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ORIGINAL ARTICLE

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Risk factors and prevention of cardiotoxicity induced by 5-fluorouracil or capecitabine

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Abstract *Aim:* 5-Fluorouracil (5-FU) and its prodrug capecitabine are cardiotoxic. This retrospective study aimed to identify risk factors and to give practical measures to make such chemotherapy feasible if cardiotoxicity occur. *Method:* Review of cardiotoxicity among 668 patients treated with 5-FU or capecitabine for gastrointestinal cancers. *Results:* Cardiotoxicity occurred in 29 cases (4.3%). The number of cases according to cardiotoxicity CTC grades 2–4 for patients with and without pre-existing cardiovascular disease were none, 10, and 2 cases, and 3, 14, and no cases, respectively ($P=0.16$). In three patients intercurrent decrease of renal clearances to <30, 48 and 71 ml min^{-1} led to markedly increased cardiotoxicity. Chemotherapy dose reduction to 70 or 50%, either alone or in addition to antiangina medication prevented cardiotoxicity during subsequent chemotherapy in nine (60%) and three (20%) cases out of 15 assessable patients ($P=0.001$), respectively. To abolish symptoms of cardiotoxicity, sublingual nitroglycerine was efficient for 15 patients and inefficient for two ($P=0.001$). *Conclusion:* Cardiac and renal co-morbidity are risk factors for 5-FU induced cardiotoxicity. In this situation, rechallenge with modified 5-FU-based chemotherapy regimen supported by symptomatic medical treatment is feasible.

Keywords Beta-blockers · Calcium channels blockers · Capecitabine · Cardiotoxicity · 5-Fluorouracil · Nitrates

Introduction

The pyrimidine antimetabolites 5-fluorouracil (5-FU) and its prodrug capecitabine are widely used in the palliative and adjuvant treatment of various solid tumours. Both drugs are cardiotoxic [1–8].

The most frequent symptom of 5-FU associated cardiotoxicity is chest pain with projection to the left arm or neck. Other clinical presentations include arrhythmias, heart failure, myocardial infarction or cardiogenic shock, leading to hypotension, diaphoresis, dyspnoea, confusion or sudden death [1–8]. An overall incidence of 1.2–18% for 5-FU associated cardiotoxicity has been reported previously [1–8]. Prospectively performed ECG monitoring in patients undergoing 5-FU chemotherapy have revealed symptomatically silent reversible ST segment depression, showing these figures may be underestimated [1, 9]. Incidents with fatal course have been reported with overall mortality rates of 2.2–13.3% [1–8].

The pathogenesis of 5-FU induced cardiotoxicity is unknown. The proposed mechanisms of action class with impact on cardiac vasculature, interference with the metabolism of myocytes or destruction of these [10–15]. Coronary vasospasms have been suggested to be involved in the pathophysiology of this syndrome [16] based on the characteristic electrocardiographic and clinical similarities to reversible ischaemic heart disease [1, 7, 9]. However, several characteristics of the syndrome are inconsistent with ischaemic heart disease. Thus, no vasospasms were demonstrated by coronary angiography during symptomatic attacks of cardiotoxicity [17], nor was any significant atherosclerosis of the coronary arteries detected in affected patients [1]. In addition, echocardiography has demonstrated reduced ejection fraction and significant akinesia of the left myocardium during attacks. This global akinesia did not correspond to the segmental distribution of the major coronary arteries, suggesting a direct drug or drug-metabolite mediated toxic action on the myocytes [7].

Pre-disposing factors for development of 5-FU associated cardiotoxicity is not well described. Increased risk of 5-FU associated cardiotoxicity for patients with previous symptoms of coronary artery disease has been reported in some studies [4, 5], whereas a meta-analysis

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found the prevalence of cardiac disease in patients with 5-FU associated cardiotoxicity not to differ significantly from that of age and gender matched patients [6]. Also, the prognostic value of pre-existing heart disease for severity of cardiotoxicity is unclear.

Individual susceptibility to cardiotoxicity may result from genetic pre-disposition. Besides, cardiotoxicity may occur late in the course of chemotherapy, suggestive of variable clinical parameters may have unrecognized prognostic significance.

As 5-FU and capecitabine are widely used in cancer therapy and have few alternatives, practical measures for the safe application of these drugs would be of paramount importance. No widely accepted recommendations for rechallenge with 5-FU by this specific toxicity have been described. Currently, the therapeutic options are adjustment of the chemotherapy regimens in association with antiangina therapy, though the evidence of efficacy is ambiguous [6, 18].

The aim of this report is to review retrospectively the incidence, severity, and risk factors of 5-FU or capecitabine induced cardiotoxicity among a cohort of 668 patients consecutively treated for various gastrointestinal cancers. Also measures for therapeutic prevention and intervention of cardiotoxicity during subsequent chemotherapy are evaluated.

Patients and methods

Patients

The patients included were consecutively treated for colorectal or gastric cancers from February 1996 to February 2005. Data on patients, disease status and chemotherapy were obtained from surgical, pathological and oncological records. The local research ethics committee approved this study.

Cardiotoxicity

Cardiotoxicity is ranked in common toxicity criteria grades 2–4 corresponding to symptoms at work-load, at rest or being a myocardial infarction with cardiac enzyme elevation.

Chemotherapy regimens

Chemotherapy regimens were capecitabine 1,250mg m^{-2} d^{-1} bid for 2 weeks for palliative treatment of colorectal cancer; capecitabine 1,250 mg m^{-2} d^{-1} bid with oxaliplatin 130 mg m^{-2} day^{-1} i.v. each 3 weeks (XELOX) for palliative treatment of colorectal cancer; capecitabine (1,000 mg m^{-2} bid for 2 weeks), carboplatin (AUC 5) and docetaxel (60 mg m^{-2}) every 4 weeks for treatment of gastric cancer; bolus infusion of 5-FU (425 mg m^{-2}) and isovorin (10 mg m^{-2}) for 5 days, every 4 weeks for six courses (5-FU Mayo) for adjuvant treatment of colorectal cancer; 5-FU (400 mg m^{-2}) bolus injection followed by (600 mg m^{-2}) flat continuous infusion for 22 h and oxaliplatin (85 mg m^{-2}), for 2 days (FOLFOX−4) for treatment of colorectal cancer; 5-FU (400 mg m^{-2}) 2-hours bolus infusion followed by (2,400 mg m^{-2}) flat continuous infusion for 46 h (de Gramont) for treatment of colorectal cancer.

Statistics

Difference in incidence between regimens were analysed by Chi-squared test for trend across ordered groups. Efficacy of chemotherapy dose reduction in association to antiangina treatment to prevent cardiotoxicity was analysed using sign test. Chemotherapy regimen, gender, age, previous heart disease and renal clearance were evaluated as covariates for time to appearance and duration of symptoms of cardiotoxicity using Cox's multivariate proportional hazard linear regression. Efficacies of antiangina prevention and intervention were analysed using sign test. Difference in cardiotoxicity according to gender and pre-existing heart disease was analysed using Mann–Whitney *U*-test. Relationship between grade of cardiotoxicity and age or renal clearance was analysed using Spearman Rank correlation. The serum creatinine concentrations were analysed using non-parametric rank test. Values of $P \leq 0.05$ were regarded significant. Statistics was performed with Statistica software (Statsoft Inc. Tulsa, OK, USA).

Results

Cardiotoxicity

The 29 cases of symptomatic cardiotoxicity appeared among 668 patients treated for gastrointestinal cancers (Table 1) making an overall incidence of 4.3%.

Chemotherapy

Differences in incidences pertaining to capecitabine, 5-FU Mayo and de Gramont-based regimens (Table 2) were statistically significant ($P = 0.01$).

Three patients had modified regimen (11) or second line 5-FU or capecitabine-based chemotherapy (25, 29) (Table 3), which allowed for direct comparison of cardiotoxicity according to dose intensity. To case 11 first course of 5-FU (Mayo) was given in 5 days with no cardiotoxicity, whereas the second course given in 4 days using the same total dose led to grade 3 cardiotoxicity. To case 25 capecitabine was given with no cardiotoxicity, whereas shift to FOLFOX-4 regimen led to grade 3 cardiotoxicity. On the contrary, for case 29, grade 3 cardiotoxicity occurred during 5-FU (Mayo),

Table 1 Patient characteristics, atherosclerosis risk factors, renal function and cardiotoxicity according to pre-existing heart and renal disease

Pre-existing disease	No.	Gender	Age	BMI	Smoking	Atherosclerosis risk factors	Heart disease	Renal function		Cardiotoxicity	
								P-creatinine (mM)	Clearance (ml min^{-1})	CTC	Symptoms
Heart	1	M	45	Normal	Previous	Hypercholesterolemia	AMI, Angina	0.069	126[a]	3	Angina
	2	F	55	Moderate	Never	Diabetes, hypertension	AMI, Angina	0.083	84[a]	4	AMI
	3	F	56	Moderate	Previous	Hypertension	Heart insufficiency	0.089	90[a]	3	Angina
	4	F	57	Normal	Never	Hypertension	Angina	0.089	63[a]	3	Angina
	5	M	65	Moderate	Current	Claudicatio	AMI, Angina heart insufficiency	0.087	96[a]	4	AMI
	6	M	66	Severe	Current	Hypertension	Angina, Arrhythmia heart insufficiency	0.105	105[a]	3	Angina
	7	F	66	Normal	Previous		AMI, Angina	–	–	3	Angina
	8	F	67	Normal	Current		Angina	0.075	60[a]	3	Angina
	9	F	72	Normal	–		Angina, heart insufficiency	0.095	54[a]	3	Angina
	10	M	73	Normal	Never		Angina	0.099	60[a]	3	Angina
	11	F	75	Normal	–	Diabetes, hypertension	Angina heart insufficiency	0.108	42[a]	3	Incompensatio dyspnoea, angina
	12	M	77	Moderate	Previous	Hypertension cerebral ischaemia	Angina heart insufficiency	0.097	66[a]	3	Angina
Renal	13	M	46	Normal	Never			0.398	< 30	3	Angina, arrhythmia
	14	M	54	Normal	Never			0.123	75[a]	3	Angina
	15	M	57	Normal	Previous		Transient arrhythmia	0.089	101-71	3	Incompensatio, dyspnoea, angina
	16	F	69	Normal	Never			0.084	48	3	Angina
None	17	M	24	Normal	Current			0.112	84[a]	2	Angina
	18	M	33	Normal	Current			0.112	84[a]	3	Angina, arrhythmia
	19	F	34	Normal	Never			0.055	106	3	Angina
	20	M	38	Moderate	Current			0.067	150[a]	3	Angina
	21	F	44	Normal	Previous			0.081	75[a]	3	Angina
	22	F	58	Normal	–			0.067	66[a]	2	Angina
	23	F	59	Moderate	Never			0.084	66[a]	3	Angina
	24	M	59	Normal	Previous			0.102	78[a]	3	Angina
	25	M	59	Moderate	Current			0.059	144[a]	3	Angina
	26	M	62	Normal	Never			0.085	78[a]	2	Angina
	27	F	65	Moderate	Never			0.090	72[a]	3	Angina
	28	M	70	Normal	Never			0.065	85	3	Angina, arrhythmia
	29	F	75	Normal	Never			0.079	63[a]	3	Angina

[a]Estimated from p-creatinine

Table 2 Chemotherapy regimen, number of patients treated and incidence of cardiotoxicity

Chemotherapy	*n*	Cardio-toxicity No. (%)		*P*
Capecitabine	214	4	(1.9)	0.01
Capecitabine, carboplatin, docetaxel	81	3	(3.7)	
5-FU	352	19	(5.3)	
5-FU de Gramont	10	1	(10)	
FOLFOX-4	11	2	(18)	

whereas subsequent capecitabine was given with no cardiac complaints.

In the study sample, following first occurrence of cardiotoxicity subsequent treatment using the same regimen at reduced dose of 70 or 50%, alone or in association to antiangina medication, prevented cardiotoxicity in nine (60%) and three (20%) out of 15 assessable cases (Table 3)($P = 0.001$), respectively.

The first occurrence of cardiotoxicity was during course 1 (1–5) median (range) (Table 3). The day in the course of first occurrence of cardiotoxicity was 4 (2–15), 5 (3–7) and 3 days (2–6) median (range) for capecitabine (XELOX), low-dose intensity 5-FU (Mayo) and high-dose intensity 5-FU (FOLFOX-4, de Gramont) regimens, respectively. Symptoms of cardiotoxicity subsided 45 (24–168) and 31 (4–120) h median (range) after discontinuation of capecitabine (XELOX) and 5-FU (Mayo, FOLFOX-4, de Gramont)-based regimens, respectively. Symptoms of cardiotoxicity tended to last longer following cease of capecitabine administration as

Table 3 Chemotherapy regimens, time point of first appearance of cardiotoxicity, and efficacy of chemotherapy dose reduction and antiangina treatment of cardiotoxicity

No.	Chemotherapy					Anti-angina therapy			
	First line Second line Third line	Appearance of cardiotoxicity course (day)	Subsequent chemotherapy at minimum dose			Prevention		Intervention	
			Dose (%) baseline	Courses	Cardiotoxicity		Efficacy		Efficacy
8	Capecitabine	1 (5)							
10	Capecitabine	1 (2)	75	4	No	CCA	No	NTG	Yes
12	Capecitabine	5 (15)	70	4	No	BB, nitrate	No	NTG	Yes
15	Capecitabine, carboplatin, docetaxel	1 (4)	70	3	No	CCA, nitrate	Yes	NTG	–
19	Capecitabine, carboplatin, docetaxel	1 (3)	50	–	–	CCA, nitrate	–	NTG	No
28	Capecitabine, carboplatin, docetaxel	1 (7)	50	5	Yes	CCA, nitrate	No	NTG	No
26	5-FU	2 (4)	100	4	–	None		None	
27	5-FU	4 (7)	100	2	–	None		None	
17	5-FU	1 (6)	100	5	–	None		None	
6	5-FU	1 (4)	100	5	–	BB	No	NTG	Yes
21	5-FU	1 (4)	100	5	–	None		NTG	Yes
2	5-FU	3 (3)	80	–	Yes	CCA	No	NTG	Yes
1	5-FU	1 (6)	75	4	No	CCA, nitrate	No	NTG	Yes
14	5-FU	5 (5)	70	1	No	None		None	
22	5-FU	2 (5)	70	4	No	None		NTG	Yes
23	5-FU	5 (6)	50	1	No	None		None	
4	5-FU	5 (5)	50	1	No	CCA	Yes	NTG	Yes
3	5-FU	1 (4)	–		–	BB	No	–	
5	5-FU	2 (6)	–	0	–	None		None	
7	5-FU	1 (3)	–	0	–	CCA, nitrate	–	NTG	Yes
9	5-FU	5 (6)	–	0	–	–		–	
11	5-FU	2 (5)	–	0	–	None		None	
29	5-FU	3 (6)	100	3	–	None		None	
	Capecitabine	None	100	6	No				
24	5-FU	3 (3)	70	3	No	CCA,	Yes	NTG	Yes
	XELOX	1 (3)	100	2	No	Nitrate			
16	5-FU	1 (3)	70	5	No	CCA	Yes	NTG	Yes
	Capecitabine	1 (3)	50	7	No				
25	Capecitabine	None	–		–				
	FOLFOX-4	2 (6)	70	5	No	Nitrate	Yes	NTG	–
13	5-FU	None	–	–	–				
	Capecitabine	1 (4)	66	0	Yes	CCA	No	NTG	Yes
	5-FU de Gramont	1 (3)	40	0	Yes				
20	5-FU de Gramont	1 (2)	60	3	No	CCA, nitrate	Yes	NTG	Yes
18	FOLFOX-4	1 (3)	50	7	Yes	CCA, nitrate	No	NTG	Yes

CCA calcium channel antagonist, *BB* beta-blocker, *NTG* nitroglycerine

compared to 5-FU-based regimens ($P = 0.14$), whereas gender ($P = 0.95$), age ($P = 0.92$), previous heart disease ($P = 0.42$), renal clearance ($P = 0.74$) were neither related to time to occurrence nor to duration of cardiotoxicity.

Antiangina therapy

Data for antiangina prophylaxis with calcium channel antagonists (CCA), beta-blockers (BB) or long acting nitrate, and for intervention with nitroglycerine (NTG) are shown in Table 3.

Six patients had antiangina treatment ahead of chemotherapy. Following cardiotoxicity another 11 patients received antiangina therapy. During subsequent chemotherapy at reduced dose in association with antiangina treatment symptoms of cardiotoxicity did not recur in nine (75%) out of 12 assessable patients ($P = 0.008$). For one (24) case, antiangina therapy prevented symptoms of cardiotoxicity during subsequent chemotherapy at unchanged dose. In order to abolish symptoms of cardiotoxicity, sublingual NTG was efficient in 15 and inefficient in two patients ($P = 0.001$).

Clinical factors

The relationships between CTC grades of cardiotoxicity and gender ($P = 1.0$), and age ($R = 0.20$; $P = 0.30$) were non-significant (Table 1).

Cardiac comorbidity

Patients with pre-existing heart disease tended to have worse cardiotoxicity. The number of cases according to cardiotoxicity CTC grades 2–4 were none, ten and two cases (in 12 patients), and 3, 14 and none cases (in 17 patients) with and without pre-existing cardiovascular disease (Table 1)($P = 0.16$), respectively.

Patients having cardiotoxicity but no previous symptoms of heart disease in the anamnesis, were not stigmatized by other atherosclerotic events, nor had they any obvious risk factors to this (Table 1). In addition, coronary angiography, echocardiography and ECG during work load in three cases (13, 24, 26) found no evidence of gross coronary vascular disease.

Renal comorbidity

In four cases either serum creatinine was outside normal range or renal clearance had decreased intercurrently as cardiotoxicity occurred (Table 1).

In three patients intercurrent decrease of renal clearances to < 30, 48 and 71 ml min^{-1}, in cases 13 and 16 due to tumour obstruction of renal outlet and tubular necrosis, precipitated markedly increased cardiotoxicity at reexposure to chemotherapy. For case 13, 5-FU (Mayo) treatment at normal renal function was tolerated with no cardiotoxicity. At relapse cardiotoxicity was recurrent as renal clearance decreased to < 30 ml min^{-1}, though capecitabine and 5-FU treatments in turn were given at reduced doses of 66 and 40%, respectively. For case 16, 5-FU (Mayo) treatment at normal renal function caused frequent cardiotoxicity that subsided to dose reduction to 70%. At relapse, renal clearance decreased to 48 ml min^{-1}, which required capecitabine dose reduction to 50%. For case 15 angina and palpitations worsened during succeeding capecitabine courses as renal clearance decreased.

During cardiotoxicity serum creatinine concentrations were 0.173 (0.084–0.398) and 0.085 (0.055–0.112) mM mean (range) in patients having impaired and normal renal function, respectively, whereas in patients having no cardiotoxicity creatinine concentrations were 0.099 (0.031–0.406) mM ($P = 0.03$). Correlation between renal clearances and cardiotoxicity CTC grades (Table 1) were non-significant ($R = 0.19$; $P = 0.33$).

Discussion

Occurrence of 5-FU induced cardiotoxicity may depend on dose, route of administration and schedule of chemotherapy. In keeping with previous reports [2, 6, 7], the regimen specific incidences reported here (Table 2), and the fact that reduction of dose relieved or abolished symptoms, suggest high-dose intensity to be critical for cardiotoxicity to develop. In addition, second line chemotherapy that allowed for a direct comparison also showed a ranking order of cardiotoxicity pertaining to regimens.

Whereas the range of cardiac symptoms from various regimens was similar, the temporal pattern of events differed. Usually, symptoms have their onset hours after completion of the last administration following several doses of chemotherapy (Table 3) [3, 6, 7]. Considering the relatively short half-life of 5-FU [19], accumulation of cardiotoxic metabolites during repeated dosing may account for this phenomenon. The protracted symptoms seen for capecitabine were consistent with ample substrate being provided for delayed generation of 5-FU and in turn cardiotoxic metabolites.

Once cardiotoxicity has occurred, the therapeutic options of rechallenge with 5-FU-based chemotherapy are dose reduction in addition to medical prevention with CCA, BB and long-acting nitrates, and intervention with NTG. No major controlled trial has assessed the efficacy of anti-angina therapy in this situation. In a prospective study including 58 patients, who received CCA during 5-FU therapy, signs of ischaemia using electrocardiography appeared as often as in a control group not receiving CCA [18]. Most data derive from case studies reporting varying efficacy of these agents. In a review of 134 cases of chemotherapy induced cardiotoxicity, NTG or CCA were efficient in ten patients, whereas these were inefficient in 11 patients [6].

While in this study, a clear benefit from NTG intervention could be demonstrated, results for antiangina prophylaxis were ambiguous (Table 3). In few cases, occurrence of cardiotoxicity despite of antiangina prophylaxis at initiation of chemotherapy did not exclude that symptoms had been alleviated. In other cases, cardiac symptoms did not recur during subsequent chemotherapy at occasionally reduced dose in association with antiangina prophylaxis. Although from these data it is not possible to discern the specific contribution of antiangina prophylaxis, it is concluded that these agents may be reasonable to employ for 5-FU induced cardiotoxicity. It remains to be clarified as to which patients may benefit from an optimum antiangina therapy.

Few prognostic factors for 5-FU induced cardiotoxicity have been identified. Pre-existing heart disease may imply higher risk of 5-FU induced cardiotoxicity. In a review of 390 patients treated with 5-FU, 13 had cardiac events with higher incidence (15.1% vs. 1.5%) among patients who had previous cardiac disease [4]. Similarly, in a retrospective study of 1,083 patients treated with 5-FU, 17 cases of cardiotoxicity were recognized, with a significantly greater incidence (4.5% vs. 1.1%) for patients with a positive anamnesis of heart disease [5]. On the other hand, in a series of 76 patients, 14 (18%) had adverse cardiac effects from 5-FU with no excess events in the subset of patients with previous heart disease [20]. In a prospective study silent ECG changes suggestive of ischemia were more common among patients with known heart disease [21], whereas a similar study found no such association [8].

More severe 5-FU cardiotoxicity also may be a risk aspect of previous heart disease, as suggested in this report (Table 1), whereas a valid estimate of incidence of heart disease in the whole study sample was not obtainable due to incomplete recordings in oncology records, unless there were cardiac complaints during chemotherapy.

The greater risk from significant atherosclerosis as reflected by incidence and severity of 5-FU cardiotoxicity may indicate increased susceptibility of already restricted aerobic metabolism. The notion of cardiac vasospasms as the final common pathway appear less likely, as the majority of cases never had symptoms of coronary vascular disease nor risk factors to this, which was corroborated by cardiac examinations for some.

Impaired renal function may be another risk factor for 5-FU induced cardiotoxicity, which has not been recognizd previously. In few cases of this study, intercurrently decreased renal function and simultaneous markedly increased susceptibility to chemotherapy induced cardiotoxicity rendered renal impairment likely to have had a permissive pathophysiological effect. Clearly, in the subset of patients not having cardiotoxicity there were also noticeable high-renal parameters, showing the significance of other critical prerequisites to cardiotoxicity. Other case reports have noticed reduced renal function and simultaneous markedly increased cardiotoxicity without ascribing this coincidence any causality [3, 6, 22].

It is not clear as to which hypothetic cardiotoxic metabolites are undergoing renal excretion. Following administration, 5-FU is catabolized in the liver by dihydropyrimidine dehydrogenase (DPD) into 5,6-dihydrofluorouracil and eventually to α-fluoro-β-alanine (FBAL). Urine FBAL and fluoro-metabolites excretion by the kidneys accounts for 60–90% of an intravenous dose within 24 h [23]. The cytotoxic effect of 5-FU is attributed to intracellular conversion to 5-fluorouridine and 5-fluoro-2′-deoxyuridine and corresponding phosphates for incorporation into RNA and DNA, respectively. A minor part of fluoro-2′-deoxyuridine-monophosphate irreversibly inhibits thymidylate synthase.

Interestingly, the coincidence of 5-FU cardiotoxicity and different patterns of pharmacologic and genetic dependent interference in these enzyme pathways may help to elucidate which are pathogenetic to cardiotoxicity.

Accordingly, the 5-FU cardiotoxicity observed with inhibition of synthesis of 5′-fluorouridine-5′-monophosphate from allopurinol [24–26], suggest that involvement of this pathway is not likely. On the contrary, the paucity in the literature of cardiac toxicity from 5-FU administered with DPD enzyme inhibitor eniluracil [27–29] suggest that the metabolic pathway leading to FBAL generation may be pathophysiologic to cardiotoxicity. Also, severe non-cardiac toxicity from 5-FU seen in patients with DPD deficiency may argue for this assumption [30–32].

In conclusion, integrated clinical and genetic parameters may provide the foundation for tailoring of 5-FU-based therapy as regards active agent, dose, schedule and supportive medical treatment in order to avoid cardiotoxicity. With these reservations, 5-FU and capecitabine therapy to most patients still is safe in that respect without the hazard of irreversible cardiac sequelae.

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