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Cardiotoxicity of de Gramont's Regimen: Incidence, Clinical Characteristics and Long-term Follow-up

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Background: The incidence of 5-fluorouracil (5-FU)-related cardiotoxicity seems to be dosage and schedule dependent. It was reported as 1.6–3% with earlier bolus regimens whereas this increased up to 7.6–18% with prolonged (4–5 days) infusion regimens. Knowledge of the cardiotoxicity incidence in patients treated with the widely used de Gramont's regimen (2 days infusional 5-FU) and the long-term follow-up of affected patients is still limited.
Methods: We investigated the incidence and clinical characteristics of the cardiotoxicity of de Gramont's regimen and long-term follow-up of the affected patients.
Results: Nine of a total of 231 patients receiving de Gramont's regimen experienced cardiac events, revealing an overall incidence of 3.9%. Four (2.5%) cases were receiving de Gramont's regimen only. Cardiac manifestations were acute coronary syndrome ($n = 6$), congestive heart failure ($n = 2$) and atrial fibrillation ($n = 1$). Cardiotoxicity occurred in the first cycle in eight patients, and in the second cycle in one. The median onset day was day 2. Cardiac symptoms occurred mostly at night time (seven patients) and the onset was a few hours after the bolus part of the regimen in four out of seven patients. After the cardiotoxicity, treatments were continued safely without 5-FU.
Conclusions: de Gramont's regimen has a lower incidence of cardiotoxicity compared with more prolonged 5-FU-based infusion regimens. Nevertheless, patients should still be carefully monitored especially in the first cycles and at night time.

Key words: 5-fluorouracil – cardiotoxicity – de Gramont's regimen – follow-up – leucovorin

INTRODUCTION

Cardiotoxicity is a serious side effect of 5-fluorouracil (5-FU)-based regimens. The overall incidence of 5-FU-related cardiotoxicity varies widely owing to the dosage, schedule (bolus or infusional) and additional drugs. In early studies, the overall incidence was reported as 1.6–3% with various bolus regimens (1,2). In current clinical practice, continuous infusion of 5-FU is the treatment of choice because of its lower toxicity profile and improved efficiency; however, the incidence of cardiotoxicity has increased up to 7.6–18% (3–5). These incidences were mostly reported with more prolonged (4–5 days) infusion regimens. Nowadays, there are many different 5-FU-based regimens, which have distinct efficiency and toxicity profiles. de Gramont's regimen (combination of high dose leucovorin and 5-FU bolus with continuous infusion, biweekly) is one of the most widely used schedules in many centers (6). de Gramont's regimen-related cardiotoxicity was studied in previous reports to demonstrate its effects on the myocardium and electrocardiograms (7,8). However, its true cardiotoxicity incidence is still not fully known.

During the continuous infusion, a circadian rhythm is observed for plasma concentrations of 5-FU because of the diurnal activity of dihydropyrimidine dehydrogenase (DPD), which rapidly eliminates >80% of the administered 5-FU (9). Although the clinical characteristics of 5-FU-related cardiotoxicity are well defined, up to now its occurrence related to 5-FU chronopharmacokinetics has not been investigated. Moreover, knowledge of the long-term outcome of the affected patients is rather limited. Only three patients have been reported so far who previously had experienced 5-FU-related cardiotoxicity, and raltitrexed was safely administered in these patients (10,11).

In this study, we evaluated the incidence and clinical characteristics (including the occurrence times) of de Gramont's regimen-related cardiotoxicity and the long-term outcome of the affected patients.

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PATIENTS AND METHODS

Overall, 231 patients treated with de Gramont's regimen were evaluated retrospectively at two reference centers, Adnan Menderes and Dokuz Eylul University Hospitals. The primary site of the tumor, combination drug(s), application routes of the regimen, history of coronary artery disease (CAD) and other risk factor(s) such as congestive heart failure (CHF), diabetes mellitus and hypertension were noted. For the patients who experienced cardiotoxicity, we evaluated the clinical and laboratory characteristics of the cardiac manifestations including onset times (cycle, day and time), and anticancer treatment(s), toxicities and survival after the cessation of 5-FU. Treatment-related cardiotoxicity was defined as cardiac symptoms (including angina pectoris (AP), palpitation, hypotension, dyspnea, etc.), and/or ECG findings occurring during or just after the chemotherapy and/or increased cardiac enzymes.

De Gramont's Regimen

The regimen was composed of a 2 h intravenous (i.v.) infusion of leucovorin (calcium leucovorin DBL, Orna, Turkey) 200 mg/m^2, followed by an i.v. bolus of 5-FU (5-fluorouracil biosyn DBL, Orna, Turkey) 400 mg/m^2 and then an i.v. infusion of 600 mg/m^2 for 22 h on days 1 and 2, biweekly.

Statistics

All two group comparisons were evaluated by Fisher's exact test or χ^2 test. The Kruskal–Wallis H test was used to define the differences among the various combination regimens. A P-value < 0.05 was considered statistically significant. The statistical analyses were performed by SPSS for Windows release 10.0 program.

RESULTS

We evaluated 231 patients of mean age 59 (ranges 23–87) years and a female/male ratio of 93/138. Symptomatic cardiotoxicity was determined in nine (3.9%) patients. The characteristics of the study populations and cardiotoxicity are showed in Table 1.

The incidence of cardiotoxicity was not significantly different between the de Gramont's regimen and its combinations with other drugs [2.5 versus 7.4%, odds ratio (OR) 3.2, 95% confidence interval (CI) 0.8–12.1, $P = 0.128$].

The overall incidence of cardiotoxicity was not significantly different between the patients with and without CAD (OR 4.5, 95% CI, 0.8–24.1, $P = 0.11$), with and without any cardiac disease and/or risk factors (OR 1.5, 95% CI 0.4–6.5, $P = 0.40$) and route of application (OR 1.7, 95% CI 0.4–6.9, $P = 0.52$).

The clinical characteristics of cardiotoxicity are demonstrated in Table 2. Cardiotoxicity was mostly ($n = 6$, 67%) in the form of acute coronary syndrome. The main symptom 'unstable angina pectoris' (U-AP) was responsive to cessation of 5-FU infusion and medical treatment (aspirin and nitrates) in five patients. It could be relieved in the first 30 min, though accompanying symptoms such as dyspnea (patients 4, 5 and 8) and palpitations (patients 2, 4 and 5) had continued for a period of 5 h to 2 days. Unfortunately, patient 3 suffered a myocardial infarction. Cardiotoxicity occurred in first administrations in eight patients. The symptoms mostly occurred at night (six out of nine, 67%) and a few hours after the bolus part of the regimen in patients 1, 6, 7 and 8. There was no cardiotoxicity-related death.

Table 1. Characteristics of the study population and cardiotoxicity

Characteristics	Overall, n (%)*	Cardiotoxicity, n (%)+
Age (range), years	59 (23–87)	61 (52–75)
Gender (F/M)	93/138	2/7
Cancer		
Colorectal	142 (62)	5 (3.5)
Gastric	36 (16)	0 (0)
Pancreas and gallbladder	27 (12)	2 (7.4)
Breast	14 (6)	0 (0)
Neuroendocrine	5 (2)	1 (20)
Head and neck	3 (1)	1 (33)
Other	4 (1)	0 (0)
Treatments		
DG (only)	163 (71)	4 (2.5)
Combinations	68 (29)	5 (7.4)
DG and gemcitabine	25 (11)	2 (8.0)
DG and CPT-11	14 (6)	1 (7.1)
DG and epirubicin	11 (5)	1 (9.1)
DG and cisplatin or carboplatin	11 (5)	1 (9.1)
DG and docetaxel	7 (3)	0 (0.0)
Total	231 (100)	9 (3.9)
Cardiac diseases		
Diagnosed CAD	15 (6.5)	2 (13.3)
CAD and/or risk factors	55 (24)	3 (5.4)
None	176 (76)	6 (3.4)
Application routes		
Out-patient (central)	103 (45)	3 (2.9)
Hospitalized (peripheral)	128 (55)	6 (4.7)

DG, de Gramont's regimen.
*Percentage of patients with the defined characteristic in the whole study population ($n = 231$).
+Percentage of patients with 5-FU-related cardiotoxicity in the group of patients with the defined characteristic.

Successive Chemotherapy Regimens, Their Toxicities and Overall Survival of Patients After 5-FU-related Cardiotoxicity

The follow-up results of the patients after cardiotoxicity are showed in Table 3. The treatments of patients 1 and 3, both of

Table 2. Patients with 5-FU-related cardiotoxicity: clinical characteristics, laboratory findings and treatments

Patient	1	2	3	4	5	6	7	8	9
Age (years)/ gender	56/M	57/F	56/M	52/M	57/M	59/M	68/M	75/F	73/M
Localization	Pancreas	Neuroendocrine	Pancreas	Colon	Rectum	Nasopharynx	Rectum	Rectum	Colon
Combination drug	Gemcitabine	Epirubicin	Gemcitabine	–	–	Carboplatin	–	CPT-11	–
History of CAD	No	No	No	Yes	No	No	No	Yes	No
Treatment	Adjuvant	Palliative	Palliative	Adjuvant	Adjuvant	Palliative	Adjuvant	Palliative	Palliative
Application route	Peripheral	Peripheral	Central	Central	Central	Peripheral	Peripheral	Peripheral	Peripheral
Treatment start time (hour)	17:00	13:00	13:00	12:30	10:00	19:00	18:30	19:00	16:00
Symptoms and signs									
Onset (day)	2	3	2	1	1	2	2	1	16
Time (hour)	21:00	00:30	11:00	22:30	02:00	21:30	03:00	04:30	15:00
Angina pectoris	+	+	+	+	+	–	+	+	–
Dyspnea	+	–	+	+	+	+	–	+	–
Palpitations	+	+	–	–	+	+	–	–	+
Hypotension	+	–	–	–	–	+	–	–	–
Cardiac enzymes	Normal	Normal	High	Normal	Normal	Normal	Normal	Normal	Normal
ECG	$D_{1–2–3}$, $V_{1–6}$ ST↑	D_1, aVL, $V_{5–6}$, ST↑	$D_{1–2}$, $V_{1–4}$, ST↑	$D_{1–3}$, aVF, ST↑, RBB	$D_{1–2}$, aVL, ST↑	D_1, aVL, $V_{1–6}$ T (–)	NSR	NSR	AF
Angiography	–	–	–	LAD %20, Cx %70	Normal	–	–	–	–
Type of cardiotoxicity	Pericarditis, CHF	U-AP	AS-MI	U-AP	U-AP	CHF	U-AP	U-AP	AF
Echocardiography	GH, PF, MR, EF: 25%	Normal	–	–	LV apical hypokinesia	GH, MR, TR, EF: 31%	Normal	–	Normal
Treatments	Aspirin, ramipril	Aspirin, perlinganit, heparin	Aspirin, metaprolol, perlinganit, heparin,	Aspirin, perlinganit, LMWH	Asprin, perlinganit, LMWH	Asprin, kumadin	Aspirin, nitrates, LMWH	Asprin, perlinganit	Aspirin, propafenon
Duration of symptoms	4 h	2 days	1 day	1 day	1 day	2 days	30 min	5 h	4 h

CAD, coronary artery disease; AF, atrial fibrillation; RBB, right bundle block; U-AP, unstable angina pectoris; AS-MI, antero-septal myocardial infarction; LMWH, low molecular weight heparin; EF, ejection fraction; GH, global hypokinesia; PF, pericardial fluid; MR, mitral regurgitation; TR, tricuspid regurgitation; LAD, left anterior descending; Cx, circumflex; NSR, normal sinus rhythm; ST↑, >1 mm.

whom were treated with combination regimens, were completed without 5-FU. For patient 4, surgical resection and radiotherapy were performed because of local recurrence after the third cycle of CPT-11 treatment. He died in the second week of the first oxaliplatin course. Patient 5 was hospitalized at the first week of a CPT-11 course with pancytopenia, fever and hypotension. *Pseudomonas aeruginosa* was detected in blood, urine and catheter cultures. He died of upper gastrointestinal system bleeding 1 week later. Patient 6 died of CHF after the first course of UFT treatment that was started in another hospital. Adjuvant treatment of patient 7 was continued during 6 months without any changes. The same clinical findings occurred in all cycles of the treatments. Symptoms were controlled easily with sublingual nitrates, but it was not preventive. Patient 8 refused any further treatment after the fourth course of CPT-11 treatment. de Gramont's regimen and its combinations were the first treatments in all the patients with cardiotoxicity.

DISCUSSION

In a retrospective study, Labianca et al. (1) reported that the overall incidence of cardiotoxicity was 1.6%, with bolus 5-FU (15 mg/kg/wk). In another study, it was found to be 3% in patients treated with five different bolus schedules, which contained 5-FU 500–2100 mg/m^2/day for 1–3 days (2).

Recently, 5-FU has mostly been used as continuous venous infusion and at higher doses, thanks to the technical advances in portable infusion pump devices. In spite of a lower toxicity profile and improved efficiency, continuous infusion of high

Table 3. Follow-up of patients after 5-FU-related cardiotoxicity: consecutive chemotherapy regimens, their toxicities and overall survival

Patient	Second line treatments		Third line treatments		Fourth line treatments		Overall survival[+] (months)
	Drug courses*	Toxicity (grade 3–4)	Drug course*	Toxicity (grade 3–4)	Drug course	Toxicity (grade 3–4)	
1	Gemcitabine only (5)	Neutropenia (febrile), anemia	–	–	–	–	6 (dead)
2	Best supportive care	–	–	–	–	–	2 (dead)
3	Gemcitabine only (5)	Neutropenia, anemia,	–	–	–	–	6 (dead)
4	CPT-11[†] (3)	Neutropenia, anemia, alopecia, diarrhea, emesis	Raltitrexed[‡] (3)	–	Oxaliplatine (1)	–	24 (dead)
5	CPT-11[†] (1)	Infection (septic schock), DIC, pansitopenia	–	–	–	–	1 (dead)
6	UFT	CHF	–	–	–	–	7 (dead)
7	–	–	–	–	–	–	20 (alive)
8	CPT-11 only** (4)	Diarrhea	–	–	–	–	12 (dead)
9	Raltitrexed (6)	–	Capecitabine (3)	–	Gemcitabine (1)	–	14 (dead)

DIC, disseminated intravascular coagulation.
*Number of courses.
[+]Time since diagnosis.
[†]The CPT schedule was 375 mg/m^2 thrice weekly.
[‡]The raltitrexed regimen was 3 mg/m^2 thrice weekly.
**The CPT schedule was 180 mg/m^2 biweekly.

dose fluorouracil was suggested to be much more cardiotoxic than conventional bolus regimens (3–5). Gradishar and Vokes (12) stated that the cardiac events in up to 10% of the patients were related to high dose (>800 mg/m^2) 5-FU administrations. In a prospective study, de Forni et al. (3) reported that the cardiac events occurred in 28 (7.6%) of 367 patients receiving an infusional 5-FU regimen of 600–1000 mg/m^2/day for 4–5 consecutive days. In another study, Eskilsson et al. (5) found that the incidence was 18% in patients treated with head and neck cancers under a combined treatment schedule of 5-FU 1000 mg/m^2/day for 5 days with cisplatin. In our study, the overall cardiotoxicity incidence of de Gramont's regimen was lower, as compared with previous studies with various infusional 5-FU regimens despite the approximately similar 5-FU dosage. Furthermore, the incidence was similar to bolus schedules among the patients treated with de Gramont's regimen only (1,2). These findings suggested that there was not any strict linear relationship between the cardiotoxicity incidence and 5-FU doses, and that the occurrence of cardiotoxicity was schedule dependent as well as dependent on the administered 5-FU doses. The regimens administered only for two consecutive days might be reasonable, especially for patients who have CAD and/or cardiac risk factors, for two reasons: (i) the 5-FU-related AP occurred at ~72 h or later in 63% of the patients (13); and (ii) the active metabolites of 5-FU may cause diffuse hypoxia due to depletion of the high-energy phosphate compounds in the ventricular myocardium (3,14–16). This accumulation is caused by the formation of fluoroacetate, a cardiotoxic metabolite, from α-fluoro-β-alanine, a major degradation product of 5-FU. Moreover, two degradation compounds, namely fluoroacetaldehyde (Facet) and fluoromalonaldehydic acid, are also present in the injected vials (15). These compounds are formed with time in the basic medium and the level of the former increases after 2–3 days, when the patients are treated using volumetric infusion pump devices (17). These transformations may also contribute to cardiac toxicity in long-term regimens. The duration of de Gramont's regimen is only 2 days, which is too short for these compounds to be sufficiently formed.

It is now becoming known that there is a marked circadian rhythm in the onset time of acute cardiovascular events in patients with ischemic heart disease: they occur most often after awakening, before noon (18). As an interesting new finding, in our patients, acute coronary syndromes mostly occurred at night (five out of six) contrary to the general expectation. The cardiotoxicity mostly occurred at night and a few hours after the bolus part of the regimen despite the different starting times of the courses (Table 2). These findings were more prominent in the patients with acute coronary syndrome. The timing of the symptoms was not carefully studied in previous reports. The difference in the times of occurrence probably arose from the circadian rhythm of DPD activity. The elimination rates of 5-FU and its metabolites vary over a 24 h period with a circadian rhythm in association with the light and dark cycle. The peak activity of DPD was observed at 4 p.m. (2.96 nmol catabolites/min/mg) and the trough at 4 a.m. (0.40 nmol catabolites/min/mg) under standardized conditions of a light and dark cycle. The 'reverse' conditions of light and dark also exhibited a circadian pattern (9). Petit et al. (19) determined the mean lowest and highest 5-FU values as

254 ± 33 ng/ml at 13:00 h and 584 ± 160 ng/ml at 01:00 h during constant rate continuous infusion for 2–5 days. The peak drug concentration was observed in the first half of the night. Therefore, it is essential that the persons on duty should take special care of patients at night, when attention and nursing become relatively poor. Additionally, the bolus parts of de Gramont's regimen may contribute to the cardiotoxicity by generating excessive blood 5-FU levels when superimposed on continuous infusion on day 2. In addition to circadian rhythm, an inverse relationship has also been defined between DPD and the toxicity of 5-FU (20). In our study, the overall cardiotoxicity incidence was higher than expected for the reported heterozygote frequencies of DPD gene mutation (1.5%) among Turkish patients (21). This suggested that additional factors other than DPD enzyme deficiency and/or activity may contribute to the 5-FU-related cardiotoxicity. The relationship between the diurnal variation of blood 5-FU levels and the time of occurrence of the cardiotoxicity must be evaluated in further studies.

Leucovorin is mostly administered with 5-FU. In previous studies, the incidence of cardiotoxicity did not differ with the addition of leucovorin to single-agent bolus 5-FU chemotherapy (2,22). In our study, the high dose leucovorin combination also did not show an additive effect on either the frequency or type of 5-FU-related cardiotoxicity. To the best of our knowledge; this is the first report on cardiotoxicity of 5-FU in combination with high dose leucovorin as a standard regimen.

Anthracyclines are a group of well-known cardiotoxic compounds in oncology practice. In contrast to 5-FU, their toxicities are cumulative and mostly appear as CHF, while 5-FU-related cardiotoxicity is usually acute and appears during the first course of the treatment, and clinical diagnosis is acute coronary syndrome in most of the patients (13). The clinical findings in patient 3 in our study suggested 5-FU-related toxicity rather than that of epirubucine (Table 2). The impact of other cardiotoxic drugs on 5-FU-related cardiotoxicity should be evaluated in future studies.

In some studies, a history of cardiac disease was reported as the only important risk factor associated with cardiotoxicity. The reported incidences in patients with and without cardiac diseases were 4.5–15.1 and 1.1–1.5%, respectively (1,2). However, in other studies, this hypothesis was not supported (4,5,13). This discrepancy might be due to the absence of standardization in defining cardiac disease. In this study, we evaluated patients in two categories: patients with cardiac diseases and patients with both cardiac diseases and risk factors (Table 1). The risk of cardiac toxicity appears to be higher in patients with diagnosed CAD, and the difference between the two may be meaningful, although the number of patients with cardiotoxicity was too small for a significant conclusion to be drawn in this study.

The long-term outcome of patients with 5-FU-related cardiotoxicity was not well studied in the literature. When cardiotoxicity occurs, 5-FU treatment is usually discontinued due to its very high recurrence rate (90%) (3,13). In our patient 7, 5-FU treatment was continued despite the cardiotoxicity because of the absence of registered alternative drugs for the adjuvant treatment of colorectal cancer in our country at that time. The symptoms were without serious clinical and hemodynamic consequences and could be easily controlled with sublingual nitrate treatments in subsequent treatment courses. In one study (10), two patients previously experiencing 5-FU-related cardiotoxicity were safe under raltitraxed. We also administered raltitrexed to our patients 5 and 9, and did not experience recurrent events. However, another patient (patient 6) with clinical CHF died while undergoing treatment with UFT, an oral fluoropyrimidine. In some reports, it was demonstrated that capecitabine, another oral fluoropyrimidine carbamate, has cardiotoxic potential (23,24), and the authors advised that patients with symptoms suggestive of cardiotoxicity during previous treatment with a fluoropyrimidine should not be treated with capecitabine (23). From the viewpoint of reappearance of cardiac diseases, the cardiotoxicity risk of continuing with other 5-FU-related drugs may be high. Finally, for the remaining patients, treatments could be continued either by removing 5-FU from a combination regimen or preferring an alternative drug other than 5-FU analogs.

In conclusion, this study suggested that de Gramont's regimen might have a lower incidence of cardiotoxicity compared with more prolonged infusional 5-FU-based regimens. Nevertheless, patients should still be carefully monitored especially in the first few cycles and at night.

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