INTRODUCTION

QT prolongation has been associated with the development of a dangerous and potentially life-threatening form of polymorphic ventricular tachycardia known as torsades de pointes (TdP). Despite this association, the QT interval has been shown to be a poor predictor for the development of TdP. Unfortunately, there are few other readily available methods to better determine risk. Multiple factors have been implicated in QT interval prolongation, including electrolyte abnormalities or underlying genetic disorders. In addition, pharmaceutical agents have been shown to prolong the QT interval and in rare circumstances lead to TdP. As a result, QT monitoring has become an essential part of pharmaceutical development and significant increases in the QT interval may prevent a drug from gaining approval. Given that QT interval prolongation does not always translate into increased clinical risk of arrhythmia, current guidelines may be too restrictive for novel oncology drugs. New strategies should be considered for monitoring the QT interval and risk of abnormal ventricular repolarization in anticancer pharmaceutical agents. Given the significant influx of novel oncology pharmaceutical agents with associated QT prolongation, experience in both cardio-oncology and electrophysiology is necessary to provide appropriate clinical guidance.

KEYWORDS
- QT prolongation
- Cardiotoxicity
- Cardio-oncology
- Chemotherapy
- Cancer treatment
- Torsades de pointes

KEY POINTS
- Many pharmaceutical agents interact with cardiac ion channels resulting in prolongation of the QT interval, which is associated with the development of torsades de pointes (TdP).
- QT interval monitoring is an essential part of pharmaceutical development and significant increases in the QT interval may prevent a drug from gaining approval.
- Given that QT interval prolongation does not always translate into an increased clinical risk of arrhythmia, current guidelines may be too restrictive for novel oncology drugs.
- New strategies should be considered for monitoring the QT interval and risk of abnormal ventricular repolarization in anticancer pharmaceutical agents.
- Given the significant influx of novel oncology pharmaceutical agents with associated QT prolongation, experience in both cardio-oncology and electrophysiology is necessary to provide appropriate clinical guidance.
interval monitoring in the development of cytotoxic oncology drugs are discussed and agents are identified that may require more intensive evaluation when given to patients. It is also posited that given the relative target specificity of some of these novel therapies, QT prolongation may provide insight into basic electrophysiology.

BASIC ELECTROPHYSIOLOGY OF THE QT INTERVAL AND TORSADES DE POINTES

On a surface electrocardiogram (ECG), the QT interval is measured from the beginning of the QRS complex to the end of the T wave and represents the entirety of ventricular depolarization and repolarization (Fig. 1). At a cellular level, this electrical process, also known as the action potential, is mediated by channels in the myocardial cell membrane that regulate the flow of ions into and out of the cardiac cells (Fig. 2). Normal depolarization is due to the rapid inflow of positively charged ions (sodium and calcium), whereas repolarization is due to outflow of potassium ions. The action potential consists of 5 distinct phases. Phase 0 (depolarization) occurs with the opening and closing of Na\(^+\) channels, represented by a sharp initial upstroke. Phase 1 begins the repolarization process with the rapid transient outflow of K\(^+\) ions. Phase 2 (plateau phase) is the result of a balance between inward Ca\(^{2+}\) current and outward flow through K\(^+\) channels (particularly the slow delayed rectifier potassium channel IKs). During phase 3 (rapid repolarization), the Ca\(^{2+}\) channels close and the K\(^+\) channels remain open. The channel predominantly responsible for phase 3 is the rapid delayed rectifier potassium channel, IKr. Phase 4 is a return to baseline (resting membrane potential) when the cell is not being stimulated.

Sustained inflow of Na\(^+\) ions or impaired outflow of K\(^+\) ions leads to delay in the action potential and thus QT interval prolongation. In the 1950s and 1960s, genetic syndromes of QT prolongation were first identified, most of which are due to mutations in these ion channels involved in the cardiac action potential. In addition, electrolyte abnormalities and specific drug effects can also lead to QT prolongation. Most pharmaceutical agents that prolong the QT interval do so by impacting the function of the IKr channel, which is encoded by the gene KCNH2. This gene is also referred to as the human ether-a-go-go gene (HERG). This channel is known to interact with a variety of structurally diverse compounds.

Afterdepolarizations are abnormal oscillatory changes in cell membrane voltage that disrupt normal repolarization. They are called early afterdepolarizations (EAD) when they occur during phase 2 or 3 of the action potential and delayed afterdepolarizations when they occur during phase 4. EADs most frequently occur in the setting of a baseline prolonged action potential duration. The resulting myocardial electrical heterogeneity renders it vulnerable to the development of TdP, typically occurring after a salvo of several EADs; this is manifested by long-short sequences on the ECG. Although transmural dispersion of repolarization is a significantly better predictor for TdP compared with QT prolongation, it is not easily measured, and the QT interval is a frequently
used surrogate to determine risk.\textsuperscript{8,9} Certain cell populations within the heart, specifically those constituting the Purkinje fibers and the midmyocardium (M cells), are particularly vulnerable to this phenomenon.\textsuperscript{10,11}

**QT INTERVAL MEASUREMENT AND ANALYSIS**

Accurate measurement of the QT interval can be challenging (\textbf{Box 1}). One study revealed that less than 25% of cardiologists and only 62% of “arrhythmia experts” could accurately identify QT prolongation.\textsuperscript{12} When measuring the QT interval, the longest QT interval should be used (typically in the limb leads); however, if this measurement differs by more than 40 ms from other leads, it may be erroneous and measurement from other leads should be considered. It is recommended that this measurement should be averaged over 3 to 5 beats. It can be particularly challenging to determine the end of the T wave to appropriately measure the QT interval. One recommendation is to draw a tangent from the steepest slop of the descending end of the T wave to the isoelectric line, typically in lead II or V5 (\textit{Fig. 3}).\textsuperscript{13} In addition, measurement of the QT interval should not include U waves unless they clearly merge with the T wave. It is essential to manually validate the QT measurement recorded by an electronic ECG machine because errors frequently occur.\textsuperscript{3,14,15}

\textit{Fig. 2.} Ventricular myocyte action potential curve with associated ion channels. APD, action potential duration; NCX, sodium-calcium exchanger. (\textit{From} Nattel S, Carlson L. Innovative approaches to anti-arrhythmic drug therapy. Nat Rev Drug Discov 2006;5:1034–49; with permission.)

\begin{figure}
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\includegraphics[width=\textwidth]{figure2}
\caption{Ventricular myocyte action potential curve with associated ion channels. APD, action potential duration; NCX, sodium-calcium exchanger. (\textit{From} Nattel S, Carlson L. Innovative approaches to anti-arrhythmic drug therapy. Nat Rev Drug Discov 2006;5:1034–49; with permission.)}
\end{figure}

\begin{table}[h]
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\begin{tabular}{|l|}
\hline
\textbf{Box 1} \textit{Key points for accurate QT measurements} \\
\hline
1. Measure longest QT interval \\
2. Average measurement over several beats \\
3. Use tangent method to determine the end of the T wave \\
4. Avoid measuring U waves in most circumstances \\
5. During atrial fibrillation, average the QT interval more than 10 beats \\
6. Use the JT interval in patients with bundle branch blocks or ventricular pacing \\
7. Always manually verify electronic QT measurements \\
\hline
\end{tabular}
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\textit{Atrial fibrillation and wide QRS complexes (due to either conduction defects/bundle branch blocks or ventricular pacing) pose unique problems for accurately assessing the corrected QT (QTc) interval. There is no consensus as to the correct way to measure and interpret QTc intervals in the setting...}
of atrial fibrillation. Because of the variability of the R-wave intervals during atrial fibrillation, the QT interval can change in each beat. Some experts recommend averaging QTc measurements greater than 10 beats; others suggest averaging the QTc measurements associated with the shortest and longest R-R intervals. Similarly, there is no clear consensus for the measurement of the QTc in the setting of wide QRS complexes. Experts recommend using the JT interval (QTc-QRS duration); however, this can be confusing and cumbersome especially for noncardiologists. It has been suggested to avoid initiation of a drug if the QTc interval is greater than 500 ms in the setting of ventricular conduction delay.

The QT interval is longer at slower heart rates and shorter at faster heart rates. Several formulae have been developed to adjust for this variation (Table 1). The Bazett formula, in which the QT interval is divided by the square root of the RR interval, is most frequently used in clinical practice; however, this method is inaccurate at slower and faster heart rates. Other formulae include the Fridericia formula (QT interval divided by the cubed root of the RR interval) and the Framingham Linear Regression Equation. The Framingham equation is supported by empiric epidemiologic data and may be a more accurate approach when evaluating large populations. The Bazett and Fridericia formulae are based on mathematical modeling/reasoning and are most often used for drug development monitoring. Unfortunately, none of these methods have been evaluated and compared with one another to determine which is most accurate at predicting risk of TdP.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>QT correction formulae</th>
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<tr>
<td><strong>Bazett</strong></td>
<td>QTC = QT/(RR^{1/2})</td>
</tr>
<tr>
<td><strong>Fridericia</strong></td>
<td>QTC = QT/(RR^{1/3})</td>
</tr>
<tr>
<td><strong>Framingham</strong></td>
<td>QTC = QT + 0.154 ( \frac{1000}{RR} )</td>
</tr>
<tr>
<td><strong>Hodges</strong></td>
<td>QTC = QT + 1.75 ( \frac{HR-60}{HR} )</td>
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<table>
<thead>
<tr>
<th>Type</th>
<th>Nonlinear</th>
<th>Nonlinear</th>
<th>Linear</th>
<th>Linear</th>
</tr>
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<tbody>
<tr>
<td>Advantages</td>
<td>Simple; most widely used in practice</td>
<td>More accurate at slower HR (risk of TdP is greater at slower HR)</td>
<td>Adaptable across genders; population-based formula</td>
<td>Useful with multiple populations</td>
</tr>
<tr>
<td>Disadvantages</td>
<td>Overcorrects at fast HRs and underr corrects at slow HRs</td>
<td>Overcorrects at high HRs</td>
<td>Uncertain validity in populations other than Framingham Heart Study; overcorrects at high HRs</td>
<td>Less correlation with HR variability; overcorrects at high HRs</td>
</tr>
</tbody>
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**RISK FACTORS FOR CORRECTED QT PROLONGATION AND TORSADES DE POINTES**

Multiple pharmaceutical agents are known to prolong the QT interval, typically by inhibiting or modulating the function of the HERG channel. Nevertheless, most episodes of drug-induced TdP occur in the setting of other patient-specific or acquired risk factors. For example, genetic conditions (long QT syndrome [LQTS]) have been...
identified that phenotypically present with QT prolongation and an increased risk of sudden cardiac death, typically due to mutations that affect the ion channels responsible for the action potential. Most forms are due to either a reduction in the outward potassium currents (LQTS-1: IKs; LQTS-2: IKr) or an enhancement of the inward sodium current (LQTS-3: INa). Other forms of LQTS are due to abnormalities in proteins that affect ion channel trafficking or function. When these patients are treated with certain drugs, the additive QT prolonging effect can be substantial.20,21

Nonpharmacologic factors can also impact the QT interval (Box 2). Electrolyte abnormalities (hypokalemia or hypomagnesemia), bradycardia, left ventricular hypertrophy and congestive heart failure, intracranial pathologic abnormality, HIV infection, connective tissue disorders, and hypothermia are also all known to prolong the QT interval.19 Age and gender also impact normal QT/QTc intervals. It is thought that sex hormone levels play a role in these QT interval changes.22–25 After puberty, men have shorter QT intervals than women, which may be related to increased testosterone levels. As both genders age, the QT interval gradually increases. Progesterone has been reported to affect HERG trafficking, and postmenopausal women treated with estrogen demonstrated prolonged QT intervals compared with controls.26,27 In addition, female hearts have fewer ion channels, which render them more susceptible to repolarization abnormalities.28 For these reasons, using the Bazett formula, a normal QTc is less than 450 ms for men and less than 460 to 470 ms for women.33–35

For patients with prolonged QT intervals, treatment is focused on correcting the underlying cause. In particular, medications that are known to prolong the QT interval should be stopped if at all possible. In addition, potassium and magnesium should both be regularly evaluated and aggressively corrected. Magnesium repletion has been shown to shorten the QT interval as has potassium repletion with a goal serum concentration of 4.5 to 5 mmol/L.33–35

**HISTORY OF DRUG-INDUCED QT PROLONGATION AND TORSADES DE POINTE**

Antiarrhythmic medications were the first class of medications found to prolong the QT interval and increase the risk of TdP. Syncope associated with quinidine exposure was first observed in the 1920s; however, TdP was not identified as the causative mechanism until the 1960s.36 The term TdP was first used by the French cardiologist Despertenne37 in 1966 to describe this unique arrhythmia. Over the next several decades, the association of QTc prolongation and TdP was identified. It was found to occur relatively frequently during the administration of class III antiarrhythmic medications, which are known to block IKr, with rates exceeding 1% in some series.38,39 At the same time, other classes of pharmaceutical agents, including psychiatric medications and antibiotics, were reported to cause TdP; however, the rates were quite low and little attention was paid to the arrhythmogenic potential of noncardiac drugs.

The landscape changed dramatically in the fall of 1989 when the first case of QT prolongation and TdP associated with terfenadine administration was reported. Terfenadine was a widely prescribed nonsedating antihistamine. Although it had potent HERG-channel blocking effects, its impact on the QTc at standard clinical doses was insignificant. Further studies revealed that terfenadine underwent extensive first-pass hepatic metabolism by cytochrome P450 3A4 to its active metabolite, which has no effect on the HERG channel. In patients with impaired hepatic metabolism, systemic terfenadine levels were significantly elevated, leading to marked QTc prolongation.40,41 Although the exact number of cases of TdP and death from terfenadine is not certain, one review cited at least 125 deaths in the United States from this drug.42 Given that this medication treated a benign condition and there were other safer alternatives, it was ultimately withdrawn from the market in 1997. Since then, 6 additional drugs have been removed from the market for increased rates of TdP and death,
including the antibiotic grepafloxacin (at least 13 arrhythmia-associated deaths) and the gastroprokinetic cisapride (80 arrhythmia-associated deaths reported to the US Food and Drug Administration [FDA]) and many others have received updated labeling and/or black box warnings.

CORRECTED QT MONITORING AND REGULATION IN DRUG DEVELOPMENT

Because of the significant consequences associated with the QT prolonging effects of the aforementioned drugs, regulatory agencies were developed to provide guidance and oversight in the drug development process. In 2005, the International Committee on Harmonization (ICH), a multinational regulatory body, published guidelines for QT monitoring of novel non-antiarrhythmic pharmaceutical agents in both the preclinical and the clinical settings. These guidelines have since been adopted by regulatory agencies in both the United States and the European Union.

Preclinical Assessment

ICH safety guideline 7B (S7B) is the portion of the ICH document that deals with drug development before human administration. The goal of these preclinical studies is to identify the potential of a drug and its metabolites to delay ventricular repolarization. The recommendation is to conduct both in vitro IK, and HERG assays and in vivo QT analyses using laboratory animals such as canines or nonhuman primates. The choice of species is important because some animals, for example mice and rats, have very different mechanisms of repolarization compared with humans. Tests may be also conducted to evaluate action potential effects in Purkinje or ventricular muscle fibers. When conducting in vitro assays, appropriate positive controls must be used and testing of metabolites (separate from the parent compound) should be considered. Despite significant improvements in these tests, there are several limitations. No gold standard has been established and although the sensitivity of these nonclinical tests is quite good, the specificity of these tests has been questioned. The degree in which a drug interacts with the HERG channel poorly correlates with the likelihood and extent to which the QT interval will be prolonged in the clinical setting. In fact, recent data suggest that simply screening for IK, inhibition may not be sufficient; rather, arrhythmogenic potential may more closely linked to inhibition of the phosphatidylinositol 3-kinase pathway and augmentation of the late sodium current (INa-L). Last, drugs that do not increase transmural dispersion of repolarization are unlikely to cause TdP regardless of HERG inhibition or QT prolongation. The issue of transmural dispersion of repolarization is not discussed or recommended in these documents.

Clinical Assessment and the “Thorough QT/Corrected QT Study”

ICH efficacy guideline 14 (E14) is the portion of the ICH document that provides guidance about the clinical evaluation of a drug’s effect on ventricular repolarization and the QT interval. A specific trial, coined the “Thorough QT/QTc Study (TQTS)” should be conducted early in clinical development of the pharmaceutical agents. This study is typically conducted in healthy volunteers to determine if a drug has a threshold effect on cardiac repolarization. The goal of the TQTS is to exclude a drug prolongs the QTc interval by 10 ms or more at the one-sided upper 95% confidence limit. The results of this study will help determine if further testing and evaluation is required during later phases of development (ie, if a drug effect exceeding 10 ms cannot be excluded). A TQTS is required as a part of drug development even if preclinical testing is negative for HERG inhibition or QT prolongation. Until the QT effects of the drug are delineated, certain exclusion criteria have been established for study volunteers. Those individuals with a prolonged baseline QTc interval (>450 ms) or those with a history of additional risk factors for TdP (such as cardiac disease, congenital syndromes, or electrolyte abnormalities) should be excluded from the TQTS.

Healthy volunteers receive placebo, a positive control that prolongs the QT interval slightly. The study drug is dosed at the therapeutic dose as well as at a supratherapeutic dose. This trial is conducted in either a randomized crossover or a parallel fashion. Given that there is less intrasubject variability, the crossover study design is preferable and requires a smaller sample size to exclude a QT prolongation effect. The parallel design may be preferred if the drug must be dosed for an extended period of time to achieve appropriate serum levels. The placebo drug is included to account for random variability associated with the study. The positive control is included to ensure adequate sensitivity. It is necessary for the study to detect changes in the QT interval as small as 5 ms; changes smaller than this are unlikely to cause TdP. The fluoroquinolone moxifloxacin is used as the positive control in the overwhelming majority of TQTS cases. Ideally, the positive control should have a QT prolonging effect of about 5 ms; however,
moxifloxacin typically prolongs the QTc by 8 to 15 ms. This excess QT prolonging effect of a positive control is considered acceptable provided that it is not so long as to hinder the study’s ability to detect small QTc changes. In addition, the QT prolonging effect of the positive control should be similar to values obtained in prior TQTS. If the effect of the positive control is substantially different, the sensitivity of the current TQTS would be questioned.54

Recent updates to the ICH E14 recommendations have focused on issues of gender representation in these studies and the appropriate algorithm for QT correction. It is well known that women have longer QT intervals compared with men, but the exact cause for this difference is not completely understood. The current recommendations suggest equal representation of genders in TQTS and to perform subgroup analysis whenever a TQTS is positive. Regarding QTc assessment, earlier iterations of the ICH E14 document did not specifically address which correction formula should be used during a TQTS. Although the current document does not go so far as to recommend one specific method, they do suggest that the Fridericia formula is likely to be appropriate in most situations.56,57

It is important to note that the TQTS is not designed to determine the likelihood that a new pharmaceutical will cause TdP. In fact, a positive study cannot adequately determine the proarrhythmia effects of a drug because there is not a linear relationship between the QT interval and the risk of TdP.9 Rather, the TQTS is conducted to identify those drugs that will require more thorough ECG and safety evaluation.

**QT/CORRECTED QT MONITORING IN ONCOLOGY DRUG DEVELOPMENT**

It is well recognized that the TQTS cannot be applied to every new pharmaceutical agent in development. This reasoning holds particularly true for oncology drugs and other cytotoxic agents. The E14 guidelines acknowledge that the administration of chemotherapeutic agents to healthy volunteers would be unethical.47 An alternative, TQTS-like studies are sometimes conducted in target patient populations as part of phase 1 oncology trials. This can still be a significant challenge because most oncology patients enrolled in phase 1 trials have advanced malignancies. These patients are often elderly and have comorbid conditions such as underlying cardiovascular disease that would otherwise exclude them from a TQTS. They are also frequently taking other drugs such as antiemetics and antibiotics, which can also prolong the QT interval, thus making accurate interpretation challenging.4,58

Determining reasonable and appropriate inclusion and exclusion criteria for these modified QT monitoring studies for oncology drugs is of significant importance. The guidelines set forth for TQTS is likely far too restrictive for oncology drug studies. As already indicated, many of these patients have concomitant medical conditions that can prolong the QT interval, which would otherwise exclude them from a TQTS. They may also be taking other medications with a QT prolonging effect, which cannot be safely stopped.58 In addition, the QTc cutoff of 450 ms may be too restrictive for this population. There appears to be greater variability in the QT interval among patients with cancer compared with healthy controls. These data suggest that if the current QT/QTc exclusion of 450 ms is applied to oncology trials, more than 10% of potential study participants would be excluded.59,60

Phase 1 oncology trials often have multiple protocol issues that make QTc evaluation challenging. Conversely, the rigorous QTc protocols outlined in the ICH E14 document can be applied to healthy volunteer populations but are not appropriate when treating patients with advanced cancer. For example, oncology trials are often not randomized and the administration of either a placebo or a positive control drug would be completely inappropriate for patients with advanced cancer. It should also be recognized that oncology patients themselves may be either physically or psychologically incapable of participating in the intensive time-sensitive ECG collection and cardiac monitoring necessary for these types of studies.4,58

With this in mind, the E14 document suggests that when a TQTS is impossible, other methods of monitoring the QTc must be developed so as to ensure safety and mitigate risk. This method can include extensive preclinical assessment for HERG inhibition and QT prolongation as well as robust ECG collection at different time points during the trial itself. Some experts suggest applying the National Cancer Institute’s toxicity criteria for QTc prolongation (Version 4 of the Common Terminology Criteria for Adverse Cardiac Events [CTCAE.v4]) to guide decision-making during these studies.61

Based on these criteria, it is recommended to define dose-limiting toxicity as grade 2 or higher QTc prolongation. These definitions, however, may be too restrictive to guide dosing in oncology patients. For example, diurnal variation of more than 60 ms has frequently been observed in oncology patients, and oncology patients have a wider range of QTc intervals compared with
healthy controls.⁴,⁶²,⁶³ Because the QT interval is so poorly correlated with the development of TdP, these parameters may unnecessarily prevent patients with cancer from receiving life-saving therapy. Although it is still mandatory to determine the QT prolonging effects of cytotoxic agents to ensure appropriate patient safety, it is clear that the current guidelines cannot be uniformly applied to oncology drug development.

Despite all of this, there remains little uniformity in the definition, management, and monitoring of QT interval prolongation in the realm of oncology drug development. The authors recommend liberalizing the definition of dose-limiting QTc prolongation for oncology trials to grade 3 toxicity or higher, especially because the overwhelming majority of TdP cases occur at QTc values greater than 500 ms and those with substantial QT changes (>100 ms) from baseline. In addition, patients with baseline QTc measurements of 480 ms or less should be considered for enrollment in these trials. Frequent ECG monitoring has not been shown to provide significant improvement in the prediction or diagnosis of future cardiac events.⁶⁴,⁶⁵ It would be reasonable therefore to obtain an ECG at baseline (before the initiation of the drug), and at least 2 consecutive measurements within 48 hours of receiving the drug. Finally, pharmaceutical companies should standardize the method used for QT correction. Given the current data, the authors would advocate for universal use of the Fridericia formula in oncology drug development.

**CORRECTED QT PROLONGATION ASSOCIATED WITH SPECIFIC CHEMOTHERAPEUTIC AGENTS**

**Arsenic Trioxide**

The medicinal properties of arsenic were first identified by the Chinese as early as the first century BC; however, arsenic’s toxicity profile and association as a poison have limited its medical use in the modern era and led to substantial regulations.⁶⁶ In the 1990s, arsenic trioxide was identified as an effective therapy for patients with relapsed or refractory acute promyelocytic leukemia (APL). APL accounts for 10% to 15% of all adult acute myeloid leukemias, and although first-line therapy with all-trans-retinoic acid has substantially improved survival, 20% to 30% of patients will relapse.⁶⁷–⁷¹ Initial single-center studies reported complete remission rates between 85% and 93% for patients with relapsed APL treated with arsenic, and these results were confirmed in a multicenter study that reported similar complete remission rates of 85% in patients treated with arsenic.⁶⁹,⁷²–⁷⁴ QTc prolongation and TdP are known cardiovascular complications associated with arsenic poisoning.⁷⁵ Several early studies suggested only minor asymptomatic ECG abnormalities in APL patients treated with arsenic trioxide; however, multiple case reports were published of patients with TdP in the setting of arsenic trioxide treatment.⁷²,⁷⁶,⁷⁷ Several studies have been conducted to more systematically evaluate arsenic associated cardiotoxicity. In a smaller study from Japan, 8 patients treated with arsenic were monitored with continuous ambulatory ECG during infusion of the drug. Although all patients in this trial experienced QT prolongation, there were no episodes of sustained VT or TdP.⁷⁸ In a larger study evaluating 99 patients from several different phase 1 and phase 2 trials, the risk was significantly lower with 38% demonstrating QT prolongation, and 26% having a QT greater than 500 ms. Only one patient had TdP and that was in the setting of significant hypokalemia. In all arsenic trials, the median daily dose was 0.15 mg/kg with a dose range of 0.06 mg/kg to 0.35 mg/kg.⁷⁹ A recent study evaluating more than 3000 ECGs in 113 patients treated with arsenic for non-APL malignancies produced similar results: QT prolongation occurred in 26% of patients with 12% demonstrating a QT interval greater than 500 ms. Despite this, no clinically significant cardiac events were noted.⁸⁰ Although arsenic clearly prolongs the QT interval, these studies demonstrate that the risk of TdP is quite low. Given the great success arsenic has had against relapsed APL, it would be a disservice to withhold this medication based solely on QTc criteria outlined in regulatory committee documents. At this time, labeling instructions recommend that arsenic trioxide should be stopped if the absolute QT interval exceeds 500 ms or if the patient develops symptoms suggestive of ventricular arrhythmias, but it can be resumed if the QT interval decreases to less than 460 ms. In addition, the potassium should remain greater than 4 meq/L and the magnesium greater than 1.8 meq/L.⁸¹ Arsenic trioxide represents an excellent example of successful risk mitigation strategies for a necessary therapeutic.

**Molecularly Targeted Agents**

**Tyrosine kinase inhibitors**

Protein kinases are a family of enzymes that regulate cellular signaling and function by transferring a phosphate group, typically from ATP, and attaching it to amino acids with a free hydroxyl group.⁸² One group of protein kinases act on tyrosine, whereas the other group acts on serine and
threonine, with a minority of enzymes acting on all 3 amino acids. Because of their aberrant activation in multiple types of cancers, protein kinases have become important targets for oncology drug development.82–84 Specifically, small molecules inhibit tyrosine kinase (TK) enzymes by interfering with ATP or substrate binding of TKs, thus inhibiting their catalytic activity. Such tyrosine kinase inhibitors (TKIs) are relatively nonselective and generally have potency against more than one receptor TK. In 2001, imatinib (Gleevec), an inhibitor of BCR-ABL1 chimeric TK aberrantly active in chronic myeloid leukemia (CML), became the first success story using this strategy by dramatically changing the prognosis of CML patients.85 Since then, more than 30 TKIs have already been FDA approved for various cancers with many more TKIs currently in clinical trials. Although TKIs have been generally well tolerated, specific classes have been associated with cardiotoxicity.86 For example, TKIs that target vascular endothelial growth factor receptor (VEGFR) and platelet-derived grown factor (PDGFR) signaling have been associated with hypertension, thrombosis, and, less frequently, heart failure.87 In 2013, ponatinib, which had potent activity against BCR-ABL1 kinase, but also against other TKs (including VEGFR), was temporarily withdrawn from the market because of vascular toxicity.88 Nilotinib, a TKI with potent activity against BCR-ABL1 kinase and FDA approved for treatment of CML, has been associated with peripheral vascular atherosclerotic disease.89

Several TKIs have been associated with QT prolongation, although incidence of TdP is exceedingly rare.84 For example, nilotinib was associated with a 5- to 15-ms prolongation of the corrected QT interval in a subset of patients in early clinical trials.90 Subsequent follow-up revealed no evidence of TdP.

Interestingly, QT prolongation associated with TKIs may be more complex than simple inhibition of the HERG subunit of the IKr channel. Lu and colleagues90 showed that 3 TKIs associated with QT prolongation in early clinical trials, dasatinib, sunitinib, and nilotinib, prolonged the action potential of the cardiac myocytes via inhibition of the phosphoinositide 3-kinase (PI3K) signaling pathway. Dasatinib, sunitinib, and nilotinib caused an increase in action potential duration that was reversed by intracellular infusion of phosphatidylinositol 3,4,5-triphosphate in a study using canine myocytes. PI3K inhibition has downstream effects on many ion channels, including increases in the late sodium current, $I_{Na-L}$, as well as decreases in the potassium current via IKr. Experiments using specific PI3K inhibitors and transgenic mice with reduced PI3K signaling, which had prolonged QT intervals at baseline compared with wild-type controls, supported a critical role for PI3K signaling. Despite these data, there is no clear class-related QT prolonging effect of TKIs. The chemical structure of the TKI may be the only feature that can predict the likelihood that the drug will prolong the QT interval. It has been observed that the presence of a fluorinated phenyl ring on the TKI may lead to an increased risk of QT prolongation and should lead to more intensive monitoring.84,91

As mentioned previously, the results of preclinical data on cardiac repolarization do not always translate into QT prolongation in the clinical arena. As was the case with nilotinib, this concept applies to several other drugs in this class. At least 9 of the TKIs carry either standard or black box warnings regarding QT prolongation. Among the TKIs, nilotinib, vandetanib, and sunitinib are frequently implicated for their QT prolonging effects. Sunitinib, a small-molecule TKI, affects the VEGFR, PDGFR, and c-kit and has been FDA approved in the treatment of gastrointestinal stromal tumors and metastatic renal cell carcinoma. Preclinical studies indicated significant effects on cardiac repolarization, interacting with HERG, and prolonging AP duration in Purkinje fibers and the QT interval in primate studies. In clinical trials, QT prolongation was only observed with high concentrations of the drug; however, no clinical events were reported. The mean increase in the QTc using the Fridericia formula was 15.4 ms (90% confidence interval 8.4–22.4 ms). Other clinical studies with sunitinib failed to show any impact on the QT interval. Some experts suggest that the FDA warnings are too restrictive for this medication given the clinical findings.84,92,93

Vandetanib is a potent TKI, which affecting VEGFR-2, RET, and endothelial growth factor receptor, is FDA approved for the treatment of locally advanced or metastatic medullary thyroid cancer. Preclinical studies suggested the potential for QTc prolongation; this was confirmed in multiple clinical trials.58,94 Several phase 1 trials reported QTc prolongation rates between 9% and 61%.95,96 In a phase 2 trial assessing vandetanib in combination with docetaxel for patients with drug refractory non-small-cell lung cancer (NSCLC), the rate of QT prolongation was 15% and all events were classified as grade 1 or 2. No clinical events were observed and each episode was effectively managed with dose reduction or interruption.97 Several other phase 2 trials confirmed these results.98,99 In a phase 3 trial evaluating vandetanib in patients with advanced NSCLC, QTc prolongation occurred in 5.1% of patients. Although most events were asymptomatic, one patient developed
Tdp leading to cessation of the drug. QT prolongation was defined as a single measurement of greater than 550 ms or an increase of greater than 100 ms from baseline, 2 consecutive measurements (within 48 hours) that were greater than 500 ms but less than 550 ms, or an increase of greater than 60 ms but less than 100 ms from baseline to a value of greater than 480 ms.100,101 A large meta-analysis of 9 vandetanib trials reported an incidence of all-grade QTc prolongation of 16.4% and high-grade QTc prolongation of 3.7% in patients with nonthyroidal cancer compared with 18% and 12% in patients with thyroid cancer.102 Given these data, vandetanib has a black box warning for QTc prolongation, and physicians must complete the Vandetanib Risk Evaluation and Mitigation Strategy Program to prescribe this medication.84

As discussed above, nilotinib is used in the treatment of Philadelphia chromosome-positive CML. It targets the BCR-ABL fusion protein, c-Kit, and PDGFR receptors. In preclinical studies, cardiac repolarization was affected with this drug, and clinical studies suggested substantial QT prolonging effects. In healthy volunteers, the mean QTc change was 18 ms; however, prolongation of more than 60 ms (using the Fridericia formula) was reported in 1.9% of CML-chronic phase patients and 2.5% of CML-accelerated phase patients.58,103 Sudden cardiac death has been reported in approximately 0.3% of patients treated with nilotinib. Abnormal ventricular repolarization is thought to have contributed to these events, and as a result, nilotinib has received a black box warning for QTc prolongation.104

**Histone deacetylase inhibitors**

Histone deacetylase inhibitors (HDI) are group of molecularly targeted pharmaceutical agents that modulate the posttranscriptional activity of proteins by inactivating histone deacetylase enzymes. The resultant abnormal proteins are stuck in G1 and G2 of the cell cycle, leading to apoptosis.105 QTc prolongation has been observed with some HDIs and is thought to be due to interaction with the HERG channel. A recent study confirmed that the pharmacophore for HERG and histone deacetylase-1 is quite similar, suggesting one possible reason for the QT prolonging effects of some HDIs.106 Vorinostat is an HDI with FDA approval for the treatment of cutaneous T-cell lymphoma. In a phase II study, 3 patients were observed to have grade 1 or 2 QTc prolongation without any clinical sequelae or need for dose adjustment.107 There is one case report of a severely prolonged QT interval leading to polymorphic ventricular tachycardia in a patient treated with vorinostat; however, this patient also had concomitant hypokalemia.108 Depsipeptide, also known as romidepsin, is an HDI used to treat a variety of malignancies including T-cell lymphoma. Romidepsin can cause QT prolongation, and although sudden cardiac death has been reported in several studies, this association with QT prolongation is not certain because most patients had multiple risk factors for sudden cardiac arrest and the QT interval was not clearly documented before the event.58,60,93 In a study of patients with T-cell lymphoma, the mean QTc prolongation (using the Bazett formula) was 14 ms in patients receiving romidepsin.60 Oral panobinostat is another HDI known to impact HERG activity and increase the Fridericia QTc up to 20 ms in a dose-related fashion without clinical sequelae.93 Although these data confirm HDI-associated QTc prolongation, this has not translated into increased clinical risk.

**Other Chemotherapeutic Agents**

Left ventricular dysfunction is the most commonly recognized cardiotoxicity of anthracyclines; however, these chemotherapeutics can also cause QTc prolongation. In a study evaluating patients with non-Hodgkin lymphoma treated with epirubicin, all patients experienced some degree of QTc prolongation. The QTc prolonging effects were mitigated when concomitant dexamethasone was given to the patients, however.109 In a Finnish study, 18% of patients exposed to doxorubicin experienced QTc prolongation of greater than 50 ms. These changes were independent of LV function.110 Tamoxifen has also been shown to cause QTc prolongation in both clinical and preclinical studies, likely related to HERG interaction.111

Several other classes of molecularly targeted agents are still relatively early in their development. Certain vascular disruption agents such as CA4P (combrestatin) have been shown to prolong the QTc in clinical trials, whereas others (plinabulin) have not shown this effect.58,112 Therefore, QTc prolongation does not appear to be a class-related effect of the vascular disruption agents. A similar finding has been observed with farnesyl protein transferase inhibitors. The agent L-778123 has been shown in several trials to induce QTc prolongation without clinical sequelae.113-115 In contrast, there are conflicting data regarding lonafarnib because QTc prolongation has been noted in some studies but not others.93 Last, inhibitors of the serine/threonine kinase, protein kinase C (PKC), have been shown to cause QT prolongation. Overexpression of PKC has been implicated in many different
malignancies including hepatocellular cancer, colon cancer, and diffuse large B-cell lymphoma. Enzastaurin is a potent selective inhibitor of PKC; however, phase I and II studies have documented dose-limiting QTc prolongation without clinical consequence.

SUMMARY

Safety and efficacy are the 2 paramount aspects of drug development. In general, the benefits of the pharmaceutical agent should outweigh any risk associated with it. In most instances, even a small risk of a serious complication cannot be tolerated. QTc monitoring is a central part of the drug-approval process, and most pharmaceutical agents are subjected to the TQTS, a protocol established by the ICH to ensure appropriate QTc evaluation. Although it is well known that the QT interval is a poor surrogate for TdP, the potential for this life-threatening arrhythmia in the setting of a prolonged QTc has led to the withdrawal of several drugs from the market and more intense labeling and warnings for many others. This issue becomes more complex when dealing with oncology pharmaceutical agents because the disease is often life threatening and alternative therapies may not exist. A true TQTS cannot typically be performed with cytotoxic agents and oncology patients are not an ideal population in which to rigorously test these drugs. Although the TQTS has been adapted to evaluate the QT interval and provide oversight for new chemotherapeutics, it will be necessary to develop dedicated protocols to appropriately evaluate cancer therapeutics. Many of these drugs have been shown to have excellent antitumor efficacy, and although QTc prolongation may be present, implementing appropriate risk mitigation strategies allow these patients to receive lifesaving therapies without exposure to serious increased risk.

REFERENCES


