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*Letter to the Editor*

# Circulating Drug Levels in Patients Presenting Cardiotoxicity to 5-FU

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ADMINISTRATION of 5-FU, particularly by continuous infusion, is increasingly common [1]. Cardiac manifestations attributable to 5-FU have been reviewed recently [2], and both the incidence (1.6%, [3]) and mortality (12.5%) are far from negligible. The risks of such potential clinical problems are increased 10-fold when 5-FU is administered by continuous infusion [4]. The etiology of this drug-related complication remains unclear [5]. Clinical features are in favor of cardiac ischemia rather than direct myocardial toxicity, which was suggested by experimental data on rodents [6]. Clinical reports on 5-FU toxicity have not mentioned any individual 5-FU blood concentration at the time of symptoms. A good correlation has been found between abnormal circulating 5-FU levels and digestive and/or hematologic toxicity [7]. One of the basic hypotheses requiring investigation would thus be whether abnormal systemic levels predispose patients to 5-FU cardiotoxicity or not.

In our institution, we systematically monitor 5-FU blood levels to control the individual toxicity inherent to 5-FU. Over a 4-year period we have observed 13 cases of 5-FU cardiotoxicity in patients treated by continuous 5-FU; courses were stopped when angor occurred. Blood drug levels just before cardiac manifestations were available for four of these patients (Table 1).

None of the patients reported here had prior evidence of heart disease, angina or arteritis of any type.

The individual concentration × time product values (AUC) of these patients were in the same range as those of patients free of digestive and/or hematological toxicity. Moreover, patients with a significantly higher AUC (group with digestive and/or hematologic toxicity) did not show any sign of cardiotoxicity. In particular, blood samples obtained 1–3 h before symptoms occurred were similar to the usual concentrations in most patients treated at this dose range.

Systemic pharmacokinetic abnormalities are thus probably not an underlying mechanism in the etiology of 5-FU cardiotoxicity, and other possible causes still require investigation.

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*Table* 1.

| Patients and treatment* | Pharmacokinetic data† |
|---|---|
| Male, 62 years, T3NO<br>Oropharyngeal carcinoma<br>Angor D6 first course | AUC D2-D6 (1st course): 36,588 ng/ml.h<br>Concentration before angor = 217 ng/ml (1st course) |
| Angor D4 second course<br>No previous cardiac history | Concentration before angor = 381 ng/ml (2nd course) |
| Female, 72 years, stage B2<br>Urothelial carcinoma<br>Angor D4<br>No previous cardiac history | AUC D2–D4 = 11,398 ng/ml.h<br>Concentration before angor = 347 ng/ml |
| Male, 70 years, T2NO<br>Oral cavity carcinoma<br>Angor D4<br>No previous cardiac history | AUC D2–D4 = 5515 ng/ml.h<br>Concentration before angor = 89 ng/ml |
| Female, 53 years, T2NO<br>Tonsillar carcinoma<br>Angor D5<br>No previous cardiac history | AUC D2–D5 = 26,832 ng/ml.h<br>Concentration before angor = 92 ng/ml |

*Planned treatment: day 1, cisplatin 100 mg/m$^2$; days 2–6, continuous i.v. 5-FU 1 g/m$^2$/day [8].
†Concentration × time products (AUC), ng/ml.h (medians and extremes) for patients treated as above at our institution (unpublished data):
Toxic cycles (≥WHO grade 2 hematologic and/or digestive toxicity) ($n$ = 21)
D2–D4 = 11,500 (2500–71,600)
D2–D6 = 35,000 (14,500–290,000)
Non-toxic cycles ($n$ = 113)
D2–D4 = 5500 (1000–19,200)
D2–D6 = 25,500 (3500–51,000).
Concentration before angor = blood sample obtained 1–3 h before symptoms.