5-Fluorouracil induces arterial vasoconstrictions


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Background: From 2% to 10% of cancer patients treated with 5-fluorouracil (5-FU) will develop symptomatic cardiotoxicity. Nevertheless, the underlying pathophysiology is mostly unknown.

Patients and methods: We investigated the influence of intravenous chemotherapy (CTX) on the diameter of the brachial artery using high resolution ultrasound in patients with malignant tumors, mostly gastrointestinal cancer. Cytostatic drugs included 30 cases with 5-FU and 30 cases with non-5-FU CTX (cis/carboplatin, anthracycline and cyclophosphamide). In addition, plasma levels of big endothelin were assessed prior to and after CTX.

Results: Fifteen of 30 patients (50%) showed a contraction of the brachial artery after the end of 5-FU application (median 11%, range 4.3–18.5), whereas no single contraction was noticed in 30 patients following non-5-FU-based CTX. Vessel tonus generally normalized within 30 min after stopping 5-FU. Five patients positive for 5-FU associated vessel contraction were repeatedly exposed to 5-FU. Vessel contractions reoccurred in 86% (18/21) of these administrations. When patients with 5-FU bolus application were pre-treated with glyceroltrinitrate no contraction of the brachial artery was detected in five out of five occasions. There was a trend towards increased big endothelin plasma levels after 5-FU application (median 1.52 versus 1.99 fmol/ml; \(P = 0.07\)), whereas big endothelin levels remained unchanged after non-5-FU CTX (1.83 versus 1.83 fmol/ml; \(P = 0.99\)).

Conclusions: Application of 5-FU is commonly accompanied by arterial vessel contractions, which is likely to represent the first step in 5-FU-induced cardiotoxicity. 5-FU-associated vessel contractions were highly reproducible on re-exposure and were in the case of bolus application completely preventable by glyceroltrinitrate.

Key words: big endothelin, cardiotoxicity, 5-fluorouracil, vasoconstriction

Introduction

Fluorouracil (5-FU) is a pyrimidine analog which is widely used in systemic cytostatic treatment of solid tumors. Common toxicity include diarrhea, mucositis, neurotoxicity, palmo-plantar dyesthesias and myelosuppression. The first case of an adverse cardiovascular event related to 5-FU was described by Roth et al. in 1975 [1]. Since then case reports and small series with 5-FU-induced cardiac events have been published with increasing frequency [2]. More recent prospective clinical trials demonstrate that 2–10% of patients exposed to 5-FU will develop cardiovascular complications [3–5].

Cardiotoxicity typically occurs as angina-like chest pain, but to a lesser extent, hypotension, cardiac arrhythmia and left ventricular dysfunction have also been observed. Angina is most noticeable during infusions, but occasionally it is delayed until 3–18 h after 5-FU application. Lethality of symptomatic patients may be as high as 12–29% and usually occurs as sudden death or cardiogenic shock [3, 6]. Patients with pre-existing ischemic heart disease or myocardial infarction appear to be at higher risk and continuous infusions and high doses of 5-FU have been regarded as additional risk factors for 5-FU-induced cardiotoxicity [2, 3].

Although the clinical feature of 5-FU cardiotoxicity is well recognized, little information concerning the underlying pathophysiology has been generated. Thus, hypotheses proposed include direct myocardial toxicity, thrombogenic effects, an immunologic reaction and ischemia secondary to coronary artery spasm [7, 8]. The letter pathophysiological concept was based on reports which failed to show angiographic evidence of a fixed coronary stenosis in several patients subsequent to acute 5-FU-induced cardiotoxic events. Furthermore, Mosseri et al. demonstrated 5-FU-induced vasoconstrictions in aortic rings isolated from rabbits in in vitro experiments [9]. However, in vivo proof of 5-FU-induced vasoactivity is still lacking. Therefore, we studied the influence of 5-FU application on the diameter of the brachial artery by high resolution ultrasound in a prospective clinical trial.

Patients and methods

In this prospective unicenter study diameter of the brachial artery was serially analyzed during 60 infusions with cytostatic drugs. The patients treated suffered from gastrointestinal (GI) cancer (31 patients), lung cancer (12),
lymphoma (nine), head and neck cancer (three) and others (two). Measurements were performed on 30 patients receiving 5-FU-based chemotherapy (21 patients, bolus; nine, infusional). 5-FU regimens contained the following additional drugs: two patients, cis-/carboplatin derivatives; three, oxaliplatin and leucovorin; eight, irinotecan and leucovorin; and 16, leucovorin. Thirty patients receiving platin derivatives (16 patients, cis-/carboplatin), anthracyclines (seven) and cyclophosphamide (seven) in a 5-FU-free regimen were used as the control group. Until June 2002, 34 men and 23 women were enrolled, median age was 63 years (range 28–87). Three patients were investigated on two different occasions following either 5-FU or non-5-FU chemotherapy. All patients gave their informed consent. Cytostatic drugs were applied as clinically indicated.

Six patients in the 5-FU group and two patients in the control group had a history of cardiovascular disease (previous myocardial infarction and/or angina pectoris) but all were asymptomatic when enrolled into the study. Seven patients in each group received cardioprotective drugs (calcium channel blockers, nitrates or β-blockers) during the study period. Chemotherapy was applied via central Port-a-Cath system in eight patients of the 5-FU group. In cases of peripheral access measurement of arterial diameter, the procedure was performed on the opposite arm.

Assessment of the brachial artery diameter

The brachial artery diameter was measured by B-mode imaging generated by an ultrasound system with a high resolution, 13-MHz linear-array transducer with an axial resolution of 0.12 mm (ESAOTE/Biomedical, Munich, Germany; scanning probe: 13.0 MHz). Scans were documented using a Sony video-graphic printer (UP-890CE). The sonographic measurement was performed according to the method described in detail elsewhere [10]. Briefly, the vessel diameter (VD) of the brachial artery was measured in a longitudinal section in B-mode standby modus. Scans of the brachial artery were performed at 5–10 cm proximal to the bifurcation. Transducer position was marked on the skin. Initially, resting scans were obtained and flow-mediated dilation (FMD%) was determined within 45–60 s after sudden deflation of a forearm tourniquet lasting 5 min. Thereafter, a cytostatic drug was applied and VD and FMD were measured again immediately after the end of the drug infusion. A significant vasomotor response was defined as a change in the A. brachialis diameter of ±4% following application of the cytostatic drug, since pretest studies confirmed an intraobserver variability below this threshold.

Measurement of big endothelin plasma levels

Blood specimens in ethylenediamine tetra-acetic acid (EDTA) were collected prior to (basal value) and immediately after the end of application of the cytostatic drugs. All samples were processed immediately in a precooled centrifuge at 3000 g and plasma was stored at −20°C until analysis. Plasma concentrations of big endothelin were determined by a commercially available solid-phase enzyme-linked immunosorbent assay (Biomedica, Vienna, Austria). Analysis was performed according to the manufacturer’s instructions.

Statistical analysis

The Mann–Witney U-test was used to compare differences between big endothelin plasma levels in the study population. Values of $P < 0.05$ were considered significant. All calculations were made with the Statistical Package of Social Sciences (SPSS) for Windows, version 10.0 (SPSS, Chicago, IL).

Results

Baseline sonographic measurements revealed that prior to chemotherapy diameters of the A. brachialis were comparable in the 5-FU and non-5-FU group [median, 3.89 mm (range 3.03–5.35) versus 4.08 mm (range 2.54–5.15); $P = 0.48$]. Following CTX application vasodilations (defined as an increase in vessel diameter ≥4%) were present in both study groups (Figure 1). However, no single case of significant vasocontraction (defined as reduction of the vessel diameter ≥4%) was detected in patients receiving cis-/carboplatin, anthracycline or cyclophosphamide (Figure 1). In contrast, 15 of 30 patients (50%) developed vasoconstriction following 5-FU application [median, 11% (range 4.3–18.5)]. This group included four of six patients with a history of cardiovascular disease (66%). Vasocontraction was more prevalent in infusional 5-FU (six of nine cases, 66%) when compared with bolus applications (nine of 21 patients, 44%).

Serial diameter measurements revealed that 5-FU-induced vasoconstrictions were short lived and ceased within 30 min in the four cases investigated. Five patients who had demonstrated 5-FU-induced vasoconstrictions were repeatedly exposed to 5-FU. Significant vasoconstrictions were noticed in 18 of 21 measurements (86%) (Figure 2). Pretreatment of patients with proven 5-FU-associated vasoconstriction with the NO donor glyceryltrinitrate (0.8 mg s.l.) prevented 5-FU-induced vasoconstrictions following 5-FU bolus applications in all five cases investigated (Figure 2).

Figure 1. Changes in the diameter of the brachialis artery after application of chemotherapy ($n = 60$). Dotted line indicates significant vasoconstriction. CTX, intravenous chemotherapy; 5-FU, 5-fluorouracil.

Figure 2. Changes in the diameter of the brachialis artery in patients positive for 5-fluorouracil-induced vasoconstriction on repeated re-exposure ($n = 26$). Dotted line indicates significant vasoconstriction. NTG, glyceryltrinitrate.
Plasma levels of big endothelin obtained prior to application of cytostatic drugs, in this study population with mostly metastasized cancer, exceeded values from normal controls (≤0.7 fmol/ml) with 1.52 and 1.83 fmol/ml, respectively. Levels demonstrated a high interindividual variation among patients. Whereas these levels remained virtually unchanged following non-5-FU cytostatic drugs [median, 1.83 fmol/ml (range 0.25–5.75) versus 1.83 fmol/ml (range 0.23–5.45); P = 0.99], there was a trend towards increased big endothelin plasma concentrations in patients after 5-FU application [median, 1.52 fmol/ml (range 0.09–6.69) versus 1.99 fmol/ml (range 0.19–4.89); P = 0.07]. However, increases in big endothelin levels were not significant in the group of patients (n = 15) who exhibited significant 5-FU-induced vasoconstriction [prior to application, 1.66 fmol/ml (range 0.09–6.69); at the end of infusion, 2.14 fmol/ml (range 0.21–4.89); P = 0.3].

Discussion

In the current study, we were able to substantiate the finding that arterial vasoconstriction following exposure to 5-FU is a frequent occurrence in cancer patients. From our findings, it is reasonable to assume that vasoconstriction is a leading force in 5-FU-induced cardiotoxicity for several reasons. First, both commonly appear during drug application and ease off soon after drug discontinuation. Secondly, symptomatic cardiotoxicity and 5-FU-induced vessel contractions have a comparable risk of reappearance on drug re-exposure (≤90%). Thirdly, like symptomatic cardiotoxicity, 5-FU-induced vasoconstriction appears to be more frequent during infusional as compared with bolus 5-FU applications.

However, none of the 15 patients positive for 5-FU-induced vasoconstriction had a symptomatic cardiotoxic event during the study period. Still, these findings are in accordance with observations made by Rezkalla et al. [11]. They documented ECG changes suggestive of ischemia in 17 of 25 patients (68%) who received continuous ECG monitoring during infusional 5-FU. In their study population only one patient became symptomatic.

Most patients in the 5-FU group were treated with multiagent regimens but vasoconstriction was only observed in connection with 5-FU application. Combinations of 5-FU with cis- and carboplatin have been implicated in the increase in the rate of cardiotoxic events when compared with 5-FU monotherapy [12]. However, in our study neither cisplatin nor carboplatin demonstrated vasoconstrictive activity when used without concomitant 5-FU.

Patients receiving 5-FU exhibited a trend towards increases in big endothelin plasma levels. However, this finding was independent of whether or not patients developed 5-FU-induced constriction of the brachial artery. Therefore, it is unlikely that big endothelin is an important mediator of 5-FU-induced vessel constriction. In contrast, increased plasma levels of endothelin-1 have been reported in patients who developed 5-FU-associated cardiotoxicity [13]. Thus, one might argue that direct measurement of short-lived endothelin-1, which derives from endothelial cells and represents the mediator with the strongest vasoconstrictive activity, may have been more appropriate in order to exclude any significant role of the endothelin network in 5-FU-induced vessel contraction. Nevertheless, from our study we favor the direct effect of 5-FU on the vascular smooth muscle cells. This suggestion is supported by the short length of vasoconstriction which is in accordance with the short serum half-life (8–20 min) of 5-FU in humans [14]. Furthermore, Mosseri et al. demonstrated in their in vitro model that 5-FU-induced constriction of vascular smooth muscle was not impaired by demudation of the endothelium from the arteries investigated [9].

5-FU-induced cardiotoxicity has been reported to be more frequent during the initial cycle of 5-FU chemotherapy than during later courses [4], but this observation may be biased since patients with an initial cardiotoxic event are usually not rechallenged. After re-exposure, there is a high rate of recurring cardiotoxicity [3], and mortality from myocardial infarction may be as high as 12.5% [6]. Thus, alternative drugs which also target thymidylate synthase but without known cardiotoxicity, such as raltitrexed, have been recommended as a replacement for 5-FU in patients after the first cardiotoxic event [15]. However, this practice results in a substantial limitation of treatment options in patients who have experienced 5-FU-induced cardiotoxicity. Even more, comparable cardiotoxicity has recently been observed following oral fluoropyrimidine analogs, such as capecitabine [16, 17]. A frequency of 3% for symptomatic events has been calculated from two large phase III trials in patients receiving capecitabine monotherapy, which appears to be comparable with the frequency reported for patients treated with infusional 5-FU [18]. This rate of cardiotoxic events during capecitabine is surprising in view of the fact that low systemic peak levels of 5-FU can be expected, due to the intracellular activation process of this prodrug [19].

There is no standardized drug regimen for intervention in cases of acute symptomatic 5-FU-induced cardiotoxicity. Furthermore, in spite of high reoccurrence rates, no effective drug regimen for prophylaxis has been established. Several vasodilators, such as nitrates and calcium antagonists, have been investigated for treatment or prevention of 5-FU-associated cardiotoxicity. Both effective and ineffective results have been reported, but no controlled prospective trial has been undertaken [20–22].

In summary, the available clinical data on the effects of vasodilative drugs remain inconclusive and appear to be especially unsatisfactory for continuous 5-FU applications. Based on the hypothesis that vasoconstriction represents the initial step in 5-FU-induced cardiotoxicity, our study design may offer a simple and sensitive technique to search systematically for reliable new protective agents in vivo.

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References