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ORIGINAL ARTICLE

5-Fluorouracil-based therapy induces endovascular injury having potential significance to development of clinically overt cardiotoxicity

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Abstract
Aim This study aimed to elucidate the influence of 5-fluorouracil (5-FU)-based therapy on the vascular endothelium and its association with 5-FU-induced heart ischemia.
Methods The study prospectively accrued patients ($n = 106$) having completely resected colorectal cancer and receiving adjuvant treatment with 5-FU, folinic acid, and oxaliplatin. The levels of plasma von Willebrand factor (vWf), urine albumin-to-creatinine ratio (UACR), coagulation factor II + VII + X, and fibrin D-dimer were serially assessed before, during, and after chemotherapy.
Results The vWf level increased from median (range) 1.43 kU/l (0.48 to >3) to 2.64 kU/l (0.23 to >3) ($P = 0.001$), the UACR increased from 1.1 ± 0.2 mg/mmol (mean ± SE) to 2.1 ± 0.3 mg/mmol ($P = 0.001$), the coagulation factor II + VII + X activity decreased from 1.00 ± 0.02 to 0.94 ± 0.02 U/l ($P = 0.001$), and the fibrin D-dimer level increased from 1.1 ± 0.2 to 2.1 ± 0.3 kU/l ($P = 0.001$) at baseline and during chemotherapy, respectively. The changes in the levels of vWf ($P = 0.3$), UACR ($P = 0.8$), coagulation factor II + VII + X ($P = 0.8$), and fibrin D-dimer ($P = 0.6$) in nine (8.5%) patients having clinical signs of cardiotoxicity were not significantly different from that of the patients not having cardiotoxicity. The 5-FU-induced rise in plasma biomarkers was not significantly related to the cardiovascular morbidity or its risk factors ($P = 0.9$).
Conclusions 5-FU therapy induces global reversible endothelial injury leading to a procoagulant state. The ensuing endothelial dysfunction may be of significance to the pathogenesis of 5-FU-induced clinically overt cardiotoxicity. Cardiovascular disease is not significant for the vulnerability of the endothelium to 5-FU-based chemotherapy.

Keywords Fluorouracil · Cardiotoxicity · Colorectal neoplasms · Plasma von Willebrand factor · Urine albumin · Fibrin D-dimer · Coagulation activity · Endothelial dysfunction · Glomerular damage

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Introduction

The pyrimidine antimetabolite 5-fluorouracil (5-FU) is widely used for the treatment of various solid tumors. Cardiotoxicity induced by 5-FU is a serious side effect leading to arrhythmias, myocardial ischemia, or heart failure, which presents with symptoms such as chest pain, hypotension, dyspnoea, or sudden death [1–6]. Incidences between 1 and 18% of 5-FU-induced cardiotoxicity have previously been reported [1–6].

The pathogenesis of 5-FU-induced cardiotoxicity is not clarified. Based on electrocardiographic changes being characteristic of ischemia, influence on the cardiac vasculature leading to reduced myocardial blood perfusion is assumed to be a mechanism involved [7–12]. Experimental histological studies suggest that coronary arteries seem especially susceptible to 5-FU-induced endothelial injury leading to the disruption of the intima sheet, which may be a subsequent focus for platelet aggregation and fibrin formation [13–15].

The endothelium plays a central role in the regulation of the arterial vasodilation, the hemostasis and the selective vascular permeability, which is essential for proper vascular function [7, 16]. The endothelium regulates arterial

vasomotor tone by releasing the physiologic transmitter nitric oxide that induces relaxation of the surrounding smooth muscle [16]. Indeed, exposure of aorta to 5-FU in an experimental setting resulted in reversible vasoconstriction dependent on the endothelial dysfunction [17, 18]. Moreover, significant increases in proteinuria following 5-FU-based chemotherapy have been reported, suggesting that the endothelial dysfunction may have global extent [19–21].

Thromboembolic disease is a recognized complication of cancer and 5-FU therapy, which is related to the endothelial injury as well [22–25]. The plasma level of fibrin D-dimer, reflecting the activity of coagulation and fibrinolysis, has been correlated with the tumor stage and the prognosis in some malignancies, including colorectal cancer [24, 26–28]. In addition, the level of fibrin D-dimer has been significantly associated with the risk of deep vein thrombosis in such situations [25].

Likewise, the plasma level of vWf, which is synthesised and stored in endothelial cells, has been applied as a marker for endovascular injury by malignant disease and has been reported to correlate with tumor stage and prognosis of colorectal cancer [23, 29, 30]. The elevated plasma vWf, mediating the adherence and the aggregation of platelets to the subendothelium during primary hemostasis, may be a contributory factor to thrombosis in such situations [22–25].

Whether impaired vasoactivity or thromboembolic occlusion is the key mechanism involved in 5-FU cardiotoxicity in a clinical setting remains to be clarified. This study aimed to elucidate the influence of 5-FU-based therapy on the vascular endothelium and its prothrombotic risk and potential association with cardiotoxicity. In addition, the significance of clinical cardiovascular risk factors was evaluated for the prediction of the endothelial vulnerability to 5-FU-based chemotherapy.

The levels of plasma vWf, UACR, coagulation factor II + VII + X, and fibrin D-dimer were assessed before, during, and after adjuvant 5-FU and oxaliplatin chemotherapy in patients who had completely resected colorectal cancer [31].

Patients and methods

Patients and chemotherapy

Consecutive patients completely resected for colorectal cancer stages II-IV who received adjuvant FOLFOX-4 chemotherapy at Department of Oncology, Rigshospitalet, Copenhagen, were prospectively accrued into this study from August 2005 to September 2008. Among 161 patients screened, 106 patients remained in the study for evaluation, whereas another 55 patients either declined to participate or to receive chemotherapy, or were excluded because of disease recurrence during treatment and before final study evaluation could be performed. In these latter patients, there was no preponderance of cardiac morbidity. The FOLFOX-4 chemotherapy regimen consisted of oxaliplatin 85 mg/m^2 2-h infusion, folinic acid 400 mg/m^2 2-h infusion, and 5-FU 400 mg/m^2 bolus injection followed by 2,400 mg/m^2 flat continuous infusion for 46 h repeated every 2 weeks for 12 treatment courses. Patients were accrued after informed consent. This study was approved by the local Research Ethics Committee (KF 01-267812).

Medical history

An extensive medical history was obtained for all participants including previous hospital admission for heart failure, angina pectoris, myocardial infarction, cerebral transient ischemic attack, stroke, or leg claudicatio. Cardiotoxicity from 5-fluorouracil therapy was classified according to the Common Toxicity Criteria version 2.0 as grade 2 or 3 according to whether it occurred during workload or at rest, respectively.

Hypertension was assessed either by self-reported physician diagnosis and previous or current medication with antihypertensives or by systolic/diastolic blood pressures >140/90 mmHg at repeated measurements according to WHO guidelines [32].

Diabetes was assessed by either self-reported physician diagnosis, use of diabetes diet or any antidiabetic medication, or an incidental plasma glucose ≥11.1 mmol/l, or fraction of glycosylated hemoglobin HgbA1c >6.5%, which is the upper 95%CI corresponding to a mean blood glucose 7.0 mmol/l [33].

Hypercholesterolemia was defined either by the use of cholesterol-lowering drugs or by total cholesterol >6.5 mmol/l or LDL-cholesterol >4.0 mmol/l based on three analyses sampled 3 months apart from nonfasting patients [34]. Measurement of triglyceride lipids in fasting patients was not feasible.

Body mass index (BMI) was calculated from the weight in kilograms divided by the height in square meters and categorized according to the WHO classification scheme 20–24.9 kg/m^2 (normal), 25–29.9 (overweight), and ≥30 (obese) [35]. Smoking habits were assessed by self-reported previous or current consumption of cigarette pack-years and categorized as ever or never smoking.

Sampling procedures and analyses

Three serial assessments were made before chemotherapy (baseline), immediately after one of the courses 5–7, and at

follow-up at least 2 weeks after cessation of last chemotherapy course, including plasma levels of vWf, coagulation factor II + VII + X activity, fibrin D-dimer, and HDL- and LDL-cholesterol. Urine samples were taken on the same days for the assessment of albumin and creatinine concentrations.

The vWf antigen was assessed by ELISA (Dako, Glostrup, Denmark) using the ANTHOS reader (Biochrom Ltd., UK) with a measuring range of 0.12–3 kIU/l. The coefficient of variation (CV_{max}) was 10%. The reference interval according to the blood type was A, AB, and B: 0.58–1.69 kIU/l and type O: 0.42–1.30 kIU/l.

Proteinuria was assessed as the excreted urine albumin-to-creatinine ratio (UACR) using a single-spot urine sample. Urine albumin was analyzed by immunoturbidimetry using Modular Analytics-P (Roche Diagnostics, Mannheim, Germany) with a measuring range of 3–400 mg/l and a CV_{max} of 10%. Urine creatinine was analyzed using Modular Analytics-P with a measuring range 0.027–53 mmol/l and a CV_{max} of 5%. Microalbuminuria was defined as a UACR of 3.5–25 and 2.5–25 mg/mmol in male and female patients, respectively [36].

The coagulation factor II + VII + X activity was analyzed on an ACL TOP (Instrumentation Laboratories, Milan, Italy) with a measuring range of 0.05–1.5 U/l and a CV_{max} of 8%. The reference interval is >0.6 U/l.

The fibrin D-dimer plasma level was analyzed by an immunoturbidimetric assay using Modular P (Roche Diagnostics) with a measuring range of 0.2–21 mg/l and a CV_{max} of 7%. The reference interval is <0.5 mg/l.

The analyses were performed blinded regarding the clinical characteristics and the metabolic status of the patients at the time of examination, and all data and clinical information were integrated and described after data collection was completed.

Statistics

Ratios of clinical characteristics were compared using nonparametric tests. The distributions of UACR, Factor II + VII + X, and Fibrin D-dimer were compared using two-way analysis of variance (ANOVA) of repeated measures based on sampling times (baseline, chemotherapy, and follow-up) and groups (having cardiotoxicity or not). A significant test for the difference between repeated measures indicated a 5-FU treatment effect, whereas significant interaction between treatment and groups indicated different response to 5-FU treatment between groups. Because the measuring range of vWf was truncated at >3 kU/l, the repeated assessments were compared using nonparametric Friedmans analysis of variance. Using nonparametric statistics, the ratios of vWf values being outside the reference interval in patients without cardiac complaints were compared with those in patients having cardiotoxicity or cardiovascular disease. Values of $P < 0.05$ in two-sided tests were regarded significant. Statistics was performed with Statistica software (Statsoft Inc., Tulsa, OK, USA).

Results

Clinical characteristics and cardiovascular morbidity

Clinical characteristics, cardiovascular comorbidities, and risk factors are displayed in Table 1. There were no significant differences in the distributions of clinical characteristics between patients having symptoms of cardiotoxicity or not. The study cohort had a minor preponderance of women represented. The overall age median (range) was 64 (37–81) years. Most patients had stage III colon cancers.

Eight patients (8%) had a history of cardiac or peripheral atherosclerotic vascular disease. More patients (25%) previously had hypertension. Hypercholesterolemia was detected in 14 individuals (13%), whereas 17 patients (16%) used statins as cholesterol-lowering agents. Among 16 patients with diabetes mellitus, 8 patients (8%) were not treated for this diagnosis, while another 8 patients (8%) were treated by diet, peroral antidiabetics, or insulin. The distribution of BMI had an overall median (range) of 24.5 (16.5–41.9) kg/m^2. Current and previous smokers had been smoking at a median of (range) 40 (2–50) and 15 (0.5–50) pack-years, respectively. Overall, 83 (78%) patients had either a history of symptomatic cardiovascular disease or at least one of the risk factors hypercholesterolemia, hypertension, diabetes, obesity, or ever smoking.

Because of side effects early in the course of chemotherapy, blood sampling was obtained at 70 or 50% of planned 5-FU dose in 18 and 5 patients, respectively, while the remaining 83 patients were reevaluated after having received the full doses.

Cardiac influence from 5-fluorouracil chemotherapy

Nine (8.5%) patients developed symptoms of 5-FU-induced cardiotoxicity that occurred during work-load (CTC 2) in two and at rest (CTC 3) in seven patients, respectively. For six patients, episodes of angina lasted for 5–10 min, whereas three patients with symptoms at rest (CTC 3) had recurrent episodes for several hours with angina and projections to upper extremities associated with near fainting and dyspnoea. During these episodes, ECGs displayed significant ischemic changes in precordial leads. Nitroglycerin treatment immediately resolved the symptoms and normalized the ECGs. Except for episodes of angina, no significant ECG changes appeared during 5-FU treatment. None of the patients developed myocardial infarction according

Table 1 Clinical characteristics, cardiovascular disease, and risk factors in 106 completely resected colorectal cancer patients according to the clinical signs of 5-FU-induced cardiotoxicity during adjuvant chemotherapy

	Cardiotoxicity		*P*
	No	Yes	
	n = 97	*n* = 9	
	No. (%)	No. (%)	
Gender			
Female	53 (55)	6 (67)	0.6
Male	44 (45)	3 (33)	
Age			
<70 years	72 (74)	6 (67)	0.7
≥70 years	25 (26)	3 (33)	
Primary tumor			
Colonic	69 (71)	5 (56)	0.4
Rectal	28 (29)	4 (44)	
Stage			
II	21 (22)	1 (11)	0.3
III	58 (60)	5 (56)	
IV	18 (18)	3 (33)	
Cardiovascular disease	7 (7)	1 (11)	0.8
Hypercholesterolemia	26 (27)	5 (56)	0.2
Hypertension	24 (25)	2 (22)	0.9
Diabetes mellitus	16 (16)	0 (0)	0.4
Body mass index			
Normal	52 (54)	4 (45)	0.6
Overweight	30 (31)	3 (33)	
Obese	15 (15)	2 (22)	
Smoking			
Never	40 (41)	4 (45)	0.6
Previously	34 (35)	4 (45)	
Currently	23 (24)	1 (10)	
Renal clearance			
≤60 ml/min	14 (14)	0 (0)	0.5

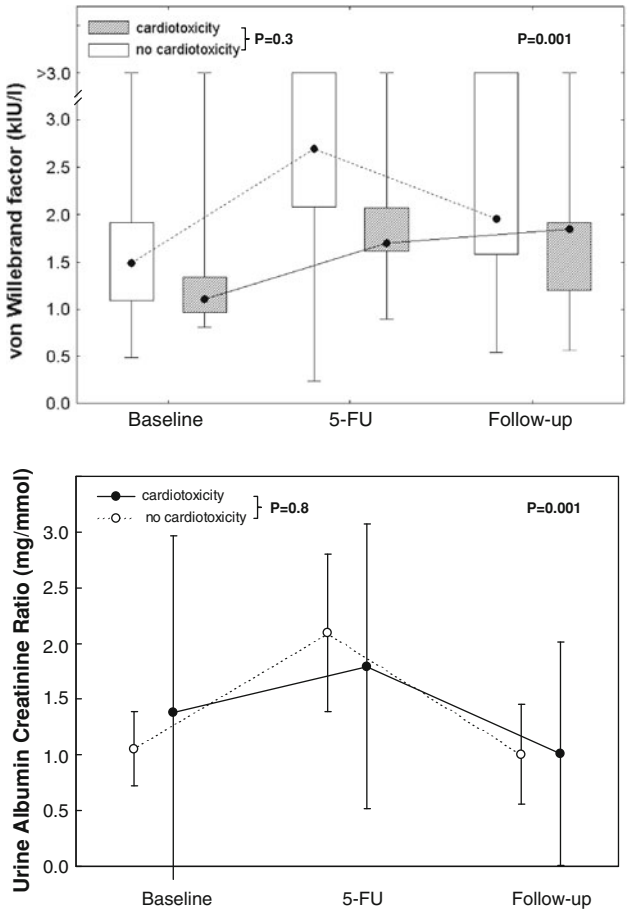

Fig. 1 5-FU-induced alteration of plasma von Willebrand factor antigen level (*upper*) in patients having cardiotoxicity or no such side effects. The median, the interquartile limits (*box*), and overall range (*whiskers*) are indicated. Alteration of urine albumin-to-creatinine ratio (*lower*) induced by chemotherapy in patients according to 5-FU cardiotoxicity. The means and 95% confidence intervals of the means (*whiskers*) are indicated. *P* values relate to the effect of 5-FU treatment between repeated measures and to difference in response between groups. In five out of nine patients having cardiotoxicity, reassessments of biomarkers were done during the subsequent course of chemotherapy at reduced 5-FU dosing

to the diagnostic cutoff concentrations of plasma CKMB enzyme or troponin T protein. At follow-up, probands of cardiotoxicity had no sequelae such as symptoms of cardiac insufficiency.

Reassessments of plasma and urine biomarkers were done following the full 5-FU dose or following a subsequent course at reduced 5-FU dose including antiangina treatment in 4 and 5 patients having cardiotoxicity, respectively.

The influence of chemotherapy on the endothelium and the coagulation

The influence of chemotherapy on the levels of plasma vWf and UACR is shown in Fig. 1. Plasma vWf significantly ($P = 0.001$) increased from median (range) 1.43 kU/l (0.48 to >3) at baseline to 2.64 kU/l (0.23 to >3) during 5-FU therapy and partially reverted to 1.93 kU/l (0.54 to >3) at follow-up. The vWf level was above the reference interval at baseline and during 5-FU therapy in 47 and 91 patients, respectively. The increase in plasma vWf induced by 5-FU did not significantly differ between patients having clinical cardiotoxicity or not ($P = 0.3$). Likewise, the 5-FU-induced increase in plasma vWf was not significantly different in patients having preexisting cardiovascular disease or its risk factors compared with those without ($P = 0.9$) cardiovascular disease.

The UACR significantly ($P = 0.001$) increased from 1.1 ± 0.2 mg/mmol (mean ± SE) at baseline to 2.1 ± 0.3 mg/mmol

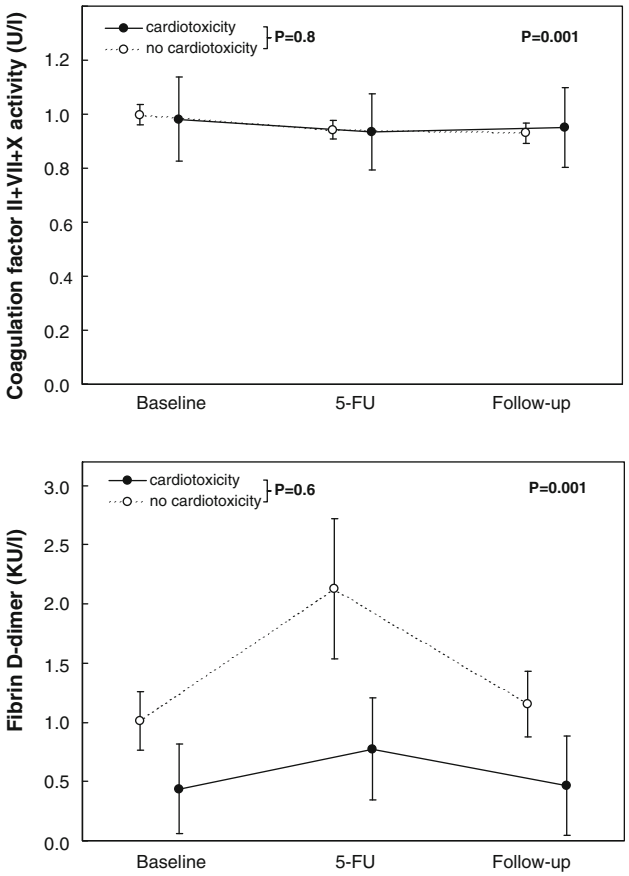

Fig. 2 Alterations of coagulation factor II + VII + X activity (*upper*) and level of fibrin D-dimer (*lower*) induced by 5-FU-based chemotherapy. Mean levels are indicated at *baseline*, during *5-FU* treatment, and at *follow-up*. *Whiskers* denote 95% CI of the means. *P* values relate to the effect of 5-FU treatment between repeated measures and to difference in response between groups

during 5-FU therapy and reverted to 1.0 ± 0.2 at follow-up. Microalbuminuria at baseline and during 5-FU therapy occurred in 10 and 27 patients, respectively. This alteration of UACR induced by 5-FU did not significantly differ between patients having clinical cardiotoxicity or not ($P = 0.8$).

The influence of chemotherapy on the coagulation factor II + VII + X activity and level of fibrin D-dimer is shown in Fig. 2. The coagulation factor II + VII + X activity significantly ($P = 0.001$) decreased progressively from 1.00 ± 0.02 U/l (mean ± SE) at baseline to 0.94 ± 0.02 U/l during 5-FU therapy and 0.93 ± 0.02 U/l at follow-up, respectively. Plasma level of fibrin D-dimer significantly ($P = 0.001$) increased from 1.1 ± 0.2 kU/l (mean ± SE) at baseline to 2.1 ± 0.3 kU/l during 5-FU therapy and reverted to 1.1 ± 0.1 kU/l at follow-up. The alterations in the coagulation activity ($P = 0.8$) and the fibrin D-dimer ($P = 0.6$) induced by 5-FU did not significantly differ between patients having clinical cardiotoxicity or not.

Eight patients had radiographically or ultrasonographically verified pulmonary or extremity deep vein thromboses during chemotherapy associated with a fibrin D-dimer plasma level of 3.6 ± 0.9 kU/l (mean ± SE). None of these patients experienced clinical cardiotoxicity.

Discussion

The present study demonstrated the increases in plasma vWf and in proteinuria following 5-FU-based chemotherapy in a clinical setting, which indicated reversible global endothelial injury from such treatment. These findings are in agreement with previous experimental histological studies showing that 5-FU induces endothelial injury with disruption of the inner vascular lining and patchy exposure of the underlying matrix [13, 14, 18].

The ensuing endothelial dysfunction caused by the exposure to FU chemotherapy may reversibly impair the vasodilatory response of the arteries [17]. The endothelium plays a central role in the regulation of arterial vasomotor tone by releasing the physiologic transmitter nitric oxide that induces relaxation of the surrounding smooth muscle, thus leading to vasodilation [16]. Administration of nitroglycerine, which is converted into nitric oxide by alcohol dehydrogenase, immediately resolves the angina symptoms during the episodes of 5-FU carditoxicity, demonstrating that impaired vasodilation is concurrent to the pathogenesis [7, 17].

On the other hand, the endothelial dysfunction alone may not fully explain for this adverse reaction by 5-FU treatment [16]. Hence, antineoplastic agents such as anthracyclines cause sustained damage to the endovascular sheet with impaired endothelial-dependent vasodilatory response of arteries though without leading to similar angina symptoms being characteristic of 5-FU-induced cardiotoxicity [16]. Moreover, endothelial damage with increasing levels of vWf and UACR following chemotherapy was not confined solely to patients having symptoms of cardiotoxicity, which suggests that 5-FU may also directly interfere with the metabolism of the myocardium [1, 11, 31, 37].

Thromboembolic disorder is a recognized complication of cancer and chemotherapy that may be ascribed to endothelial dysfunction as well [19, 21, 24, 25, 38]. Venous thromboembolic events have previously been reported in colorectal cancer patients receiving chemotherapy having an overall cumulated incidence of 11%, corresponding to a rate up to seven times higher compared with the general population [39, 40]. In keeping with this report, recent experimental and clinical studies indicated that a procoagulant state associated with increased plasma fibrin D-dimer is common in colorectal cancer patients [24–26].

The molecular mechanisms by which certain anticancer agents trigger a procoagulant state are poorly understood [25]. Exposure of vascular endothelial cells to cytotoxic drugs has been demonstrated to decrease the endothelium-based protein C receptor, which is essential for the efficient conversion of the zymogen to the activated protein C [41]. The lower plasma level of the anticoagulant protein C that appears following 5-FU therapy may provide a possible explanation for a mechanism that may contribute to the thrombogenic effect seen in cancer patients undergoing chemotherapy [10]. The significance of the rising plasma level of vWf, being a receptor for thrombocyte aggregation, for the risk of thrombosis remains to be clarified [23, 29, 30].

Cancer disease is reported to be an independent risk factor for outpatient-acquired deep vein thrombosis [40]. Tumor cell-related factors leading to a vulnerable endothelium may account for the fourfold increased risk of venous or pulmonary thromboembolism that was found among cancer patients not receiving chemotherapy [40]. Such factors present in the circulation having an injurious effect on the endothelium are hypothesized to include factor X-activating cysteine protease [42] and mucinous glycoproteins [43]. Also tissue factor-bearing microparticles derived from disintegrating vascular cells in the tumors may activate the coagulation [22, 44]. Accordingly, a number of patients in the present study had baseline plasma levels of coagulation and fibrinolysis markers indicating a procoagulant state ahead of chemotherapy [24, 26]. In a previous study, the preoperative levels of fibrin degradation products were significantly associated with the risk of encountering venous thromboembolism up to 1 year following resection of colorectal cancer [39].

The elevated plasma level of vWf that appear following recent complete resection of colorectal cancer may reflect angiogenesis and wound healing [23, 29]. Increasing levels of vWf and D-dimer also may reveal ongoing angiogenesis and vascular remodeling sustaining tumor growth and dissemination of metastases. Indeed, the levels of vWf [23, 29, 30] and fibrin D-dimer [26–28, 45, 46] have been directly correlated with the advanced tumor stage and the poor prognosis in patients with completely resected and metastatic colorectal carcinoma [24, 29, 39].

Thromboembolism may not be a mechanism involved in 5-FU-induced cardiotoxicity. Episodes of cardiotoxicity are usually transient and reversible without angiographic or electrocardiographic indications of sustained arterial occlusion [1]. However, the increases in endothelial and coagulation biomarkers following chemotherapy should be interpreted with the reservation that they cannot discern between venous and arterial thrombosis. In addition, the results should be evaluated considering that some patients with previous symptoms of cardiotoxicity were assessed during a subsequent course at reduced dosing of 5-FU.

Risk factors for the development of 5-FU-associated cardiotoxicity remain unclarified. Cardiovascular disease is assumed to be a predisposing factor in terms of greater incidence and severity of cardiac side effects from 5-FU for more reasons [1, 31]. Endothelial dysfunction with impaired vasodilation has been implicated as an early characteristic by cardiovascular disease even without clinically evident symptoms [47]. In addition, severe atherosclerosis may restrict the capacity of the myocardial perfusion [47]. While in the present study, there was no evidence that atherosclerosis may imply greater vulnerability of the endothelium to 5-FU treatment, such conclusion is made with the reservation that the degree of atherosclerosis is indirectly estimated from the cardiovascular history.

The findings of this study have inherent limitations. Because 5-FU is administered in combination with oxaliplatin to benefit from the synergistic anticancer effect, the influence on the endothelium and the prothrombotic activity of individual drugs cannot be assessed. Platinum compounds have been previously associated with a procoagulant activity [48].

In conclusion, cancer-derived factors of 5-FU-based chemotherapy in a clinical setting induce global reversible endothelial injury. The ensuing endothelial dysfunction with impaired vasoactivity may be a concurrent cause of development of 5-FU cardiotoxicity. However, direct assessment of the myocardial blood perfusion under these circumstances is required to clarify this question.

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