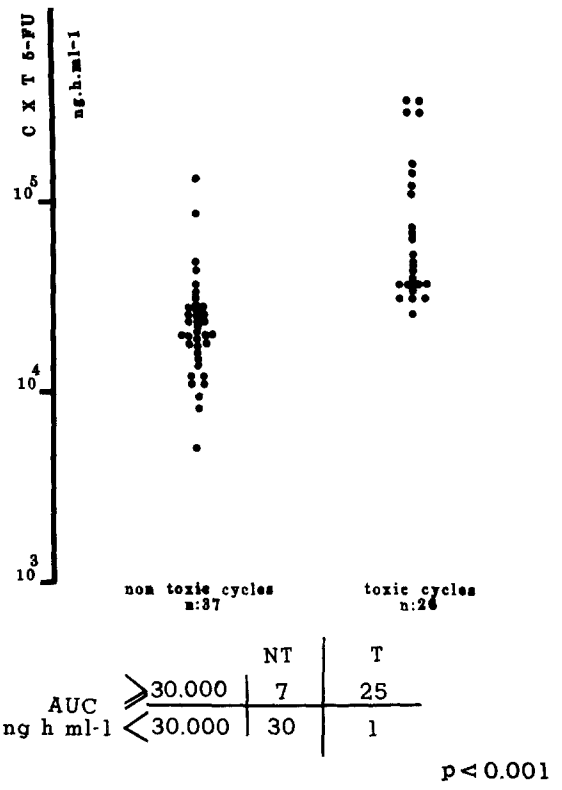

Fig. 2. Individual 5-FU cycle exposure and toxicity Statistical analysis: Chi-square test for the C × T threshold at 30 000 ng h ml^{-1}. NT, nontoxic cycles; T, toxic cycles

Discussion

First described by J. Kish et al. [9], this chemotherapy protocol for head and neck cancer patients seemed promising, since it gave a response rate of 88%. Moreover, associating CDDP with 5-FU seemed a good alternative to the CDDP bleomycin combination, which is often used for head and neck chemotherapy [5] but which involves bleomycin-inherent pulmonary toxicity that is cumulative and only partly reversible. These authors did, however, report a 26% incidence of leukopenia in their initial trial. In our study, myelosuppression and/or gastrointestinal toxicitiy (mucosisitis and diarrhea) were tolerable and were seen in 41% of the cycles. These forms of treatment intolerance can be reasonably attributed to 5-FU [4]. Our findings reveal the existence of a positive and significant association between individual total-body 5-FU exposure (C × T) during each cycle and the incidence of 5-FU-induced toxicity. The participation of intracellular 5-FU activation in the integrated mechanism of myelosuppression must also be mentioned, as recently stressed in animals [11]. Our results strengthen the findings of Au et al. [1] concerning 5-FU plus thymidine in the treatment of patients with digestive tract cancer. These authors found a positive correlation between toxicity and the 5-FU steady state of plasma levels, but their study included both untreated patients and patients who had previously received 5-FU. Our observation of a C × T threshold value (30 000 ng h ml^{-1}) highly predictive of toxicity is of practical value, since it could allow early recognition of high-risk patients. The increase observed in individual C × T values from cycle to cycle may also be of

clinical importance. To date, 73 patients have been evaluated, and findings confirm the occurrence of toxicity mainly after the second and third cycles. These pharmacoclinical observations have been used to modify the protocol: a longer interval (15 days) has been adopted between cycles to allow recovery of 5-FU body elimination capacities which are saturable [10]. No marked toxicity has been observed in the first 20 patients entered since this modified protocol has been in use, in keeping with moderate 5-FU $C \times T$ values.

As concerns response to treatment, no obvious correlation was found with 5-FU $C \times T$ during the cycles. Our results do not agree with previous data [7, 12] concerning patients with colorectal cancer, which showed an association between tumor regression and high circulating 5-FU levels [7] or decreased clearance [12]. There are two possible explanations. First of all, if we consider the complex and preponderantly intracellular activation of this drug [10, 11], circulating 5-FU blood levels per se may not sufficiently reflect antitumoral activity, as stressed by Tognoni et al. [13]. Secondly, since the 5-FU was administered in association with CDDP, the latter drug might play a role in the overall treatment effect, as suggested by the respective individual activities of these drugs when used alone for the treatment of head and neck cancer (34% response rate for CDDP versus only 27% for 5-FU [5]).

Finally, although co-administration of CDDP has recently been shown to alter bleomycin elimination [14], such a pharmacokinetic interaction between 5-FU and CDDP seems unlikely here. Indeed, no alterations were seen in post-treatment serum creatinine levels, but even in cases where CDDP-induced renal damage might not be revealed by a rise in serum creatinine, daily urinary elimination of 5-FU during continuous 5-day treatments would only account for 1%–4% [6].

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