5-Fluorouracil increases the number and complexity of premature complexes in the heart: a prospective study using ambulatory ECG monitoring

U. Yılmaz, I. Oztop, A. Ciloglu, T. Okan, U. Tekin, A. Yaren, I. Somali, A. Alacacioglu, O. Kırımlı

SUMMARY
The cardiac toxicity of LV5FU2 (de Gramont) regimen which is a widely used chemotherapy regimen in gastrointestinal system cancers is not well defined. We aimed to evaluate the impact of this regimen on cardiac rhythm. Two Holter ECG recordings were obtained in all patients with gastrointestinal system cancers treated with LV5FU2 regimen as first-line chemotherapy (one before and the second during the first 24 h of chemotherapy). Records were reviewed for the heart rate, rhythm, atrial premature complexes (APC), ventricular premature complexes (VPC), grades according to Lown-Wolf grading system and ST segment changes. Holter ECG recordings were evaluated in 27 patients. In the baseline evaluation, neither clinical symptom nor ST segment changes were observed. During the treatment period, chest pain was observed in two patients without any cardiac enzyme and ST segment changes. Moreover, a decrease in mean heart rate, and an increase in the number and complexity of premature complexes secondary to treatment were observed. The mean heart rate, APC per hour and VPC per hour (±SD) before vs. during treatment were, respectively, 93.1 ± 16.4 vs. 81.6 ± 12.7 (p = 0.001), 18.9 ± 54.0 vs. 45.3 ± 53.8 vs. (p = 0.049) and 12.7 ± 29.6 vs. 38.1 ± 42.1 (p = 0.002). LV5FU2 regimen leads to a decrease in mean heart rate and a significant increase in APC and VPC which may lead to serious arrhythmias. These effects must be better understood for a safer administration of this useful and widely used drug regimen.

What’s known
The knowledge about this topic is that cardiac adverse events secondary to 5-FU therapy are mainly ischemic events manifested as ST segment changes and rarely as myocardial infarction as well as ventricular dysfunction caused by reversible myocardial depression. Rhythm abnormalities are less frequently reported and less well studied. However, in a recent study, we found that a cumulative increase of QT interval and dispersion, which can predict further occurrence of arrhythmic events occurred in patients treated with LV5FU2 regimen.

What’s new
We found that 5-FU leads to an increase in ventricular and atrial cardiac premature complexes which can further lead to serious arrhythmias. The clinical significance and mechanisms of this kind of cardiac effects have to be elucidated to permit a safer administration of 5-FU and related drugs in patients with or without cardiac disorders.

Introduction
5-Fluorouracil (5-FU) is the mainstay of the systemic treatment of the gastrointestinal system cancers as well as of malignant tumours of other tissues (1). It is combined in general with leucovorin, which increases its efficacy by biological modulation. As a chemotherapeutic agent, it is relatively safe which permits its wide and long-lasting use. Its main toxicities concern the bone marrow and mucosal surfaces and are decreased by its administration as long-duration infusions (2,3).

Because of lesser toxicity and ease to combine with other drugs, regimens with long infusions of 5-FU substitute those with bolus administration. There are many reports on the cardiac toxicity of 5-FU. The incidence of cardiac adverse events ranges from 1.6% to 8.0% (4–7), and it is up to 10 times higher in patients with a history of cardiac disease compared with those without cardiac problems (15.1% vs. 1.5% respectively) (8). The cardiotoxicity consists generally of an angina accompanied by ST segment changes and/or left ventricle dysfunction (4,9). Myocardial infarction, rhythm abnormalities and sudden death have also been reported (4,7,9).

Cardiac toxicity is not considered as a factor limiting the use of 5-FU because of its low incidence and morbidity. Thus, routine cardiac monitoring is not an indispensable part of standard clinical practice in patients treated with 5-FU. It has been claimed that cardiac toxicity is more common when higher doses of 5-FU are administered as longer infusions instead of bolus (4). In a recent study, we found that a cumulative increase of QT interval and dispersion occurred in patients treated with LV5FU2 (de Gramont) regimen (10). These changes did not lead to any clinical morbidity during the follow-up period of the trial, but it is well known that such ECG changes
5-FU increases premature contractions in the heart

Methods

Patients with histopathologically documented gastrointestinal system cancer receiving LV5FU2 regimen as first-line chemotherapy were included into this study. Those with an established diagnosis of cardiac disease, uncontrolled hypertension or use of drugs affecting cardiac rhythm as well as significant abnormalities on the 12-lead ECG recordings were excluded.

The chemotherapy regimen (LV5FU2) consisted of classical de Gramont regimen (leucovorin 200 mg/m² IV 2 h infusion followed by 5-FU 400 mg/m² IV bolus and 600 mg/m² IV 22 h infusion on day 1 and on day 2 repeated every 14 days) (3). All patients were informed about the benefits, aim and side effects of the therapy and also the aim of the ECG recordings.

Baseline 24-h Holter ECG recordings cardio-scan (Biomedical Systems, Brussels, Belgium) were obtained within 2 days before the initiation of chemotherapy. A second 24-h Holter ECG recording was obtained in each patient during the first 24 h of the first cycle of chemotherapy. Fifteen patients received the chemotherapy via a Hickman type central catheter in the day hospital, while 12 patients received the treatment via peripheral veins and were hospitalised. Hickman catheters were placed in each patient at least 72 h before the baseline ECG recording. Patients were advised to record the exact initiation time and duration of complaints, such as chest pain, palpitation and pressure over the chest by pushing the button on the Holter ECG device and also filling a logbook.

A cardio-scan (Biomedical Systems, Brussels, Belgium) Holter ECG device was used for the monitoring of the patients. Regular ECG sequences and sequences concerning alterations of normal rhythm were automatically recorded on K-7 type cassettes. The records were evaluated with a standard computer-based Holter ECG analysis method. The mean heart rate, atrial premature complexes (APC) per hour, APC per 1000 beats, ventricular premature complexes (VPC) per hour and VPC per 1000 beats were recorded. The ventricular premature complexes were graded according to VPC-grading system described previously by Lown–Wolf grading system (12) (Table 1).

Serum creatine kinase-myocardial band (CK-MB) levels were also obtained as soon as possible when patients reported symptoms and also in each diabetic patients who were at risk for silent ischaemia at the end of the recording. ECG recordings were carefully evaluated for the periods where the patient reported some symptom for the heart disease. ST alterations over 2 mm were considered as pathological.

Finally, the records made during the chemotherapy were compared with those obtained before it in each patient. The comparisons were carried out using $t$-test (test for determining the significance of the difference between paired samples). Subgroup analyses and comparisons were made according to age (< 65 or ≥ 65), sex, setting of chemotherapy, adjuvant or metastatic disease, presence of a central catheter, diabetes and hypertension. spss 10.0 software was used for calculations.

Results

Twenty-nine patients have been subject to 24 h ambulatory ECG monitoring before and during the chemotherapy administration. Two patients were excluded; one, because malignant hypertension was diagnosed after the hospitalisation and a beta-blocking drug was initiated, and another one, because a persisting atrial fibrillation was found in the first and subsequent recordings.

The remaining 27 patients with gastrointestinal cancer (19 colon, four gastric, two distal oesophagus and two hepatic) were evaluated in this study. Fifteen patients were male and the remaining 12 were female with a median age of 54 (19–70). Twenty received chemotherapy in the adjuvant setting while the remaining seven patients were treated for metastatic disease. Two patients had a history of diabetes mellitus and were receiving oral antidiabetic drugs, and additional five patients had a history of hypertension and were receiving antihypertensive drugs without a known effect on cardiac rhythm.

In the baseline evaluation, no patient had a clinical symptom. In Holter ECG analysis, all patients had sinus rhythm and no ST segment changes were observed. The heart rate, APC and VPC results in this period are shown in Table 2. Six patients (22.3%) had VPC. In five of them (18.5%), these VPC were not clinically significant with a Lown–Wolf grade 1, while one patient (3.7%) had grade

| Grade   | VPC classification          |
|---------|-----------------------------|
| Grade 0 | VPC absent                  |
| Grade I | Less than 30 VPC per hour   |
| Grade II| More than 30 VPC per hour   |
| Grade III| Multifocal VPCs           |
| Grade IV A| Couplets                 |
| Grade IV B| Ventricular tachycardia    |
| Grade ≥ 2| Complex ventricular arrhythmia |

Table 1 Lown–Wolf grading system (12)
4b, i.e. complex ventricular arrhythmia before the chemotherapy.

During the 5-FU treatment period, two patients reported chest pain; however, cardiac enzyme values were within the normal ranges, and no ST segment changes were associated to these pain episodes. In Holter ECG analysis, all patients had sinus rhythm and no ST segment changes were seen. The heart rate, APC and VPC results in this period are shown in Table 2. During the chemotherapy, 19 patients (70.3%) had VPC, 13 (48.1%) with Lown–Wolf grade 1, one (3.7%) grade 2, one (3.7%) grade 3, two (7.4%) grade 4a and two (7.4%) grade 4b. Thus, during the treatment, six patients (22.2%) had complex ventricular arrhythmia, i.e. VPC with a Lown–Wolf grade ≥2. An increase in grade was observed during the treatment in all patients who had grade 1 VPC before the treatment, and in the patient with grade 4b VPC before the treatment, this event was still present during the treatment.

Compared with the baseline results, a statistically significant decrease in the mean heart rate (p = 0.001), and a statistically significant increase in the mean APC per hour (p = 0.049), APC per 1000 beats (p = 0.004) (Figure 1), VPC per hour (p = 0.002), VPC per 1000 beats (p = 0.003) (Figure 2) and Lown–Wolf grades of VPC (p = 0.001) were observed in Holter ECG analysis obtained during the 5-FU treatment (Table 2).

When the patients were compared according to age, sex, type and stage of disease, setting of the treatment (adjuvant vs. palliative), presence of a central catheter, diabetes and hypertension, no significant difference was observed.

**Discussion**

Twenty-seven patients were evaluated with 24 h ambulatory Holter ECG monitoring before and during the first cycle of LV5FU2 chemotherapy for cardiac rhythm and ischaemia. In these patients without significant baseline cardiac abnormalities, chemotherapy was found to cause a statistically significant decrease in the mean heart rate (p = 0.001) and a statistically significant increase in the mean atrial premature complexes per hour (p = 0.049), ventricular premature complexes per hour (p = 0.002) and Lown–Wolf grades of VPC (p = 0.001).

Cardiac adverse events secondary to 5-FU therapy are mainly ischaemic events manifested as ST segment changes with or without angina and rarely as myocardial infarction as well as ventricular dysfunction caused by reversible myocardial depression. Rhythm abnormalities are less frequently reported and less well studied (4,8,9).

Ambulatory Holter ECG monitoring is a useful way of studying cardiac rhythm. It permits the registration of cardiac activity during a long period of time. Therefore, it is more sensitive than regular ECG recordings for cardiac rhythm changes. In general, the recordings are obtained with the aid of only three leads. Meanwhile, its ability to screen the changes concerning the morphology of QRS reflections and ST intervals is not null, but limited.

The majority of the studies on 5-FU cardiotoxicity evaluated parameters, such as clinical findings, cardiac enzymes and 12-lead ECG changes. Holter ECG monitoring was less frequently used. The few studies on Holter ECG monitoring had discrepancies mainly because of the difference of 5-FU schedules. 5-Fluorouracil can be administered with different schedules according to its dose, duration of infusion and combined drugs. In each schedule, the mechanisms of action as well as of toxicity of the drug may change. So, different schedules may have different cardiac toxicity profiles.

The higher rate of cardiac events secondary to 5-FU was reported as a result of a study based on

| Table 2 The results obtained as baseline and during the chemotherapy |
|---------------------------------------------------------------|
| **Before chemotherapy** | **During chemotherapy** | **p** |
| **Heart rate** | | |
| Mean heart rates | 93.14 ± 16.35 | 81.59 ± 12.74 | p = 0.001 |
| Mean of minimum heart rates | 56.22 ± 12.37 | 54.88 ± 10.10 | p = 0.586 |
| Mean of maximum heart rates | 155.44 ± 27.82 | 138.44 ± 21.61 | p = 0.021 |
| **APCs** | | |
| Mean APC per hour | 18.88 ± 53.96 | 45.34 ± 53.80 | p = 0.049 |
| Mean APC per 1000 beats | 25.69 ± 120.31 | 33.65 ± 115.07 | p = 0.004 |
| **VPCs** | | |
| Mean VPC per hour | 12.74 ± 29.63 | 38.14 ± 42.09 | p = 0.002 |
| Mean VPC per 1000 beats | 2.74 ± 6.74 | 7.51 ± 8.76 | p = 0.003 |
| Complex ventricular arrhythmia | 1 pt (3.7%) | 6 pts (22.2%) | p = 0.001 |

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Holter ECG monitoring. This study evaluated the incidence and duration of ischaemic ST changes in 27 patients. Overt angina pectoris was found in one patient while asymptomatic ST changes were observed in six (24%) patients before the treatment and in 17 (68%) patients during the treatment. They also reported the incidence of ischaemia per hour was 0.05 ± 0.02 before therapy and 0.13 ± 0.03 during therapy (p < 0.001) and duration of ECG changes per hour was 0.6 ± 0.3 before therapy and 1.9 ± 0.5 during therapy (p < 0.01) for each patient (13). In our study with the same number of patients, we did not observe ischaemic ST-T changes. Rhythm abnormalities concerning APC and VPC were remarkable. During the therapy, mean APC and VPC per hour as well as per 1000 beats were increased.

An increase of heart rate secondary to 5-FU treatment was suggested as one of the reason of cardio-toxicity because of the increase of oxygen requirement of myocardium (13). In contrast, we

Figure 1 Holter ECG records showing baseline sinus rhythm (A) and APC during chemotherapy (B) in a patient with colon cancer receiving bolus plus infusional 5-FU and leucovorin
found a decrease in mean heart rate during chemotherapy. This decrease in heart rate during chemotherapy may be explained by some factors other than drugs. Before the chemotherapy the patients are free of treatment procedures and are more active. The relatively prolonged rest periods during chemotherapy may result in decreased mean heart rate.

It seems that cardiac side effects are more frequent with higher doses of 5-FU. In a study of Forni et al. (4), the incidence of cardiotoxicity was reported in 7% of patients treated with a higher dose of 5-FU regimen compared with 2% for conventional regimen. They also reported that, although there was a difference between these two groups, the cumulative 5-FU dosages required for the initiation of symptoms were similar and ranged between 1500 and 7000 mg.

The effect of external factors, such as folinic acid (leucovorin), antiemetics, infusion fluids and psychological factors, are not to be neglected. Folinic acid enhances the cytotoxic effects of 5-FU. By biological modification, this is accompanied also in general by an increase in toxicity. Meanwhile, folinic acid was

Figure 2 Holter ECG records showing baseline sinus rhythm (A) and VPC during chemotherapy (B) in a patient with colon cancer receiving bolus plus infusional 5-FU and leucovorin
not found to increase the cardiac toxicity of 5-FU in a study where intermediate dose folic acid was given with 5-FU in patients with advanced gastrointestinal system cancers (8).

5-Hydroxy-tryptamine 3 (5-HT3) antagonist antiemetics have been studied with respect to cardiac effects in various clinical trials and granisetron was reported to have the least cardiotoxic effect. Low-dose oral granisetron was the standard antiemetic used in these patients and do not seem to contribute significantly to the cardiac changes observed (14).

It is well known that the rate of cardiotoxicity increases significantly with the presence of previous cardiac disease. Patients with a history of cardiac disorder were not included in our study and two patients were excluded because of rhythm disorder or use of drug interfering with cardiac rhythm. Therefore, our patient group is not fully representative of all population of the gastrointestinal cancer patients where a significant proportion suffers of some cardiac disorder. In the absence of an absolute contraindication for the administration of 5-FU in cardiac patients, these latter patients are also treated with the regimens like one used in these study patients. Such arrhythmic effects observed in our study may lead to clinically significant events in patients with a baseline cardiac disorder.

The mechanism of the 5-FU cardiotoxicity is still unclear. Some mechanisms, such as coronary arterial spasm, coronary vasculitis, direct toxic effect on myocytes, immune-mediated tissue damage and thrombotic process, were proposed (15–17). In a rat model, strial loss in cardiac muscle and oedema in muscle fibres were showed after 12-h exposure to 5-FU (18). It can be concluded that longer infusion of 5-FU can induce higher adverse effects on cardiac tissues by longer exposure and by such mechanisms occurring by longer exposure. Further studies evaluating the effect of the duration of exposure to 5-FU will be important for clarifying the effects of duration on cardiac toxicity. Especially longer holter monitoring recordings can be interesting to assess when the VPCs settle and when they decrease.

In a prospective study, we have observed significant prolongations of Q-Tmax and of Q-T dispersion 24 h of LV5FU2 chemotherapy. These events persisted and became more important during all the 6-month duration of chemotherapy (p < 0.05) (10). Drug-induced prolongation of Q-T interval is found associated to significant risk of malignant arrhythmias and sudden risk. This may be also lead to less serious rhythm disorders observed in this study or the rare cases of sudden death observed during 5-FU treatment. Further studies of ambulatory ECG monitoring assessing the correlation between Q-T changes and ventricular arrhythmias in asymptomatic patients may be useful. It might be possible to define a group of patients for whom more detailed cardiac investigation/monitoring may be important and cost-effective.

Ventricular ectopic beats are found in standard ECGs of 1% (19) and in 40–75% of 24–48 h continuous ambulatory ECG recordings of clinically normal individuals (20). The prevalence of VPCs increase with age (21) and both slow and fast heart rates can provoke the development of VPCs (22). Complex forms of VPC may accompany transient myocardial ischaemia (23) and heart failure (24). In the absence of underlying heart disease, the presence of VPCs usually has no impact on the life of individuals (20). In patients with cardiac disorders, such as ischaemic cardiomyopathy with or without congestive heart failure, complex ventricular ectopy, can result in mortality via increasing the risk of ventricular tachycardia and ventricular fibrillation (25). Our findings concerning the increase in VPC can be more important for patients with cardiac disorders.

Regimen based of long infusion of 5-FU are widely used in the treatment of gastrointestinal cancers. LV5FU2 is the best known and often accompany newer agents, such as CPT-11 (26), oxaliplatine (27) or gemcitabine (28). Beside its higher efficacy, the main advantage is the lower toxicity compared with regimens based on bolus administration of 5-FU. Newer agents introduced in the treatment of gastrointestinal cancers, such as CPT-11 or oxaliplatin do not replace these regimens, but are often combined to them for enhanced activity. Newer fluoropyrimidines are becoming an alternative to 5-FU with similar activity and the ease of oral administration. These seem to share the same cardiac toxic effects as 5-FU (29).

In conclusion, 5-FU leads to an increase in ventricular and atrial cardiac premature complexes. The clinical significance and mechanisms of this kind of cardiac effects have to be elucidated to permit a safer administration of 5-FU and related drugs in patients with or without cardiac disorders.

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