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ORIGINAL ARTICLE

5-fluorouracil cardiotoxicity is a rare, dose and schedule-dependent adverse event: a prospective study

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Summary

Purpose: *Cardiotoxicity associated with 5-fluorouracil (5FU) administration is infrequently reported in the literature, albeit case reports of acute coronary syndromes have been published. In the present study, patients undergoing 5FU chemotherapy were tested for the development of cardiac-related symptoms during its administration.*

Patients and methods: *Five hundred twenty-two patients entered the study. Those experiencing any cardiac-related symptoms during 5FU infusion were subjected to electrocardiogram (ECG) and serum cardiac enzymes determination. If cardiotoxicity was confirmed, 5FU infusion was interrupted, sublingual nitrates administered and cardiac monitoring initiated, while patients with >2-fold enzyme elevation were admitted into a coronary care unit for at least 72 hours. Cases with acute myocardial infarction had to discontinue 5FU treatment.*

Results: *Overall 20 (3.8%) patients developed symptoms and/or ECG abnormalities due to 5FU. Patients with continuous 5FU infusion had a trend for higher incidence of cardiotoxicity (13/205, 6.3%) than the remaining (7/317, 2.2%; p=0.067). More specifically, increased toxicity was encountered in patients with continuous 24 h 5FU+ leucovorin (LV) infusion for 5 days compared to patients with the same schedule without LV (p <0.027) and patients with short 5FU+LV administration as well (p=0.024). Seven out of the 20 patients suffered acute myocardial infarction, 6 developed only ischemia, while ECG findings consistent with coronary vasospasm were detected in 4 patients and conduction disturbances in 3 patients (one subsequently died).*

Conclusion: *The present study indicates a toxic effect of 5FU on myocardium, which is largely schedule-dependent. High level of alert is required when using this drug, while its toxic effect on the coronary endothelium and myocardium merits further investigation.*

Key words: cancer, cardiotoxicity, chemotherapy, 5-fluorouracil, toxicity

Introduction

Cardiotoxicity has been reported in patients undergoing chemotherapy, particularly with anthracycline antibiotics such as daunomycin and doxorubicin [1,2].

5FU-associated cardiotoxicity is not frequently appreciated. Only case reports of angina pectoris or even myocardial infarction related to 5FU administration exist in the literature [3-7]. Angina has been noticed both on initial as well as on subsequent courses of 5FU and it is occasionally delayed (3-18 h after the 5FU injection). It may occur even in patients without pre-existing heart disease. Cardiotoxicity has been also recorded when 5FU was used in multi-agent chemotherapy regimens [8].

A syndrome comprising chest pain, elevation of serum cardiac enzymes, ECG changes consistent with myocardial ischemia, and normal coronary angiogram may occasionally be seen in temporal association with 5FU administration [9]. Vasospasm may represent its

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possible pathogenetic mechanism, attributed either to the parent drug or to its catabolites (fluoro-beta-alanine and fluoro-acetate). Concentration-dependent vasoconstriction occurs *in vitro* when isolated vascular smooth muscle rings are exposed to 5FU, an effect reversible by nitrates [10].

In order to assess 5FU-induced cardiotoxicity, we evaluated patients presenting with cardiovascular-related clinical symptoms during drug infusion, both electrocardiographically and by serum cardiac enzyme analyses.

Patients and methods

Patients

Between 1985 and 2004, 522 out of 604 consecutive cancer patients treated with 5FU - based chemotherapy entered the study (Table1).

Inclusion criteria

Eligibility criteria included: 5FU-based chemotherapy, absence of other cardiotoxic medications, normal clinical cardiologic examination and pretreatment ECG, and a negative medical history of coronary artery disease, other symptomatic or unstable cardiac diseases, severe uncontrolled arterial hypertension, diabetes mellitus, or peripheral vascular disease. Patients were not allowed to receive medication other than chemotherapy.

Study design

Pretreatment evaluation consisted of physical examination, pulse rate/blood pressure baseline determination and laboratory investigations including complete blood cell count, a 16-function biochemical analysis, a 12-lead ECG and a chest x-ray. Patients were allowed to enter the study only if their baseline ECG and cardiologic examination were within normal limits.

Every patient experiencing cardiac-related symptoms during 5FU administration, such as tachycardia, retrosternal chest pain, diaphoresis, shortness of breath, dizziness, precardial palpitations and malaise, was subjected to ECG and measurement of the serum cardiac enzymes (AST, ALT, LDH, CPK and CPK-MB).

Management of patients with 5FU cardiotoxicity

In patients presenting signs of cardiotoxicity or ECG ischemic changes due to 5FU, the following measures were instituted:

1. Drug infusion was interrupted
2. Sublingual nitrates were administered
3. Cardiac monitoring was initiated
4. Patients with >2-fold enzyme elevation (suggestive of myocardial injury) were additionally monitored in an intensive coronary care unit for a minimum of 72 h.

Continuation of therapy with 5FU after recovery of cardiotoxicity

Patients who experienced 5FU-induced cardiotoxicity other than infarction were treated with a 3-day course of transdermal nitrates in the subsequent 5FU infusions (24 h prior, during, and post 5FU). Patients were under continuous 24 h ECG monitoring on the days of 5FU infusion. In cases with acute myocardial infarction, further 5FU treatment was abandoned.

Table 1. Patient groups according to 5FU-based chemotherapy

Primary cancer site	*Regimen*	*Schedule*	*Patients, n*	*Non eligible patients, n*	*Eligible patients, n*	*No. of patients with ECG changes (%)*
Head & Neck	CDDP + 5FU[1]	5-day CI	167	26	141	5 (3.5)
Colorectal	MMC + LV + 5FU[2]	5-day CI	30	6	24	3 (12.5)
Colorectal	LV + 5FU[3]	5-day SI	148	9	139	3 (2.1)
Colorectal	LV + 5FU[4]	weekly SI	212	34	178	4 (2.2)
Colorectal	LV + 5FU[5]	5-day CI	19	3	16	2 (12.5)
Colorectal	MMC + 5FU[6]	5-day CI	28	4	24	3 (12.5)
Total			604	82	522	20 (3.8)

CI: continuous infusion, SI: short (<3 h) infusion
[1]Cisplatin 100 mg/m^2/day, day 1; 5FU 1000 mg/m^2/day, CI days 2 - 6. [2]Mitomycin C (MMC) 10 mg/m^2/day, day 1; LV 500 mg/m^2/day, CI days 1-5; 5FU 1.000 mg/m^2/day, CI days 1-5. [3]LV 200 mg/m^2/day (i.v. bolus) days 1-5, followed by 5FU 700 mg/m^2 (3 h i.v. infusion) days 1-5. [4]LV 200 mg/m^2 (i.v. bolus), followed by 5FU 700 mg/m^2 (2 h i.v. infusion) every week. [5]5FU 1.200 mg/m^2/day (24 h CI) days 1-5; LV 200 mg/m^2/day, CI days 1-5. [6]Mitomycin (MMC) 10 mg/m^2/day, day 1; 5FU 1000 mg/m^2/day, CI days 1-5

ECG evaluation

ECGs were examined by 4 experienced cardiologists, both separately and in cooperation, to secure the final diagnosis.

Statistics

The x^2 test (with Yates correction) was applied for comparison of 5FU-related cardiotoxicity between groups of patients with different 5FU schedules (continuous i.v. infusion *versus* bolus × 5 days *versus* bolus weekly).

Results

Out of 604 patients receiving 5FU-based chemotherapy and no other cardiotoxic agent, 82 did not met the eligibility criteria (Table1).

Of the remaining 522 patients who entered the study, 20 (3.8%) developed symptoms and/or ECG abnormalities consistent with cardiotoxicity. These patients had a free medical history of any cardiac disease according to the entry criteria.

The median age was 62 years (range 56-70). No significant difference existed between males and females in terms of cardiac toxicity.

There was a significant difference in cardiotoxicity between weekly 5FU plus LV combined with mitomycin C (MMC) and 5-day continuous infusion of 5FU plus LV ($p < 0.030$). Significant difference also existed between weekly 5FU plus LV/MMC and continuous 5–day single 5FU infusion ($p < 0.033$). No statistically significant differences were noticed between 5-day continuous infusion of 5FU combined with cisplatin (CDPP) and 5FU plus LV/MMC ($p < 0.095$), or 5-day 5FU plus LV schedule ($p < 0.098$) (Figure 1).

Overall, patients under continuous 5FU infusion showed a trend for cardiotoxicity more frequently (13/205, 6.3%) than the others (7/317, 2.2%; p=0.067). More specifically, cardiotoxicity was higher in patients with continuous 5-day 5FU plus LV infusion in comparison to patients with similar delivery of 5FU without LV ($p < 0.027$) as well as to patients with short-term 5FU plus LV administration (p=0.024).

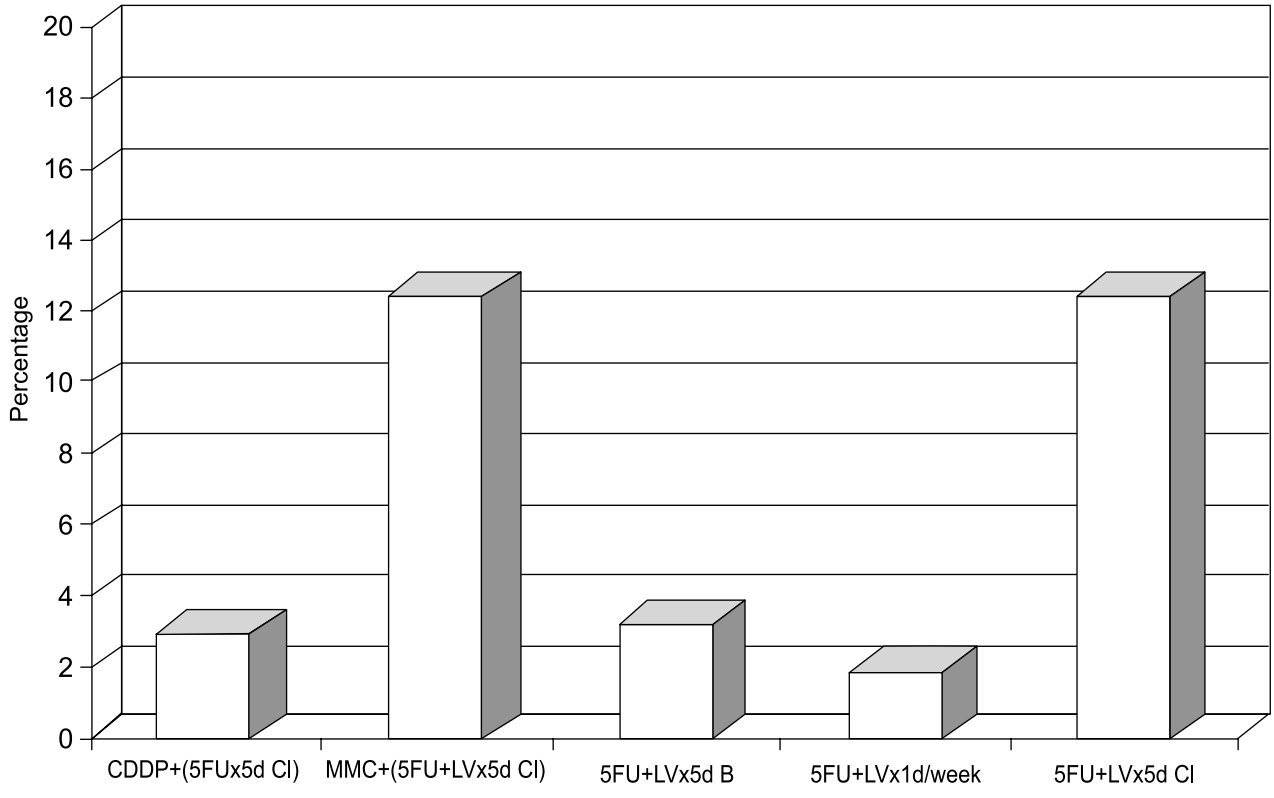

Figure 1. Percentage of patients with ECG abnormalities according to different 5FU schedules. There is a difference between weekly 5FU + LV and 5FU + LV + MMC ($p < 0.030$) or 5FU + MMC 5-day CI ($p < 0.033$). No statistically significant differences were noticed between CDDP+5FU 5-day CI and MMC+LV+5FU 5-day CI ($p < 0.095$), and LV+5FU for 5 days ($p < 0.098$).

MMC: Mitomycin C, LV: Leucovorin, CDDP: Cisplatin, CI: continuous infusion B: bolus or short infusion, d: days

Table 2. Distribution of patients with and without ECG changes during 5FU administration according to their risk factors

Risk factors	*Subgroups*	*No. of patients without ECG changes*	*No. of patients with ECG changes*	*p-value*
Hyperlipidemia (normal range,	Normal	257	13	0.18
cholesterol 120-200 mg/dl	Increase <15%	167	4	0.19
triglycerides <150 mg/dl)	Increase >15%	98	3	0.88
Obesity	Normal <25	319	15	0.22
(Body Mass Index)	Increased weight, obesity (25-40)	179	4	0.25
	Severe obesity (>40)	24	1	0.64
Family history of cardiac disease	Yes	177	6	0.89
	No	345	14	0.89
Family history of stroke	Yes	197	5	0.33
	No	325	15	0.33
Alcohol intake	Regular	334	14	0.73
	Mild	146	5	0.96
	Abuse	42	1	0.85
Chronic obstructive pulmonary disease	Normal	483	17	0.38
	Mild	39	3	0.38
	Severe (oxygen use)	0	0	
Hb (g/dl)	>11.5	276	14	0.18
	10 – 11.5	148	5	0.93
	<10	98	1	0.18
Smoking (cigarettes/day)	Non smokers	181	6	0.83
	Ex-smokers	99	3	0.86
	Opportunistic	25	1	0.62
	<10	34	0	0.45
	>10	183	10	0.23

With regard to coronary disease risk factors, no difference was noticed between patients developing cardiotoxicity and the general study population (Table 2). Moreover, there was no noticeable difference when patients with or without ECG abnormalities were examined in relation to the number of coronary risk factors (Table 3). Table 4 presents the characteristics and cardiac symptoms of patients with clinical or ECG cardiotoxicity due to 5FU. The symptoms most frequently reported were chest pain (9 patients),

Table 3. Distribution of patients with or without ECG changes according to the number of risk factors

No. of risk factors	*Patients without ECG changes*	*Patients with ECG changes*	*p-value*
0	48	3	0.41
1	54	2	0.81
2	162	6	0.94
3	207	7	0.53
>3	51	2	0.93

Table 4. Patient characteristics and cardiac symptoms

No. of patients	*Sex*	*Age*	*Tumor*	*No. of risk factors*	*Symptoms*
1.	M	56	H&N	2	Chest pain
2	M	70	CC	0	Chest pain
3.	M	66	CC	3	Numbness in left arm
4.	M	59	CC	2	Chest discomfort
5.	F	67	CC	1	Chest weight
6.	M	67	CC	0	Malaise, palpitation
7.	F	60	H&N	2	Palpitation
8.	F	56	CC	3	Malaise, diaphoresis
9.	M	59	H&N	0	Palpitation
10.	M	62	CC	>3	Chest pain
11.	F	60	CC	2	Pain in the neck
12.	F	58	CC	3	Palpitation
13.	M	64	H&N	2	Chest squeezing sensation
14.	M	62	CC	1	Palpitation, chest discomfort
15.	M	67	CC	2	Palpitation
16.	M	69	H&N	3	Syncope
17.	M	62	H&N	>3	Collapsus
18.	M	67	CC	0	Chest pain
19.	M	56	CC	2	Chest discomfort
20.	F	64	H&N	2	Palpitation

M: male, F: Female, H&N: Head and neck cancer, CC: colorectal cancer

Table 5. ECG findings in the examined patients

No.	*Pulse rate per min*	*Heart position (orientation)*	*ECG findings*	*CPK-MB elevation*	*Diagnosis*
1	75	SH	Slight QT prolongation, inverted T waves and ST depression in leads I, II, III, aVL, V3-V6	–	Ischemia
2	60	H	Slight QT prolongation, inverted T waves in leads aVL, V1 – V6	2-fold	Acute subendocardial infarction
3	50	H	Inverted T waves and ST depression in leads I, aVL, V1-V6, isolated atrial extrasystoles	–	Ischemia
4	AF 130	IN	QS in V1, V2, inverted T waves in leads II, III, aVF, ST depression in V4-V6	–	Ischemia, possible old septal myocardial infarction
5	AF 160	SH	ST depression in leads I, II, III, aVL, V2-V6	2-fold	Acute subendocardial infarction
6	ST 120	H	ST elevation in leads V1-V6	–	Coronary vasospasm
7	PST 200		Repolarization disturbances	–	Ischemia
8	ST 110		Ventricular extrasystoles, bouts of ventricular, tachycardia (300/min, duration 15 sec)	–	Ventricular extrasystoles, tachycardia
9	ST 94	H	ST elevation in leads I, aVL, V1-V6	–	Coronary vasospasm
10	a. ST 120	IN	ST depression in leads II, aVL, aVF, V4-V6, QS in V1-V3, ventricular extra-systolic arrhythmia	–	Ischemia
	b. ST 120	IN	QS in leads III, aVF, V1-V3, inverted T waves in I, aVL, V1-V6, ST elevation in V1-V3		Myocardial infarction
11	a. ST 96	UN	QS in leads V1-V6, ST elevation in leads I, aVL, V2-V6	3-fold	Acute myocardial infarction
	b. 60	V	Inverted T waves in leads I, II, aVL, V2-V6, non-specific intraventricular conduction disturbances		
	c. VT 240	V	Ventricular tachycardia		
12	60	SH	ST elevation in leads II, III, aVF, ST depression in I, aVL, V1-V4, LBBB, AVB Mobitz II, bout of ventricular tachycardia	–	Ischemia, coronary vasospasm
13	a. 75	H	ST elevation in leads II III, aVF, ST depression in I, aVL, V1-V6	3-fold	Acute myocardial infarction
	b. ST 100	H	ST elevation in leads I, aVL, V1-V6		
14	a. AF 156	IN	ST depression in leads I,II,III,aVF,V3-V6		Ischemia, coronary vasospasm
	b. AF 120	SH	ST depression in leads I, II, III, aVF, V1-V6, rare ventricular extrasystoles		
15	a. AF 156	H	QS in II, III, aVF, V1- V5, ST elevation in V1-V3, ST depression in I, aVL, V6	2-fold	Acute myocardial infarction
	b. ST 120	H	QS in V1-V5, ST elevation in V1- V6, flattened T waves in aVL, 1st degree AVB, frequent atrial extrasystoles		
	c. 72	V	ST elevation in II, III, aVF, inclination of ST elevation = 1mm in leads V5-V6, ST depression in I, aVL, V2-V3		
16	a. AVB 55		Complete AVB	–	Conduction disturbances
	b. AVB 21		AVB Mobitz II (3:1), isoelectric line		Death
17	AVB 45		Complete AVB	–	Conduction disturbances
18	74	H	Slight QT prolongation, inverted T waves in leads aVL, V1 – V6	2-fold	Acute subendocardial infarction
19	ST 140	H	ST elevation in leads I, V1-V6	–	Coronary vasospasm
20	ST 100	H	ST elevation in leads I, aVL, V1-V6	–	Coronary vasospasm

Heart position (orientation): semi-horizontal (SH), horizontal (H), intermediate (IN), undetermined (UN), vertical (V), sinus tachycardia (ST), atrial fibrillation (AF), right (or left) bundle branch block (R [L] BBB), paroxysmal supraventricular tachycardia (PST), atrioventricular block (AVB)

palpitation (7), malaise (2), numbness of arm or neck (2), and loss of consciousness (2).

The ECG findings are described in Table 5: 7 out of 20 patients with 5FU cardiotoxicity had an acute myocardial infarction, 6 presented ischemic changes, while 4 more patients developed ECG abnormalities consistent with coronary vasospasm. Three patients presented conduction abnormalities (LBBB, 1st degree atrioventricular block, Mobitz II or complete atrioventricular block) and one of them subsequently died. Overall, 11 patients developed arrhythmias, namely sinus tachycardia, paroxysmal supraventricular tachycardia, atrial fibrillation, ventricular extrasystoles, and bouts of ventricular tachycardia or sustained ventricular tachycardia (Table 5).

Among 13 patients who didn't developed myocardial infarction, none experienced any cardiac-related symptoms during subsequent 5FU infusions. Nevertheless, ECG recordings revealed subclinical ischemic abnormalities in 2 patients, conduction disturbances in 4 and arrhythmia in 2.

Discussion

Cardiotoxicity is a rare adverse event of 5FU therapy. In our study, almost 4% of the patients developed symptoms attributed to 5FU cardiotoxicity. Large prospective studies have demonstrated an incidence ranging from 1.6 to 8% [11-14]. However, the actual incidence might probably be higher if asymptomatic patients who develop ECG or echocardiographic findings consistent with impaired left ventricular function were taken into account [15]. It has been shown that patients with a history of cardiac disease, particularly coronary artery disease, are significantly more susceptible to 5FU cardiotoxicity compared to patients without a history of cardiac disease [16]. In our study such patients were excluded.

According to our analysis, continuous infusion of 5FU proved much more cardiotoxic than bolus administration ($p < 0.033$). Such a finding is suggested but not clearly depicted in the literature. The addition of LV to the continuous infusion of 5FU resulted in further increment of cardiotoxicity ($p < 0.024$). Concomitant use of other non-cardiotoxic chemotherapeutic drugs did not seem to enhance cardiotoxicity.

Cardiotoxicity usually manifests as angina with ST segment depression, but myocardial infarction, arrhythmias, conduction disturbances, hypotension or hypertension, cardiomyopathy with left ventricle dysfunction, congestive heart failure, and sudden death have also been reported.

The pathophysiology of 5FU-induced cardiac toxicity is not yet elucidated. Coronary artery thrombosis, arteriitis or vasospasm have been proposed as the most likely underlying mechanisms. However, in some patients with normal thallium scanning or coronary angiography [17], vasospasm failed to be elicited after ergonovine challenge followed by 5FU infusion. Moreover, vasodilator drugs given prior to a second 5FU infusion failed to prevent angina. Increased endothelin-1 (ET-1) levels were found in some patients, supporting the theory of coronary vasospasm, but the question whether the increased release of ET-1 from coronary endothelial cells is a primary or a secondary phenomenon remains unanswered [18].

Other mechanisms have been proposed, including direct toxicity on the myocardium [19,20], activation of autoimmune responses [21] or the production of fluoroacetaldehyde, generated in the alkaline solution of 5FU vials during storage, which is converted *in vivo* to the cardiotoxic fluoroacetate [22]. Recent experimental evidence supports a direct toxic effect of 5FU on the coronary endothelial intima [23-25]. Toxicity was more pronounced about 3 days after treatment onset, a finding consistent with the delayed 5FU cardiotoxicity that is often noticed in clinical practice. Increased release of prostacyclin has also been reported 48 h after incubation of endothelial cells with 5FU. A cascade might commence with the endothelial injury, resulting in an increased release of vasodilatory anticoagulant substances which, when exhausted, lead to predominance of procoagulant effectors and thrombus formation.

Interestingly, new data based on pathological findings have suggested toxic myocarditis as the pathogenetic mechanism of 5FU cardiotoxicity [26]. Therefore, the clinical syndrome of chest pain or discomfort, arrhythmias, reversible ST segment depression, left ventricular dysfunction, and cardiac enzymes elevation could alternatively be attributed to myocarditis rather than to coronary artery disease. The fact that some of the patients in our study diagnosed as having 5FU-related acute myocardial infarction subsequently presented normal ECGs could be explained in the context of an episode of myocarditis simulating acute coronary insufficiency.

As far as the feasibility of re-challenging with 5FU patients with evidence of cardiotoxicity is concerned (excluding those with myocardial infarction or severe unstable angina), it can be stated that intensive cardiologic monitoring and prophylactic nitrate administration may result in fairly good subsequent 5FU tolerance. However, given the small number of patients tested in the present study, one should be

cautious in re-challenging these patients with 5FU, taking into consideration the risk-benefit assessment. Certainly, this topic should be addressed in future prospective studies with larger number of patients. It also remains unclear whether nitrates, used prophylactically in the present study, did play any role in preventing or reversing 5FU-induced cardiotoxic sequelae during subsequent 5FU re-challenge.

In conclusion, our study supports the fact that 5FU has a schedule-associated toxic effect on myocardium, which might sometimes prove lethal, even in patients without previous history of cardiac disease. Thus, a high degree of alert is required when using this drug, in order to prevent or avoid possible heart damage. The underlying mechanisms by which 5FU exerts its cardiotoxicity might be multivariate. Nevertheless, further investigations of its toxic effect on the coronary endothelium and myocardium are mandatory.

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