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Electrocardiograms (ECGs) in phase I anticancer drug development: the MD Anderson Cancer Center experience with 8518 ECGs

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Background: Cardiac sequelae from oncologic drugs are important in early cancer drug development. Prolongation of the corrected QT interval (QTc) by noncardiac drugs is the most common cause of drug development delays, nonapprovals and postmarketing withdrawals by the US Food and Drug Administration.
Patients and methods: We analyzed 8518 electrocardiograms (ECGs) in 525 consecutive cancer patients enrolled in 22 industry-sponsored phase I clinical trials, starting 1 January 2006.
Results: Seventy-four patients [14%, 95% confidence interval (CI) 11% to 17%] with normal QTc at baseline had QTc intervals above upper limit of normal after treatment initiation; 33 (6%, 95% CI 4% to 9%) had prolonged QTc intervals at baseline, and only one (3%, 95% CI 0% to 16%) worsened after dosing. Seven of 33 patients (21%, 95% CI 9% to 39%) with prolonged baseline QTc had normalization of QTc intervals after dosing. All QTc prolongations were clinically insignificant; study drugs were continued uneventfully. Two of 525 patients (0.4%, 95% CI 0% to 1%) experienced cardiac serious adverse events (myocardial infarction possibly related to drug and unstable atrial flutter related to metastatic disease). Both cardiac events were detected by clinical assessment, not surveillance ECGs.
Conclusion: Frequent ECG monitoring provided no clinically significant information in 525 patients in early phase trials.
Key words: anticancer, development, drug, electrocardiogram, phase I

introduction

Early phase clinical studies typically assess the optimal dose, pharmacokinetics, and toxicity of new drugs as well as how the drug of interest affects specific molecular target(s). Recent years have seen an increased focus on extensive monitoring of multiple parameters [1]. Ascertaining the cardiac effects of oncologic drugs is an important consideration in early cancer drug development and clinical trial development [2, 3]. Consequently, electrocardiograms (ECGs) are routinely carried out, both during patient screening to assess eligibility for study entry, and for the duration of the study, often with multiple ECGs carried out on a single day.

For monitoring purposes, the Guidance for Industry on the Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs was announced on 19 October 2005, by the US Food and Drug Administration (FDA) [4]. The most common cause of delays in noncardiac drug development, nonapprovals and postmarketing withdrawals by the FDA has been prolongation of the QT interval experienced by clinical trial study patients [5]. The QT interval is the duration between the start of the Q wave and the end of the T wave in the heart's electrical cycle, and it represents electrical depolarization and repolarization of the ventricles. A prolonged QT interval is a marker for ventricular tachyarrhythmia, such as torsades de pointes, and an important risk factor for sudden death [2, 6].

The toxicity-related death rate in phase I oncology trials is 0.49% [7]. Determining the threshold for concern regarding the risk assessment of anticancer drugs *vis-à-vis* cardiac safety and their risk/benefit ratio and its evaluation is of special importance, since these drugs are being developed for the treatment of frequently fatal cancers. Here, we reviewed 8518 ECGs carried out in 22 consecutive studies (525 patients) using early phase experimental drugs.

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patients and methods

study design

We undertook a retrospective chart review study to assess the frequency of cardiac events revealed by the ECGs of patients treated on phase I clinical studies. We reviewed the medical records of 525 consecutive patients treated on 22 industry-sponsored phase I clinical trials, all using early phase experimental drugs, starting on 1 January 2006. All testing and drug administration was carried out in the Clinical Center for Targeted Therapy of the Department of Investigational Cancer Therapeutics at The University of Texas MD Anderson Cancer Center. All ECGs carried out on study patients were reviewed. QTc prolongation is most likely to occur at peak drug concentrations and in a delayed fashion when the QT prolongation is related to the accumulation of a metabolite in tissue. Most QTc prolongation was seen in the first 24 h after dosing, but this may be due to the fact that most of the ECG monitoring occurred in this time period of the study. In the 22 industry-sponsored trials comprising this study, all patients had baseline ECGs done within 1 week before the study entry. Postdose ECGs were primarily done at 1, 6, 12 and 24 h after the first dosing in the first treatment cycle. Subsequent ECGs were generally carried out during the first 4 weeks of the study on which patients were enrolled and at their withdrawal visits. For some trials, ECGs were carried out throughout the duration of the trial. These ECGs were mostly carried out in accordance with FDA requirements. In some situations, sponsors required additional ECGs based on preclinical findings. Our investigators did not, however, perform additional ECGs unless clinically indicated. This study and all treatments were approved by the MD Anderson Institutional Review Board in accordance with its guidelines.

Patient characteristics were summarized using median (range) for continuous variables and frequency (percentage) for categorical variables. A 95% confidence interval (CI) of the QTc rate was calculated based on a binomial distribution.

definition of QTc prolongation

The QT interval is dependent on the heart rate. With a faster heart rate, the QT interval is shorter. Therefore, an adjustment for the heart rate can improve the detection of patients at increased risk of ventricular arrhythmias. The standard clinical correction is to use Bazett's formula [8], which calculates the heart rate-corrected QT interval, known as QTc. Electronic ECG machines perform this task automatically.

Ideally, QTc monitoring needs to be based on the given class of drugs or degree of preclinical arrhythmogenic potential. Of the agents administered as part of this analysis, one drug was associated with second degree atrioventricular blockage in animals, two drugs had *in vitro* data showing interaction with the human *Ether-à-go-go*-related gene (hERG) channel protein, which is a potassium channel necessary for normal cardiac electrical activity, but no QT changes were demonstrated *in vivo*. One drug showed a slight QT prolongation *in vivo*. Interestingly, the protocol with this drug did not use QT interval as an exclusion criterion [9].

Some trials excluded patients with QTc ≥500 ms. We did not use National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) criteria for QTc prolongation. For CTCAE grading, grade I is QTc 450–480 ms and grade II is QTc 481–500 ms, regardless of gender. For this study, QTc prolongation was defined as a QTc interval above 470 ms for women and 450 ms for men, and an increase of 10% above baseline in patients with prolonged QTc denoted worsening of the QTc interval [10].

results

patient demographics

A total of 525 patients were included in this study, of whom 476 were enrolled on one phase I study and 49 were enrolled on more than one study ($n = 40$ for two studies, $n = 7$ for three studies and $n = 2$ for four studies). Demographics and cardiac risk factors are shown in Table 1. Two hundred and fifty-three patients (48%) were men and 272 patients (52%) were women. Patients' age ranged from 18 to 85 years, with a median of 58 years. Of the 525 patients reviewed in this study, 277 (53%) had a known history of hypertension, 122 (23%) had hyperlipidemia, 80 (15%) had diabetes mellitus and 45 patients (9%) had a known history of coronary artery disease. Thirty-five percent (188/525) of patients had only one cardiac risk factor, 20% (103/525) had two, 6% (31/525) had three and 2% (11/525) had four associated cardiac risk factors. The vast majority of studies [12/22 (55%)] were first-in-human, and the most common target was the PI3K-mTOR pathway. All studies employed single agents for therapy, and only one included a cytotoxic agent (Table 2).

ECG findings

Patients had an average of 16 ECGs, mostly in the first 4 weeks of study. Seventy-four patients [14%, 95% CI 11% to 17%] with

Table 1. Patient characteristics

Gender	
Male	253
Female	272
Age (years)	
Median	58
Range	18–85
Cancer groups (%)	
Gastrointestinal	161 (30.7)
Melanoma	113 (21.5)
Genitourinary	47 (9.0)
Head and neck	37 (7.0)
Breast	37 (7.0)
Gynecological	34 (6.5)
Thyroid	27 (5.1)
Lung	26 (5.0)
Sarcoma	26 (5.0)
Neuroendocrine	7 (1.3)
Lymphoma	5 (1.0)
Unknown primary	3 (0.6)
Neurofibromatosis	1 (0.2)
Thymoma	1 (0.2)
No. of prior therapies	
Median	4
Range	0–15
Associated cardiovascular comorbidities, *n* (%)	
0	192 (37)
1	188 (35)
2	103 (20)
3	31 (6)
4	11 (2)

Table 2. Drugs used as single agents in 22 sponsored phase I trials

First-in-human drugs	12 (55%)
Not first-in-human drugs	10 (45%)
PI3K/AKT/mTOR pathway inhibitors	4
c-MET inhibitors	2
RAS/RAF/MEK pathway inhibitors	2
Histone deacetylase inhibitors	2
Hsp90 inhibitors	1
Proteosome inhibitors	1
Cytotoxic chemotherapy	1
Other agents	9

Table 3. ECG findings

	No. of patients (%)
Normal QTc at baseline and prolonged QTc post dose	74 (14)
Prolonged QTc at baseline and	33 (6)
-prolonged QTc post dose <10% of baseline QTc	26
-prolonged QTc post dose ≥10% of baseline QTc	1
-normal QTc post dose	7

normal baseline QTc developed prolonged QTc after dosing (44 [62%] after cycle 1, 23 [31%] between cycles 2 and 6, and 7 patients [9%] after cycle 7 and beyond or unknown). Thirty-three patients (6%, 95% CI 4% to 9%) had a prolonged QTc at baseline. Of these 33 patients, 26 also had prolongation after dosing. Seven of 33 patients (21%, 95% CI 9% to 39%) with prolonged QTc at baseline had a normal QTc after dosing. One patient with a prolonged QTc at baseline had an increase in QTc interval of ≥10% after dosing (Table 3).

All QTc prolongations were deemed clinically insignificant and study drugs were continued without adverse sequelae. Two of 525 patients (0.4%) experienced cardiac serious adverse events (SAEs). These events were atrial flutter with hypotension attributable to tumor metastatic to the heart ($n = 1$), and myocardial infarction (MI) ($n = 1$). The first patient presented with dyspnea and was found to have hypotension and atrial flutter on cycle 2 day 15. The second patient was a 74-year-old woman with metastatic breast cancer and a history of hypertension. She was treated with a mutikinase inhibitor. The latter patient received one dose of the study drug; her baseline ECGs as well as those carried out on day 1 (1 h and 5 h post-treatment) were normal. On day 2 of the treatment, she presented with dyspnea and hypotension and was found to have a non-ST segment elevation MI with new congestive heart failure (ejection fraction = 30%–35%). The patient's MI was deemed possibly related to the study drug.

discussion

The QTc interval on an ECG measures the total duration of ventricular activation (depolarization) and recovery (repolarization) corresponding to the duration of the ventricular action potential [11, 12]. QTc prolongation can lead to malignant cardiac arrhythmia with torsade de pointes and sudden cardiac death [2].

Since 2005, the FDA and European regulatory agencies have mandated that almost all new molecular agents be evaluated in a Thorough QT Study, which is used to assess the potential of a drug to cause an arrhythmia, to determine a novel drug's effect on the QT interval (http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM129357.pdf). In our study, the average number of ECGs per patient was 16 in the first 4 weeks of the studies on which they were enrolled. In general, we believe this monitoring was mandated by FDA requirements, although we cannot rule out sponsor input.

Prolongation of the QTc interval by noncardiac drugs has been the most common cause of drug development delays, nonapprovals and postmarketing withdrawals by the FDA [5]. However, the most frequent types of adverse reactions leading to the decision to discontinue drugs under development have been liver damage, serious skin reactions, and hematologic abnormalities, but not cardiac, complications [13].

Previously, it was reported that more than 30% of cancer patients have ECG abnormalities at baseline, including bundle branch block, ST segment wave abnormalities, sinus tachycardia, atrial fibrillation and prior MI [14]. Also, nearly 15% of patients with cancer have been anecdotally reported to have prolonged QTc at presentation [14]. Here, we found that almost 9% of patients with advanced cancer enrolled on phase I clinical trials had a known history of coronary artery disease, and more than one-half of the patients had one or more cardiac risk factors (53% with a known history of hypertension, 23% with hyperlipidemia, 15% with diabetes). Six percent had prolongation of QTc at baseline. Seventy-four of our 525 patients (14%) developed prolonged QTc after dosing; 33 patients (6%) had prolonged QTc at baseline (only one of whom showed further prolongation (≥10%) of QTc after dosing). Seven of the 33 patients (21%) with prolonged QTc at baseline showed a normal QTc interval after dosing. None of these patients demonstrated clinically significant cardiac problems. While correcting electrolyte imbalances could play a role in normalizing QTc intervals, in general, the precise reasons for QTc normalization in 7 of 33 patients in our study are unknown. These 7 patients did not have an overt electrolyte imbalance when baseline ECGs were done.

In our study, of the two cardiac SAEs that were reported in 525 patients (0.4%, 95% CI 0% to 1%), only one (MI) was thought possibly related to a study drug, and viewed as a dose-limiting toxicity. (The other was attributed to tumor metastatic to the heart.) Both cardiac SAEs presented with symptoms suggestive of cardiac decompensation (hypotension, atrial flutter and dyspnea for the patient with cardiac metastatic disease, and hypotension and dyspnea for the patient with a MI). The ECGs carried out on these patients showed no new abnormalities that served as a warning for their ensuing cardiac problems. Neither patient had QTc prolongation.

The accumulation of longer-term data from the later phases of drug development, as well as close postmarketing surveillance, will further assist in illuminating the clinical relevance of QTc abnormalities noted in early phase trials. QTc assessment during the early drug development trajectory should balance the perceived risk of cardiac toxicity with the

benefits expected from therapy. For some treatments with potential efficacy, e.g. arsenic trioxide, which prolongs the QTc interval, the drug can be safely administered with appropriate ECG monitoring and management of electrolytes and concomitant medications [15].

While it is important to perform due diligence in assessing the risk of QTc prolongation, the need to introduce novel agents into the medical arsenal for cancer is equally important. Concern about possible QTc effects should not inappropriately impede progress in oncology drug development, and where the risk is low, it may be worthwhile to consider patients with life-threatening cancer eligible for a trial even in the presence of a prolonged QTc interval.

While safety and efficacy are first priorities, costs should not be ignored. Frequent use of diagnostic tests with low yield ultimately may escalate the price of drugs [16]. Our patients had an average of 16 ECGs each, most of which were carried out during the first 4 weeks of the study. Of the 8518 ECGs done, none predicted a cardiac event. The use of QT/QTc prolongation as a guide to dose modification in an oncologic setting is sensitive, but the specificity of QT/QTc prolongation for predicting clinical consequences has not been well established [3].

In summary, we analyzed 8518 ECGs that were carried out on 525 patients enrolled in 22 phase I trials. Prolongation of QTc intervals did not lead to arrhythmic events in our highly selected patient population, thereby avoiding the most common types of drug development delays. A caveat to our finding is to exercise caution when extrapolating this observation to larger trials in less highly selected patient populations, in combination with other agents, and potentially using different dosages of the same agents. The two patients with cardiac problems were detected by clinical assessment rather than surveillance ECGs. Our results suggest that clinical evaluation continues to be important to patient safety, and that more modest ECG monitoring should be considered in early phase trials.

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disclosures

The authors have declared no conflicts of interest.

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