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.
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/m², followed by an i.v. bolus of 5-FU (5-fluorouracil biosyn DBL, Orna, Turkey) 400 mg/m² and then an i.v. infusion of 600 mg/m² for 22 h on days 1 and 2, biweekly.

STATISTICS

All two group comparisons were evaluated by Fisher’s exact test or \( \chi^2 \) 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.

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
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/m²/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>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)/gender</th>
<th>Localization</th>
<th>Combination drug</th>
<th>History of CAD</th>
<th>Treatment</th>
<th>Application route</th>
<th>Treatment start time (hour)</th>
<th>Symptoms and signs</th>
<th>Cardiac enzymes</th>
<th>Angiography</th>
<th>Type of cardiotoxicity</th>
<th>Echocardiography</th>
<th>Treatments</th>
<th>Duration of symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>56/M</td>
<td>Pancreas</td>
<td>Gemcitabine</td>
<td>No</td>
<td>Adjuvant</td>
<td>Peripheral</td>
<td>17:00</td>
<td>Normal</td>
<td>Normal</td>
<td>–</td>
<td>Pericarditis</td>
<td>GH, PF, MR, EF: 25%</td>
<td>Aspirin, ramipril</td>
<td>4 h</td>
</tr>
<tr>
<td>2</td>
<td>57/F</td>
<td>Neuroendocrine</td>
<td>Epirubicin</td>
<td>No</td>
<td>Palliative</td>
<td>Peripheral</td>
<td>13:00</td>
<td>Normal</td>
<td>Normal</td>
<td>–</td>
<td>U-AP</td>
<td>Normal</td>
<td>Aspirin, perlinganit, heparin</td>
<td>2 days</td>
</tr>
<tr>
<td>3</td>
<td>56/M</td>
<td>Pancreas</td>
<td>Gemcitabine</td>
<td>Yes</td>
<td>Palliative</td>
<td>Central</td>
<td>13:00</td>
<td>+</td>
<td>Normal</td>
<td>–</td>
<td>AS-MI</td>
<td>Normal</td>
<td>Aspirin, perlinganit, heparin</td>
<td>1 day</td>
</tr>
<tr>
<td>4</td>
<td>52/M</td>
<td>Colon</td>
<td>–</td>
<td>No</td>
<td>Adjuvant</td>
<td>Central</td>
<td>13:00</td>
<td>+</td>
<td>High</td>
<td>–</td>
<td>U-AP</td>
<td>Normal</td>
<td>Aspirin, perlinganit, heparin, LMWH</td>
<td>1 day</td>
</tr>
<tr>
<td>5</td>
<td>57/M</td>
<td>Rectum</td>
<td>–</td>
<td>Yes</td>
<td>Palliative</td>
<td>Central</td>
<td>12:30</td>
<td>+</td>
<td>Normal</td>
<td>–</td>
<td>CHF</td>
<td>Normal</td>
<td>Aspirin, perlinganit, heparin, LMWH</td>
<td>2 days</td>
</tr>
<tr>
<td>6</td>
<td>59/M</td>
<td>Nasopharynx</td>
<td>Carboplatin</td>
<td>No</td>
<td>Palliative</td>
<td>Peripheral</td>
<td>10:00</td>
<td>+</td>
<td>Normal</td>
<td>–</td>
<td>U-AP</td>
<td>Normal</td>
<td>Aspirin, perlinganit, heparin, LMWH</td>
<td>2 days</td>
</tr>
<tr>
<td>7</td>
<td>68/M</td>
<td>Rectum</td>
<td>–</td>
<td>No</td>
<td>Palliative</td>
<td>Peripheral</td>
<td>19:00</td>
<td>+</td>
<td>Normal</td>
<td>–</td>
<td>AF</td>
<td>Normal</td>
<td>Asprin, kumadin</td>
<td>30 min</td>
</tr>
<tr>
<td>8</td>
<td>75/F</td>
<td>Rectum</td>
<td>CPT-11</td>
<td>No</td>
<td>Palliative</td>
<td>Peripheral</td>
<td>18:30</td>
<td>–</td>
<td>Normal</td>
<td>–</td>
<td>U-AP</td>
<td>Normal</td>
<td>Asprin, LMWH</td>
<td>5 h</td>
</tr>
<tr>
<td>9</td>
<td>73/M</td>
<td>Colon</td>
<td>–</td>
<td>No</td>
<td>Palliative</td>
<td>Peripheral</td>
<td>19:00</td>
<td>–</td>
<td>Normal</td>
<td>–</td>
<td>AF</td>
<td>Normal</td>
<td>Aspirin, propafenon</td>
<td>4 h</td>
</tr>
</tbody>
</table>

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.
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/m²) 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/m²/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/m²/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 fluoro-malonaldehydic 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

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

<table>
<thead>
<tr>
<th>Patient</th>
<th>Second line treatments</th>
<th>Third line treatments</th>
<th>Fourth line treatments</th>
<th>Overall survival† (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Drug courses*</td>
<td>Toxicity (grade 3–4)</td>
<td>Drug course*</td>
<td>Toxicity (grade 3–4)</td>
</tr>
<tr>
<td>1</td>
<td>Gemcitabine only (5)</td>
<td>Neutropenia (febrile), anemia</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>Best supportive care</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>Gemcitabine only (5)</td>
<td>Neutropenia, anemia, emesis</td>
<td>Raltitrexed†(3)</td>
<td>–</td>
</tr>
<tr>
<td>4</td>
<td>CPT-11†(3)</td>
<td>Neutropenia, anemia, alopecia, diarrhea, emesis</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>5</td>
<td>CPT-11†(1)</td>
<td>Infection (septic shock), DIC, pansitopenia CHF</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>6</td>
<td>UFT</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>7</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>8</td>
<td>CPT-11 only** (4)</td>
<td>Diarrhea</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>9</td>
<td>Raltitrexed (6)</td>
<td>–</td>
<td>Capecitabine (3)</td>
<td>–</td>
</tr>
</tbody>
</table>

DIC, disseminated intravascular coagulation.
*Number of courses.
†Time since diagnosis.
‡The CPT schedule was 375 mg/m² thrice weekly.
§The raltitrexed regimen was 3 mg/m² thrice weekly.
**The CPT schedule was 180 mg/m² biweekly.
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 addi-
tional factors other than DPD enzyme deficiency and/or activ-
ity 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 evalu-
ated 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 chemother-
apy (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 know-
ledge; 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 tox-
icity rather than that of epirubicine (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). How-
ever, 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 dis-
ases 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 cardio-
toxicity was not well studied in the literature. When cardio-
toxicity 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 experienc-
ing 5-FU-related cardiotoxicity were safe under raltitrexed.
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 cardio-
toxicity during previous treatment with a fluoropyrimidine
should not be treated with capecitabine (23). From the view-
point 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 reg-
imen might have a lower incidence of cardiotoxicity compared
with more prolonged infusional 5-FU-based regimens. Never-
theless, patients should still be carefully monitored especially
in the first few cycles and at night.

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