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EDITORIAL

Using the Appropriate Formula for QT Measurement Can Save Lives

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Abstract

CDK 4/6 inhibitors, in combination with endocrine therapy, are the standard of care for patients with endocrine-sensitive advanced breast cancer. This class of drug, however, is associated with QT prolongation, which serves as a surrogate marker for Torsades de Pointes (TdP), a cause of life-threatening ventricular arrhythmias and sudden cardiac death. The ICH E14 guidance document uses the Bazett formula for reporting of cardio-dynamic and safety ECG data in clinical trials. While there is substantial familiarity with the Bazett (QTcB) formula (QT/(RR) 1/2), the Fridericia (QTcF) formula (QT/(RR) 1/3) is preferred in the cancer population as it is often more accurate at heart rate extreme. Accordingly, the Fridericia formula is currently the standard adopted by the FDA when submitting QT data for review. At the King Faisal Specialist Hospital and Research Center, a total of 82 patients with advanced breast cancer, had a baseline ECG on day 1 before the initiation of ribociclib based therapy. Of the enrolled 82 patients, 19 (23%) were initially excluded from receiving ribociclib based due to a prolonged QTc >450ms, however, when the QTc-interval was manually measured and recalculated using Fridericia and Framingham formulae using MDCalC (https//:www.mdcalc.com),17 of 19 patients successfully received their treatment without any arrhythmogenic effects. Repeat ECG on day14, and day 1 of cycle 2 demonstrated that none of these patients had QTc exceeding 480 ms. Our data highlights the complexities of evaluating the QT interval in oncology patients and the utility of the Fridericia/Framingham formulae in this population. Given these findings, we recommend the adoption of the Fridericia or Framingham formulae for measurement of QTc in all cancer patients exposed to potentially QT-prolonging cancer therapy.

Keywords: QTc interval, QT correction, Cancer treatment, Drug safety, CDK4/6 inhibitors, Arrhythmia

One of the principle tasks of an oncologist is to decide whether to proceed or withhold potentially life-saving cancer treatment, when the treatment may result in significant morbidity. What would the recommendation be when facing a patient presenting with a prolonged QT interval on the assumption that the benefits of the proposed cancer therapy outweigh the risks? QT prolongation has long served as a surrogate marker for drugs which prolong ventricular repolarization, and predispose to recurrent polymorphic ventricular tachycardia, Torsades de Pointes (TdP), which can cause life-threatening ventricular arrhythmias that can lead to sudden cardiac death [1].

The main goal of screening for QT prolongation is to identify those who are at increased risk for TdP, so aggressive measures may be implemented to reduce this risk. In general, cardiovascular adverse effects are important considerations in all phases of drug development. It is well known that QT interval

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recorded by electrocardiogram (ECG) reflects the overall duration of ventricular activation and recovery. The electrophysiological measurement of QT has long served as a surrogate indicator for predicting increased risk of drug-induced Tdp; however, the relationship between QT prolongation and risk of Tdp is imperfect and complex [2].

Great controversy exists over normal values of QT or the corrected QT (QTc) duration; in the absence of broad QRS complex, the 99th percentile of QTc is 470 ms for men and 480 ms for women. It is generally accepted that a QTc above 500 ms is a high risk factor for Tdp [3]. In this regard, a value of >450 ms irrespective of sex, as suggested by the Food and Drug Administration (FDA) in their ICH E14 guidance document, is most often utilized in human clinical trial protocols [4].

The current recommendations for the assessment of QTc prolongation and arrhythmia potential were developed in 2005; a dedicated Thorough QT study was required for all medications to conform to the ICH E14 guidelines [4]. The ICH E14 guidance document relied upon the Bazett formula for reporting of cardiodynamic and safety ECG data in clinical trials. Subsequently, data has shown the Bazett corrected formula to be inferior to the Fridericia correction method and is no longer routinely warranted for reporting by the FDA. While there is substantial familiarity with the Bazett (QTcB) formula (QT/ (RR) $^{1/2}$), the Fridericia (QTcF) formula (QT/ (RR)$^{1/3}$) is preferred in the cancer population as it is often more accurate at heart rate extremes [5]. Accordingly, the Fridericia formula is currently the standard adopted by the FDA when submitting QT data for review [6].

Various correction formulas have been developed to improve QT measurement accuracy. One of the earliest efforts to acquire a standardized heart rate correction formula was made by Bazett in 1920 ($QTcB = QT/RR^{1/2}$). This exponential method enabled the comparison of QT intervals at different heart rates. In fact, in case of altered cardiac frequencies, heart rates >100 beats/minute or <60 beats/minute, the correction according to Bazett is not ideal because the value is overestimated or underestimated, respectively [7]. Since then, numerous correction formula have been generated. The Fridericia exponential correction ($QTcFri = QT/RR^{1/3)}$ has the same limitations at slow heart rates, but is considered to be more accurate than Bazett's correction at faster heart rates [8]. The Framingham linear method ($QTcFra = QT + 0.154(1-RR)$ results in more uniform rate correction over a wider range of heart rates [9]. Among these, the most widely used in clinical practice is the Bazzet formula which becomes integrated into computerized ECG acquisition carts and is still utilized today by many clinicians worldwide. Interestingly, different studies suggested different formulae to be superior, but all had one thing in common—the inferiority of QTcB [10].

How do these mechanisms translate into clinical practice? In line with the inferiority of the Bazett formula, Patel et al. [11] evaluated four methods of QT correction in more than 6,500 patients with sinus tachycardia >100 beats/minute for development of coronary artery disease, heart failure, and mortality. At a median follow-up of 4.5 years, annualized cardiovascular events rate were 2.3% and mortality rate was 2.2%. QT prolongation was 39% by Bazett, 6.2% by Fridericia, 8.7% by Framingham, and 8.7% by Hodges. It was evident that Bazett correction formula overestimated the number of the patients with a prolonged QT and was not associated with morality. Furthermore, a comparative analysis of QTc assessment using five different correction formulae performed in >6,500 patients concluded that Fridericia and Framingham correction formulae showed the best rate correction and significantly improved prediction of 30-day and 1-year mortality; Bazett performed worst. The authors suggest that the use of QTc Bazett correction formula could overestimate the number of patients with potential dangerous QTc prolongation, leading to unnecessary withholding of cancer therapy. Therefore, the questions arise whether QTc Fridericia should become the next clinical standard replacing QTc Bazett for hospital-based QT monitoring [12]. In a retrospective analysis of 130 patients in a Phase I oncology clinical trial, Borad et al. [13] assessed the effect of QTc formula selection on patient eligibility by comparing QTc interval values using seven formulae (Bazett, Fridericia, Framingham, Hodges, Mayeda, Van de Water, and Wohlfart). QTc values cutoff used to define prolongation were >470 ms and >450 ms for females and males, respectively. Ineligibility rates ranged from 3.1% to 17.7% (Framingham: 3.1%, Van de Water: 3.1%, Hodges: 3.1%, Wohlfart: 3.1%, Fridericia: 3.9%, Bazett: 10.8%, and Mayeda: 17.7%). They clearly demonstrated the profound effect of these formulae to impact patient selection patient to receive chemotherapy [13].

In the battle against breast cancer, CDK 4/6 inhibitors (palbociclib, ribociclib, and abemaciclib) have emerged as new potential therapeutic options for treatment of advanced-stage hormone receptor–positive, HER2–negative breast cancer. One of the safety considerations for ribociclib is its potential for QTc prolongation; the product monograph for ribocliclib recommends three ECGs, at

baseline, Day 15, and Cycle 2 Day 1, to ensure that the corrected QT (QTc) interval is within the normal range. Ribociclib has been proven to improve progression-free and overall survival, resulting in FDA approval in combination with endocrine therapies [14]. As per FDA approval, treatment with ribociclib should be initiated only in patients with a QTc value of ≤450 ms.

At King Faisal Specialist Hospital and Research Center, a total of 82 patients with advanced breast cancer had a baseline ECG performed on Day1 before the initiation of ribociclib therapy. A computerized ECG was analyzed primarily using MAC 5500 HD system (GE Healthcare, USA), which performs measurement on global waveforms utilizing the Bazett formula (Table 1). Of the enrolled 82 patients, 19 (23%) were initially excluded to receive ribociclib due to a prolonged QTc > 450 ms. However, when the QTc interval was manually measured and recalculated using MDCalC (https//:www.mdcalc.com) which is based on Fridericia and Framingham formulae, 17 of 19 initially excluded patients were allowed to receive their treatment. ECG was repeated on Day 14 of Cycle 1, and Day 1 of Cycle 2 demonstrated that none of these patients had QTc exceeding 480 ms. Patients were followed-up for an additional 12 weeks, and no cardiac issues were reported. When QTc values obtained by the four formulas were compared, one-way analysis of variance revealed a significant difference between the means of the three formulae ($p < .001$). Post hoc analysis indicated that the mean score for Bazett (471 ± 12 ms) was significantly different from Fridericia (439 ± 12 ms) and Framingham (434 ± 13 ms) ($p < .001$). However, the mean scores of Fridericia and Framingham showed no significant difference ($p = .75$). Appropriate ethical review boards approved the data collection (RAC# 2052−029); patients provided written informed consent as per hospital policies.

Our data highlights the complexities of evaluating the QT interval in oncology patients and the utility of the Fridericia/Framingham formulae in this population. The Bazett formula was associated with longer QTc intervals which could lead to prevention or abandonment of effective cancer therapy. Consequently, these data should incite prompt modification of the QTc calculation formula provided by computed ECG machines. Furthermore, uniform criteria and guidelines for selection of QTc formula need to be developed. Formula-specific QTc thresholds also need to be specified.

Given that the Bazett's formula is widely adopted in everyday clinic practice, one cannot escape the conclusion that the arrhythmogenic potential of QT prolongation is exposed to clinical biases that extend beyond the pharmacologic characteristics of targeted molecules. Indeed, not all clinicians are aware that Bazett formula may not be optimal to use or that their computerized ECG machines are using Bazett formula as a default. Given these findings, we recommend the adoption of Fridericia or Framingham formula for measurement of QTc in all cancer patients exposed to potentially QT prolonging

Table 1. Comparison of QTc[a] Using Different Formulae.

Computerized ECG (MAC 5500 HD system)				MDCalC.com			
Pt #	Heart rate[b]	QT, ms	QTc, ms	Bazett	Fridericia	Framingham	Hodges
1	82	398	465	465	442	439	437
2	93	370	460	460	428	425	428
3	103	372	487	487	445	436	447
4	71	442	480	481	468	466	461
5	99	376	482	483	444	437	444
6	93	366	455	456	424	421	424
7	94	382	477	478	444	438	442
8	75	424	473	474	457	455	450
9	115	350	484	485	435	424	446
10	112	360	491	492	443	432	451
11	91	368	452	453	423	420	422
12	81	406	471	472	449	446	443
13	87	394	474	474	446	442	441
14	103	352	461	461	421	416	427
15	87	400	481	481	449	448	400
16	85	386	459	459	434	431	430
17	89	372	452	452	424	422	423
18	79	406	465	466	445	443	406
19	111	350	476	476	430	421	439

[a] Measured in milliseconds. [b]Measured in beats per minute.

cancer therapy which is more aligned with a true corrected QT interval. In clinical practice, the adoption of Fridericia or Framingham formula for QTc could result in more cancer patients receiving life-sustaining therapy.

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Author's contributions

All authors contributed to all aspects of work, from manuscript writing to final approval of manuscript.

Conflicts of interest

Dr. Taher Al-Tweigeri has received speaking honoraria from Roche, Novartis, and Lilly, and has served on an advisory committee for Roche, Lilly, and Novartis. Dr. Susan Dent has received honoraria and grant funding from Novartis. Other authors dedicated no potential conflicts of interest.

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