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Evaluation of Cardiotoxicity of a Combined Bolus plus Infusional 5-Fluorouracil/Folinic Acid Treatment by Echocardiography, Plasma Troponin I Level, QT Interval and Dispersion in Patients with Gastrointestinal System Cancers

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Objective: To evaluate the cardiotoxicity of LV5FU2 regimen (bolus plus infusional 5-fluorouracil/folinic acid) treatment by non-invasive methods such as echocardiography, plasma troponin I (TnI) level, QT interval and QT dispersion on ECG.

Methods: Twenty-two patients with gastrointestinal cancer who received LV5FU2 chemotherapy were evaluated prospectively during 12 cycles of chemotherapy. Plasma TnI assay and ECG recording analyses were performed before the first cycle, at 24 h, before each cycle until cycle 6 and every three cycles thereafter. The longest QT interval measurement on each recording corrected with Bazzett's formula was considered as QTmax and the difference between the QTmax and the shortest corrected QT interval was considered as QT dispersion (QTd). A complete M-mode, 2D and color Doppler echocardiogram was performed at baseline and at the first, third and sixth months of treatment.

Results: Echocardiography did not show any significant change in either systolic or diastolic functions. Also, TnI measurements were found to be below detectable level in all patients and in all measurements. Meanwhile, significant prolongations of QTmax and QTd were observed as early as 24 h after first administration of chemotherapy. These events persisted and became more important over the duration of chemotherapy ($P < 0.05$).

Conclusions: The clinical implication of these findings as predictive factors for subsequent events such as malignant arrhythmias in patients taking 5-fluorouracil-based chemotherapy need longer follow-up and further detailed evaluations.

Key words: 5-fluorouracil – cardiotoxicity – echocardiography – troponin I – QT dispersion

INTRODUCTION

Prospective studies have demonstrated that treatment with 5-fluorouracil (5-FU) chemotherapy leads to cardiac adverse events with an incidence ranging from 1.6 to 8.0% (1–4). This incidence was found to be about 10 times higher in patients with a history of cardiac disease compared to those without cardiac problems (15.1 versus 1.5%, respectively) (5). This cardiac toxicity consists generally of an angina accompanied by ST segment changes and/or left ventricle dysfunction. Myocardial infarction, rhythm abnormalities and sudden death have also been reported (1,4,6).

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ST segment changes resolve rapidly and left ventricle dysfunction, which is the most common abnormality secondary to 5-FU, reverses within 6 months after the completion of treatment. Thus, cardiac events secondary to 5-FU are generally reversible, but severe damage to cardiac tissues or death are encountered, although rarely (6,7). Several methods have been proposed to identify early cardiac changes which lead to higher risk of irreversible and serious cardiac events. Monoclonal antimyosin antibody imaging (8,9), study of cardiac autonomic function (10) and endomyocardial biopsy (11) were used for this purpose. The complexity and high cost of these methods limit their use in daily clinical practice.

Troponin I (TnI) is a protein specific to myocardial tissue. An increase of its level in serum is an early, sensitive and specific marker of myocardial injury, including minor myocardial damage (12). It has been observed that this cell-structural protein is detected in the blood of patients with acute coronary

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syndrome (13), after coronary angioplasty (14), in heart failure (15), acute myocarditis (16) and other clinical situations in which conventional markers of myocyte necrosis are often negative (17).

Electrocardiography (ECG) is a simple method which records the electrical potential changes of the myocardium represented on the body surface. It is a very useful tool to evaluate cardiac rhythm and myocardial ischemia.

The interval between Q and the end of T corresponds to the period from the beginning of depolarization until the end of repolarization of the cardiac muscle. The differences in QT interval, i.e. QT dispersion (QTd) reflect a functional heterogeneity between different regions of the myocardium when it is larger than normal. It has been shown that the QTd is predictive of mortality in normal subjects (18) and different groups of patients including those suffering from diabetes (19–21) and myocardial infarction (22). QTd has also been related to subsequent occurrence of arrhythmias in these patients and in healthy subjects (18).

Echocardiography is a non-invasive tool of imaging which explores the cardiac structures. With the assistance of computers, it also enables observation and measurement of systolic and diastolic functions of the heart and is widely used in daily clinical practice for these purposes.

It has been claimed that cardiac toxicity is more common when higher doses of 5-FU are administered as longer infusions instead of regimens based on bolus administration (1,6). The administration method of LV5FU2, called the de Gramont schedule, is one of the preferred chemotherapy regimens in the treatment of colorectal cancer because of its lower hematological and gastrointestinal toxicity. In this study, we aimed to evaluate the cardiac effects of this regimen with non-invasive methods, namely physical examination, ECG, echocardiography and serum TnI level measurements.

SUBJECTS AND METHODS

Study Population

Patients receiving LV5FU2 chemotherapy regimen for gastrointestinal cancer in our institute from September 2002 to March 2003 were enrolled into the study. Those with a history of heart disease (angina, hypertension or valvular diseases), with a left ventricular ejection fraction (LVEF) < 50%, or with renal (serum creatinine > 1.5 mg/dl) or liver (bilirubin > 2 mg/dl, aspartate aminotransferase > 2× the upper limit of normal) disease were excluded. Twenty-two patients were included in the study. None of the patients were receiving medication affecting cardiac function and QT interval such as class Ia or class III antiarrhythmic agents.

The LV5FU2 chemotherapy regimen consisted of classical de Gramont regimen (LV 200 mg/m^2 2 h infusion; 5-FU 400 mg/m^2 bolus and 5-FU 600 mg/m^2 22 h infusion, on days 1 and 2, repeated every 2 weeks). Twenty patients received adjuvant, and two patients received palliative treatment. All patients took granisetron 1 mg/day p.o., a 5-HT$_3$ antagonist, as antiemetic prophylaxis each day of chemotherapy.

Before enrolment , patients were informed on the methods and aims of the study and written consent was obtained. Enrolment into the study did not affect treatment regimen.

Study Protocol

Clinical examination, plasma TnI assay, ECG, chest X-ray and echocardiography were part of the baseline evaluation. Chemotherapy was administered intravenously with the schedule mentioned above, via a central venous catheter. Plasma TnI assay and ECG analyses were performed before the first cycle, at 24 h, before each cycle until cycle 6 and every three cycles thereafter. A complete M-mode, 2D and color Doppler echocardiogram was performed at baseline and at the first, third and sixth months of therapy. For all patients, the duration of chemotherapy and follow-up was planned as 6 months.

Electrocardiography

Twelve-lead ECGs were recorded before, and 24 h after, the beginning of the first cycle, and in consecutive cycles before the administration of chemotherapy using the same ECG device. Parameters such as heart rate and rhythm, QRS duration (QRSd), presence of ST abnormalities, QT interval and total QRS voltage were analyzed. QT interval was corrected as described below according to heart rate. The QRS voltage was measured by summating the distance from the peak of R wave to the nadir of S wave in each of the six standard limb leads. These leads were chosen to minimize variability in QRS voltage due to lead placement.

QT Interval Duration

RR and QT intervals were measured with a ruler on the resting ECG tracing: five consecutive beats were considered on each lead. The QT interval was measured from the beginning of the QRS complex to the end of the down slope of the T wave where it reaches the isoelectric line. When a U wave was present, the QT interval was measured to the nadir of the curve between the T and U waves. The QT interval corrected for the previous cardiac cycle length (QTc) was calculated according to Bazzett's formula [$QTc = QT/(RR)^{1/2}$] (23). Two observers who were unaware of the state of the patients measured all of the intervals. The QTc for each subject was considered to be the mean value of the five calculated intervals and the mean of reading of both observers to minimize inter observer variability. In any lead, QTc > 440 ms was considered abnormally prolonged. The maximum QTc (QTmax) of each recording was considered for comparisons and calculation of means.

QT Interval Dispersion

The difference between the maximum and minimum corrected QT intervals on any of the standard 12 leads on the same ECG was considered as QTd. The measurements were performed as mentioned above by two investigators, who were ignorant as to

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the identity of the patient and to which cycle of chemotherapy would be administered. The mean of the measurement of both observers was adopted as the final result. QTc dispersion > 60 ms was considered abnormally prolonged.

Echocardiographic Evaluation

Standard 2D and M-mode echocardiographs were obtained with a Hewlett-Packard model Sonos 2000 imaging system using 2.7 and 3.5 MHz transducer. M-mode, pulsed-wave and continuous-wave Doppler recordings were made with a speed of 100 mm/s. Cardiac dimensions were measured according to the recommendations of the American Society of Echocardiography (24). To assess left ventricular diastolic function, mitral flow velocity was recorded using pulse-wave Doppler in the apical 4-chamber position with the sampling window placed at the tip of the mitral leaflets. The angle between the cursor line and the direction of diastolic flow was kept as small as possible and was determined to be <20° in each record. Measurements included peak early mitral valve filling velocity (E wave), peak atrial filling velocity (A wave), ratio of peak early and atrial filling velocity (E/A) and deceleration of the E wave (DT). The isovolumetric relaxation time (IVRT) was measured by moving the sampling window to a position between the anterior mitral leaflet and left ventricular outflow tract. A complete M-mode, 2D and color Doppler echocardiogram were performed at baseline and at first, third and sixth months of chemotherapy. Left ventricle ejection fraction (LVEF%) was calculated according to modified 20-disks Simpson formula.

Laboratory Methods

Blood samples were collected into a Monovette containing a sodium citrate solution (0.106 mol/l) with a dilution ratio after blood collection of 1/10 and were centrifuged at 1080 r.p.m. within 60 min to separate the plasma, which was immediately analyzed. The laboratory analysis for the determination of TnI was performed by immuno-enzymatic fluorescent assay (Immulite Turbo, International Inc., Miami, FL). This method utilizes two TnI-specific monoclonal antibodies for independent epitopes and has no detectable cross reactivity with skeletal muscle TnI. The lowest limit of detection was 0.50 ng/ml.

Statistical Analysis

All results are expressed as the mean (±SD). Statistical tests were performed using the Friedman Variant Analysis (non-parametric tests – K related samples) and Wilcoxon Signed Ranks Analysis (non-parametric tests – two related samples), and were considered significant at $P < 0.05$. Variations in LVEF values and E/A ratios were analyzed using a generalized linear model.

RESULTS

The study population included 22 patients treated with LV5FU2 regimen for colorectal and stomach cancers in our Institute. The median age of the patients was 63 (range, 44–76). Other characteristics of these patients are shown in Table 1. All the patients completed the planned chemotherapy.

Table 1. Clinical characteristics of the study population

Characteristic	*n* (%)
Performance status (WHO)	
0	6 (27.3%)
1	13 (59.1%)
2	3 (13.7%)
Gender	
Male	14 (64.0%)
Female	8 (36.0%)
Type of cancer	
Colorectal	20 (91.0%)
Stage III	19 (86.5%)
Stage IV	1 (4.5%)
Gastric	2 (9.0%)
Stage III	1 (4.5%)
Stage IV	1 (4.5%)
Type of treatment	
Adjuvant	20 (91.0%)
Palliative	2 (9.0%)

Clinical Course

Baseline cardiac functions were within normal limits in all patients. None of the patients had a clinically evident acute cardiological event during or soon after administration of the drugs. They did not develop symptoms of either ischemic heart disease or heart failure during the follow-up.

Cardiac TnI

A total of 198 blood samples were collected during 264 treatment cycles from 22 patients for TnI measurements. At the baseline evaluation, as well as before and at 24 h of the first cycle, before each cycle until cycle 6 and every three cycles thereafter, the TnI value was within the normal ranges in all cases.

ECG

No rhythm abnormality, ischemic ST segment or QRS duration or voltage changes in ECG records were observed either before or after chemotherapy. Baseline QTd was also within normal limits in all patients except three. However, significant increases in QTmax and QTd were observed as early as 24 h after administration of chemotherapy ($P < 0.05$). These persisted and became increasingly marked in subsequent cycles. Sample ECG tracings showing recordings at the start and at the end of study follow-up can be seen in Fig. 1. When each QTmax and QTd measurements performed every three cycles

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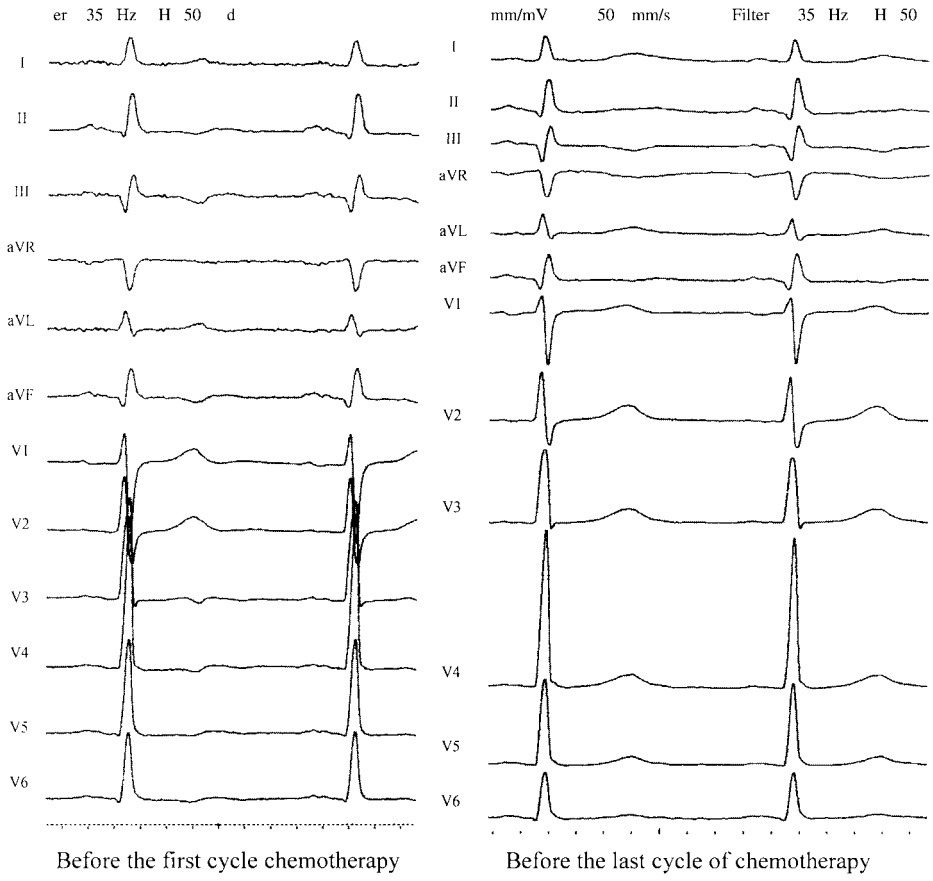


Figure 1. Sample ECG recording before the first and last cycle of chemotherapy. Subject is a 61-year-old man receiving adjuvant chemotherapy for colorectal cancer. In the first ECG, the QTmax is 372 ms on D1 and QTmin is 335 ms on V3 or V2, QTd is 37 ms. In the second recording, QTmax is 456 ms on V4 and QTmin is 380 ms on V1, QTd is 76 ms.

were compared to the previous ones, the differences were statistically significant (Fig. 2) (Table 2).

Echocardiography

Baseline echocardiographic parameters were within normal range in all patients. Any significant abnormality was observed after the chemotherapy including the parameters concerning systolic and diastolic functions. Baseline and follow-up echocardiographic findings are shown in Table 3.

DISCUSSION

In this study, 22 patients receiving LV5FU2 chemotherapy regimen were evaluated with serial echocardiographic examinations, plasma TnI assays and ECG recordings. Echocardiography did not show any significant changes in either systolic or diastolic functions. Also, TnI measurements were found to be below detectable level in all patients and in all measurements. Neither did ECG recordings show any change in favor of a coronary ischemia, injury or other serious rhythm abnormalities. Meanwhile, significant prolongations of both QTmax and QTd were observed as early as 24 h after administration of chemotherapy. These events persisted and became more important over the duration of chemotherapy.

The cardiac toxicity of 5-FU can be serious, but is not frequent. In the absence of previous history of cardiac disease, it can be observed in as few as 1.5% of patients despite careful

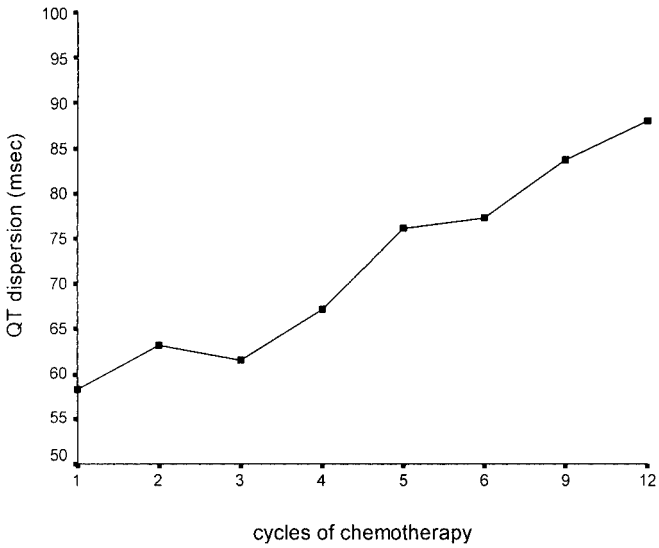


Figure 2. QT dispersion changes of whole group by the treatment according to cycles of chemotherapy. Number of cycle corresponds to the cycle before which the studies were made.

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Table 2. The corrected QTmax and QTd results of the study population

Time	QTmax (ms) (mean ± SD)	QTd (ms) (mean ± SD)
Baseline	438.65 ± 22.91[a,c]	58.27 ± 13.34[b,d]
24 h	467.08 ± 25.94[a,c]	64.31 ± 15.42[b,d]
Cycles*		
2	465.50 ± 29.72[c]	63.18 ± 11.65[d]
3	470.64 ± 33.72[c,e]	61.58 ± 10.69[d,f]
4	473.97 ± 33.88[e]	67.24 ± 12.27[f]
5	482.73 ± 33.86[e]	76.09 ± 16.11[f]
6	492.11 ± 34.08[e,g]	77.30 ± 11.15[f,h]
9	497.97 ± 30.58[g,i]	83.72 ± 8.71[h,j]
12	506.24 ± 31.05[i]	88.13 ± 9.78[j]

*Cycle before which the studies were made.
[a]$P = 0.050$; [b]$P = 0.040$; [c]$P = 0.060$; [d]$P = 0.030$; [e]$P = 0.002$; [f]$P = 0.001$; [g]$P = 0.006$; [h]$P = 0.050$; [i]$P = 0.001$; [j]$P = 0.006$.

clinical follow-up (5). It is very probable that clinical evidence of an event occurring in only a small proportion of patients would not be observed in such a small group of patients.

In contrast, the cardiac toxicity of 5-FU is at least ten times more frequent in patients with a previous history of cardiovascular disease (5). So, it can be supposed that 5-FU has some effects on cardiac function which are frequently translated into clinical symptoms or signs when a pre-existing abnormality exists. It is important to elucidate these subclinical events in order to understand the mechanisms underlying the cardiac toxicity of 5-FU, which is one of the most widely used chemotherapeutic agents.

In children receiving anthracycline chemotherapy (25) and in patients with hematological malignancies receiving anthracycline chemotherapy, an increase in TnI has been reported (26,27). Recently some authors have reported that the elevation of TnI in patients treated with high-dose chemotherapy (HDCT) for aggressive malignancy accurately predicts the development of future left ventricle ejection fraction depression (17,28–30). However, we did not observe either detectable increase of TnI in serial plasma assays or any left ventricular dysfunctions, systolic or diastolic, by echocardiographic evaluation. Although all of our patients had taken 5-FU/LV treatment with a probably more cardiotoxic schedule, i.e. as longer duration infusion, left ventricular dysfunction was not observed in any of them. These results can be explained by the fact that none of the patients had pre-existing cardiac disease and the study population comprised a limited number of patients.

The QT interval reflects the repolarization of myocardium and is affected by the heart rate. It is corrected for the heart rate and is most commonly used in the assessment of abnormalities of myocardial repolarization, which can be secondary to an increase in cardiac muscle mass or prolongation of synchronization inside the heart muscle (31). It has been shown that a prolonged QT interval is associated with sudden death and poor survival in healthy subjects (18) and in a variety of clinical conditions, including newly diagnosed type 2 diabetes (20), nephropathy (32) and type 1 diabetes (33,34). The observation that the QT interval exhibits a certain degree of spatial variability on the epicardial surface (35) has led to the hypothesis that differences in the duration of the QT interval between ECGs may reflect heterogeneity in recovery of excitability (36). Non-uniformity of repolarization provides a basis for the development of malignant ventricular arrhythmias (37).

The measurement of QT interval can sometimes be difficult because of the changes in T waves, the occasional presence of U waves and the effect of electrical axis. Automated measurement had been tried to avoid these problems, but was not found to be superior to manual measurement. No particular lead had been suggested as the lead showing the QTmin or QTmax, but to simplify QT comparisons, V2 or V3 can be considered to be sufficient as the leads to measure the representative QT interval for each ECG recording (38).

In the 1990s, it was shown that the inter-lead difference of QT interval on standard 12-lead ECG recordings might provide more powerful diagnostic information than the measurement of only the maximum QT interval (39). Despite some problems in the methodology, the majority of studies suggest that increased QTd is a risk marker for future clinical events. It has been demonstrated that QTd is predictive of mortality in normal subjects and different groups of patients, including those with myocardial infarction (22), long QT syndrome (22,39), heart failure (40) and hypertrophic cardiomyopathy (41). Furthermore, a number of studies have shown that increased QTd is a marker for arrhythmic events, sudden cardiac death (40,42,43) and drug-induced proarrhythmia (44,45), in partic-

Table 3. Echocardiographic findings of all patients

Time	Echocardiographic characteristic			
	EF* (mean ± SD)	E/A* (mean ± SD)	DT* (mean ± SD)	IVRT* (mean ± SD)
Baseline	63.72% ± 5.79	0.90 ± 0.25	255.18 ± 36.04	98.40 ± 15.91
First month	62.63% ± 5.55	0.93 ± 0.23	247.96 ± 31.83	101.27 ± 19.10
Third month	62.86% ± 4.76	0.85 ± 0.18	262.08 ± 35.96	101.36 ± 19.71
Sixth month	63.95% ± 4.22	0.91 ± 0.18	259.77 ± 31.30	102.72 ± 15.33

*EF: ejection fraction; E/A: ratio of peak early and atrial filling velocity; DT: deceleration time; IVRT: isovolumetric relaxation time.

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ular, broad QTd seems to predict the occurrence of the drug-induced Torsade de Pointes (46).

In a study conducted in patients receiving high-dose chemotherapy, including high-dose cyclophosphamide with peripheral blood stem-cell transplantation (PBSCT), it was reported that QTd could predict acute heart failure after high-dose cyclophosphamide administration. It was speculated that lengthening of the QTd showed increases in ventricular recovery-time dispersion caused by local damage, or multifocal degeneration of cardiac muscle. QTd is a sensitive marker, which can show abnormalities earlier than they would appear on echocardiography (47).

In patients receiving anthracycline-based chemotherapy, it has been reported that QTd increased with higher cumulative doses of anthracycline (48–51). This increase has shown an important inverse correlation with the decrease of left ventricular ejection fraction in two studies (48,49). This relation was not confirmed by two others studies (50,51). The effect of 5-FU on QTd was not reported previously. In our study, QTd increased after 5-FU-based chemotherapy, but this increase was not accompanied by an evident left ventricular dysfunction.

Unfortunately, it is still difficult to make any conclusive remarks on the possible impact of the QT interval prolongation and QTd increase, corrected or not, on the decisions concerning 5-FU-based chemotherapy and the cardiac outcome of patients. This is because our results concern only a small group of patients followed up only during the treatment. It is very probable that any risk for events such as arrhythmias can disappear with the reversal of the prolongation of the QT interval and QTd. Subsequent studies with longer follow up are being planned in order to answer these questions. However, it can be concluded that, with the knowledge that higher cardiotoxicity secondary to 5-FU is observed in patients with a history of cardiac disease, special attention should be paid to the cardiological follow up of patients when the ECG events mentioned above are observed.

There is no information on the possible role of folinic acid on QT interval and QTd. But it is well documented that the addition of folinic acid to 5-FU does not have any influence on cardiac effects of 5-FU (5,6). However, the increased QTd was reported to be an effect of several medications such as antiemetics. The antiemetic drug taken by our patients was granisetron. Some reports claim that 5-HT_3 antagonists can have minor reversible effects on cardiac rhythm (52–54). These are reflected by ECG changes, including QTd. Among these drugs, granisetron was found to have the least effect on cardiac rhythm and is the one proposed for most safety in patients with heart disease (53–56). It is difficult to ignore the contribution of granisetron to the changes of QT interval and QTd of our patients. But any effect of granisetron on cardiac rhythm is expected to be of short duration and rapidly reversible (54). The ECG recordings were taken before the chemotherapy and granisetron administration, and so the interval between the last granisetron dose and ECG recording was at least 12 days. Thus, we conclude that the effect of granisetron on QTd in our patients was negligible, if not absent.

In conclusion, LV5FU2 chemotherapy leads to significant increases in QT interval and QTd in a group of 22 patients without overt cardiac disease. Special care should be taken to observe whether this effect interferes with other medications such as antiarrhythmic agents with some influence on QT interval. Longer follow-up with further detailed evaluations are required to establish the clinical implication of this finding as a predictive factor for subsequent events such as malignant arrhythmias in patients taking 5-FU-based chemotherapy.

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