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ORIGINAL ARTICLE

Corrected QT prolongation among chemotherapy – treated patients: A study of a Romanian center

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Summary

Purpose: *Chemotherapy cardiotoxicity sometimes occurs as QTc prolongation, which may lead to ventricular arrhythmia. We assessed incidence of QTc prolongation among chemotherapy-treated patients.*

Methods: *We enrolled 396 consecutive patients receiving chemotherapy in the Oncology Institute of Cluj-Napoca, Romania. 870 ECGs were performed at baseline and every 2 months, for 5 assessments, during 2016.*

Results: *Most patients were diagnosed with gastro-intestinal tumors and received regimens containing more than one drug. No particular chemotherapy regimen was proved to significantly increase QTc. Maximum QTc was recorded after 4 months, when we also found the maximum incidence of increased QTc (>470ms), of 3.73% and of increased ΔQTc (>60ms), of 4%. Female gender was associated with a higher baseline QTc=421 ms, ± 26.9 (p=0.02). Age was linked to higher QTc and is also an independent variable predicting QTc prolongation (for QTc>480ms, p=0.02), as well as increase of ΔQTc (p<0.001). The number of prior chemotherapy lines correlates with baseline QTc (p<0.0001), with QTc prolongation after 2 months (p=0.01) and predicts higher ΔQTc after 2 months (p=0.01), although within normal range. There was no additive effect during all the 5 assessments.*

Conclusion: *Our results confirm QTc prolongation with chemotherapy and a special attention should be paid to previously treated patients and to elderly patients.*

Key words: *chemotherapy, cardiotoxicity, QTc prolongation*

Introduction

GLOBOCAN estimated the incidence of cancer in 2012 to more than 14 million new cases which will rise to 19 million in 2020, with more than 50% being alive at 5 years from initial diagnostic. Since virtually all systemic oncological treatment could have cardiac toxic effect, long-term survivors could develop cardiotoxicity, which became the second most frequent cause of morbidity and mortality to this population [1].

Chemotherapy cardiotoxicity, besides coronary syndromes, hypertension and left ventricular impairment, can sometimes lead to cardiac arrhythmias, including bradycardia, heart block, or QTc interval prolongation, in patients with cancer as a consequence of pre-existing health conditions or secondary to the malignancy or its treatment [2]. The QTc interval is at this time the best, although imprecise, way to measure cardiac repolarization [3].

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Prolongation of QT interval can rarely lead to a life-threatening cardiac arrhythmia (torsade de pointes). Although not the best predictor of this pro-arrhythmic risk, it represents the main clinical marker to evaluate the arrhythmogenic risk of a drug, and it has been a common cause of withdrawal from the market for several drugs [4]. Risk factors for severe arrhythmias include QTc interval >500 ms, increase in QTc interval ≥60 ms from the pretreatment value, advanced age, female sex, electrolyte imbalance, preexisting heart conditions such as myocardial infarction, heart failure with decreased left ventricular ejection fraction, bradycardia, treatment with various drugs [5,6].

Anthracyclines, taxanes, cyclophosphamide have been linked to QTc prolongation [7] as well as some targeted therapies, such as TKIs [4,8]. There is little information about cumulative effect of anticancer drugs as well as about the effect of other chemotherapeutic drugs on QTc prolongation and their arrhythmogenic risk, actual guidelines recommended usual evaluation by echocardiography [9]. The incidence of cancer treatment-induced cardio-vascular injury varies widely, depending on the specific used therapy, duration of therapy, and underlying patient comorbidities [10].

In this study, we assessed the risk of QTc prolongation among chemotherapy-treated patients.

Methods

The 396 enrolled patients were out- and inpatients of the Oncology Institute of Cluj-Napoca, Romania, who underwent various regimens of chemotherapy. The assessments were performed at baseline and every 2 months thereafter, during 2016 (for 5 assessments). We included adult patients who were on the beginning of chemotherapy, as well as previously treated patients. We excluded patients <18 years old, patients enrolled in other clinical trials and patients with cardiac defibrillators/pacemakers.

We performed 108212-lead ECGs, out of which 870 were qualitative enough in order to be processed. ECGs were performed at baseline and at 2 months, for 5 assessments, during the year 2016 and were digitally recorded with a BTL machine, and BTL Cardiopoint build-in software was used for interval measurements. Each ECG was reviewed afterwards by at least 1 physician. The QT interval was measured from the beginning of the QRS complex to the end of the T wave, and was corrected (using Bazzet's formula) for heart rate [11,12]. We considered QTc as being normal <450ms, borderline between 450-470ms, slightly increased 471-480 ms, moderately increased 481-500 ms and severely increased >500ms. The difference between 2 consecutive assessments was referred to as ΔQTc, and was defined as normal if <30ms, borderline between 30-60 ms, and increased if >60ms [13].

We used Wilcoxon test in order to assess comparisons between different variables, and Kruskal-Wallis for independent variables to find distribution of QTc at baseline between the two genders. The Friedman test assessed variations between all cycle-ECGs and the Bonferroni correction was also applied. In order to find the normal distribution of variables, we used the Shapiro-Wilk test. The logistic regression analysis (ANOVA test) was performed to find predictors for QTc prolongation. The statistical analysis was performed using IBM SPSS Statistics 27.

Results

Patients

Out of the total of 396 patients, 52,7% were men and 47,3% women. The median age was 61 years old, with a minimum age of 18 and a maximum of 92.

Most enrolled patients were diagnosed with gastrointestinal tumors (colorectal, gastric, pancreatic tumors, GISTs) (Table 1). There was also a significant percentage of patients with ovarian cancers and with lung carcinomas.

Therapy

62% of patients received more than one chemotherapy drug at the moment of the baseline ECG assessment (Table 2). Platinum compounds were

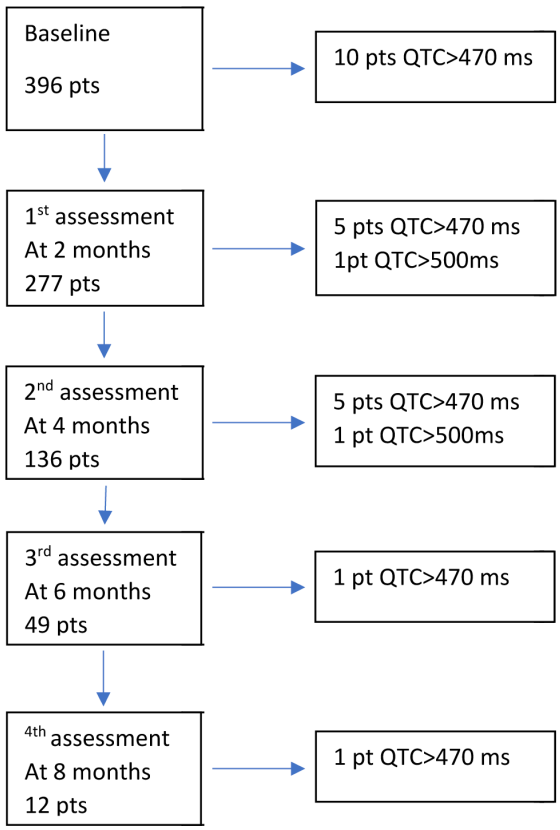

Figure 1. Flow chart of no. of patients and patients with increased QTc at baseline and during following assessments.

the agent contained in most chemotherapy regimens (42.6%). A large number of patients were also treated with fluoropyrimidine (either Capecitabine or 5-Fluorouracil). More than a quarter of patients received targeted therapies (either Bevacizumab or TKIs). Almost 20% of patients were treated with anthracyclines.

Line of treatment

At baseline, 227 patients (57%) were at the beginning of their oncological treatment, while the others were pre-treated or heavily pre-treated patients (Table 3). Included patients were followed according to general recomendations (Figure 1).

Results for QTc prolongation

Maximum QTc (of 532ms) was reached after 4 months (during the 3rd ECG assessment), when we also noticed the maximum incidence of increased QTc (>470 ms), of 3,73%. Moreover, at the same evaluation (after 4 months of treatment) we found the maximum incidence of increased ΔQTc (>60ms), of 4%.

The number of prior chemotherapy lines correlates with baseline QTc ($p<0.0001$), as well as with QTc in all ECG assessments ($p=0.02$) (Figure 2). Having ≥2 prior lines of treatment predicts QTc prolongation after 2 and 4 months ($p<0.001$) and higher ΔQTc after 2 months ($p=0.001$), although within normal range. No ventricular arrhythmia was recorded.

Age was associated with higher baseline QTc ($p<0.001$) and higher QTc in all subsequent assessments. Age was also found to be an independent variable predicting QTc prolongation, but only for baseline QTc >480ms ($p=0.03$), as well as increase of ΔQTc ($p<0.001$) throughout all ECG recordings.

As expected, female gender was associated with a higher QTc at baseline, QTc=421ms ± 26,9 ($p=0.02$). QTc was distributed rather evenly between all chemotherapy regimens. In this study, no particular regimen appears to be linked to a higher QTc.

There was no additive effect of the administered chemotherapy during all the 5 assessments of the study (Figure 3). The mean QTc at baseline was of 421ms±26.9, min QTc =327ms, max=498ms. During the following assessments, the mean QTc was of 419±26.4, 422±27.6, 418±28.8, 425±29.2ms respectively, with minimum value of QTc ranging from 326 to 369 ms and maximum QTc of 506, 532, 482 and 485 ms respectively. As seen in the following box plot, only for patients who were assessed during all the 5 ECG recordings, there is no increase of QTc during the period of the chemotherapy treatment.

Table 1. Malignancy diagnosis of the analyzed population

Neoplasm	*Percentage*
Colon	23.23
Ovary	14.65
Gastric	10.6
Lung	8
Rectal	5.8
Head and neck	4.8
Prostate	4.04
GIST	3.54
Melanoma	3.28
Hepatocarcinoma	2.78
NETs	2.5
Cholangiocarcinoma	2.27
Pancreas	1.8
Breast	1.3
Cervix	1.26
Others	10

Table 2. Main chemotherapy protocols administered to the analyzed cohort

Chemotherapy drug	*Percentage*
Platinum compounds	42.6
Fluoropyrimidine	33.3
Targeted therapy (including VGFR and TKIs)	26.5
Gemcitabine	20.9
Anthracyclines	19.1
Taxanes	17.6
Irinotecan	12.8

Table 3. Line of treatment at baseline for the analyzed patients

Line of treatment	*No. of patients*	*Percentage*
1	227	57.3
2	97	24.7
3	40	10.2
4	18	4.6
5	5	1.3
6	4	1
7	2	0.5

Discussion

Anticancer drugs are sometimes associated with QT prolongation. Additionally, drugs used for supportive care of oncological patients (e.g. antihistamines, antiemetic, antibiotics, antifungal, psychotropic drugs, etc) are also able to affect ventricular repolarization [14]. There is more and more evidence that electrophysiological changes relate both to malignancy itself and antineoplastic therapy, are clinically significant and predispose to arrhythmias. These risks are present both with traditional agents with known cardiotoxicity, such as anthracyclines, as well as newer agents, such as tyrosine kinase inhibitors and VGFR [15]. Several studies found a direct correlation between chemotherapy (especially anthracyclines) and QTc prolongation [16,17]. Kitagawa et al. found a

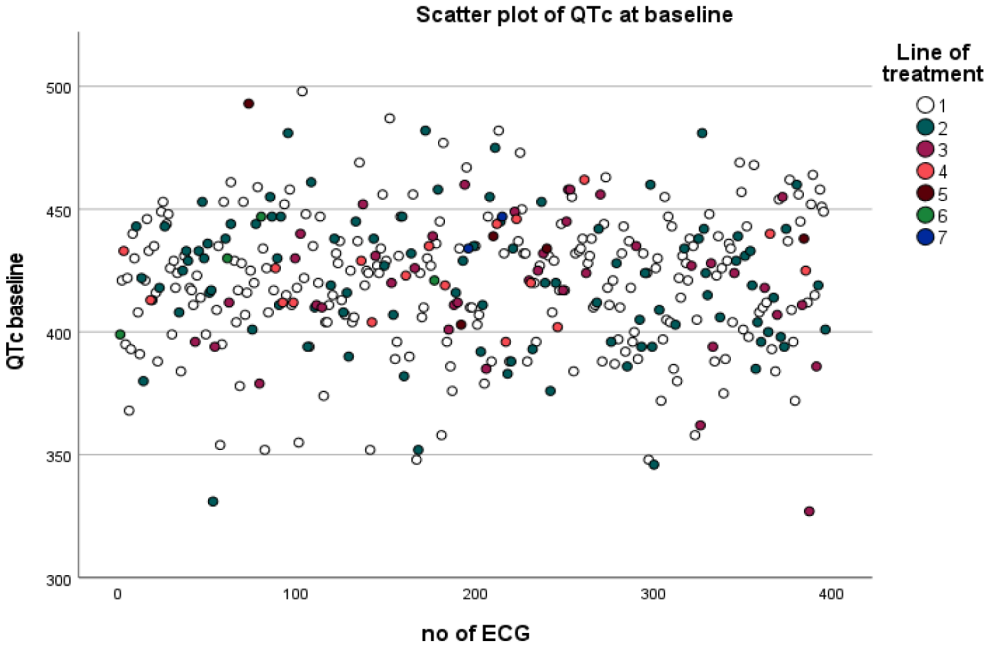

Figure 2. Scatter plot of baseline QTc, according to the line of treatment.

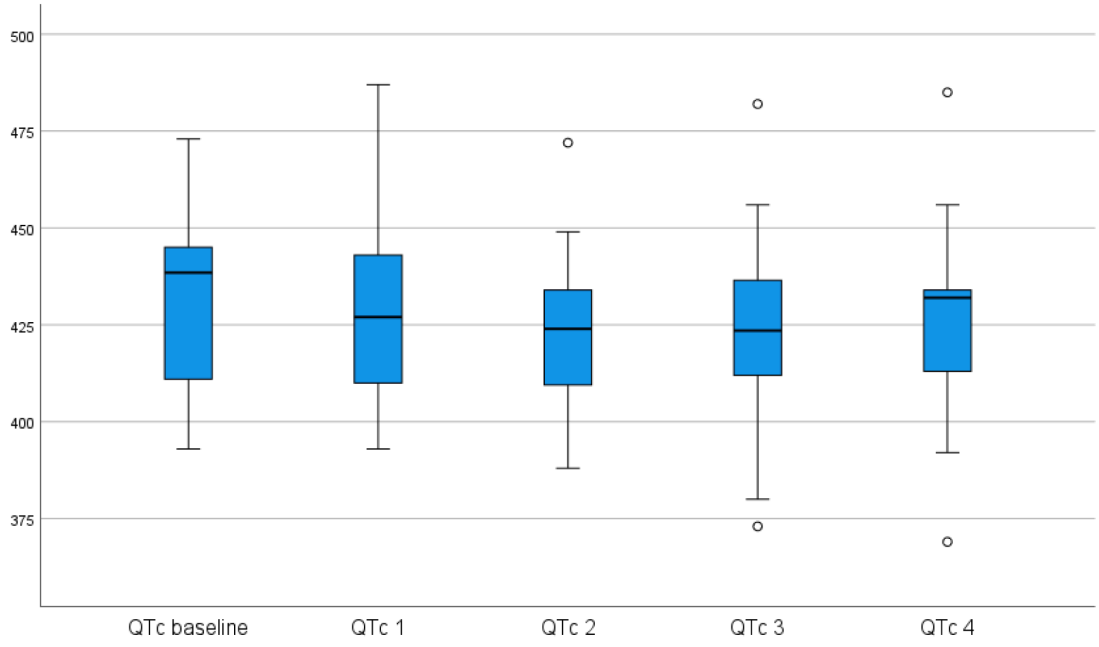

Figure 3. Box plot of QTc values among all 5 assessments, at baseline and at the other 4 assessments (performed every 2 months), only for patients who underwent all ECG recordings.

significant trend towards QTc prolongation right after chemotherapy (FEC regimen) administration, but which persisted through all cycles of chemotherapy [16].

In our study, we did not find a specific chemotherapy drug incriminated in a substantial increase in QTc. This could be explained by the fact that this study population is a very heterogeneous one, both from the point of view of malignancy as well as of the administered chemotherapeutical regimens. Moreover, most patients received more than one drug and for a lot of patients the combination of drugs contained both chemotherapy and targeted agents. Prolonged systemic treatments (maintenance strategy) control more history of the disease but with a toxicity price [18].

The dose of a QTc prolonging drug influences the risk of QTc prolongation. Although not always the case, higher doses are often associated with increased risk of QTc prolongation [19]. In this study, we found a statistically significant association between the number of lines of prior treatment and the QTc prolongation. This finding, although expected, is important as nowadays more and more patients receive multiple lines of treatment. With new emerging therapies, which become rapidly approved, our patients expect a higher chance of having better overall survival, by benefiting of multiple oncological treatments. Therefore, it is important not to ignore the cardiotoxicity hazard (referring both to impairment of the left ventricle ejection fraction and the arrhythmogenic risk) and to assess all patients from a cardiological point of view.

As expected, QTc was higher in women and in elderly patients. However, age was not a predictor of QTc prolongation in patients with normal QTc at baseline but is significantly linked to QTc prolongation if baseline QTc is >480ms, and this is also consistent with data from literature [14].

Study limitations

This is a large, prospective study on a heterogeneous population of patients undergoing various chemotherapeutical regimens. Other studies focused on more selected populations, from the point of view of pathology and chemotherapy. Our study lacked data on the patients' concomitant medication, which might play a role in the QTc prolongation as these and anticancer drugs are often metabolized by, or have the potential to inhibit, cytochrome P450 enzymes, so a pharmacokinetic interaction may cause synergistic QTc prolongation [20].

In our study, QTc did not significantly increase over the 5 assessments, but it is important to mention that we did not perform ECGs during/right after chemotherapy administration, which in other studies brought an increase in QTc, but with no cumulative effect either [14].

Conclusion

QTc is prolonged in chemotherapy-treated patients, especially in elderly patients with prolonged QTc at baseline and in pretreated patients. This reinforces the need for a continuous collaboration between oncologists and cardiologists as it is mandatory to assess and reassess from a cardiological point of view all patients undergoing chemotherapy.

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Conflict of interests

The authors declare no conflict of interests.

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