

Evaluation and Management of Cardiac Safety Using the Electrocardiogram in Oncology Clinical Trials: Focus on Cardiac Repolarization (QTc Interval)

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Non-antiarrhythmic drugs have been reported to prolong the QTc interval and induce potentially fatal ventricular tachyarrhythmias. An increasing number of drugs that are used for treating malignancies are no exception. Therefore, both oncologists and regulators expect sponsors of oncology drugs to evaluate, during the development of the drugs, their effects on the electrocardiogram (ECG), particularly on the QTc interval. In the case of agents that cannot be administered to healthy volunteers, the primary approach is to carry out an intense ECG evaluation, employing robust ECG recordings, during early-phase clinical trials, together with characterization of the concentration–QTc interval relationship, and follow this up with an appropriate intensity of ECG monitoring in the later phases of development. This article describes the broad principles of these approaches, including recommendations for exclusion criteria (relative to baseline QTc interval and to cardiac comorbidity); it also describes methods for conducting ECG monitoring and a proposed scheme for the management of any QTc-related effects that may emerge.

INTRODUCTION

Many non-antiarrhythmic drugs have been found to have electrocardiogram (ECG)-related effects; in particular, they prolong cardiac repolarization (the QTc interval). This is an adverse effect that is associated with a polymorphic form of a ventricular tachyarrhythmia known as torsade de pointes. Drugs that are used for treating malignant disorders are also associated with this effect. In light of the potentially fatal outcome of this adverse effect, regulatory authorities and the academic community have long been concerned about the potential of non-antiarrhythmic drugs—established drugs as well as new ones—to prolong the QTc interval or induce other clinically important ECG effects.

Over the past 5 years or so, it has become evident that an increasing number of drugs used in the treatment of malignant disorders are associated with this undesirable effect on cardiac repolarization. As shown in **Table 1**, there is a whole range of pharmacological classes of drugs that have been reported to affect cardiac repolarization and prolong the QT interval. Many

of the pharmacological targets of oncology pharmacotherapy are known to modify the activity of the ether-à-go-go-related gene (hERG) channel that forms the functionally decisive component of the potassium channel (IKr). This latter is primarily responsible for ventricular repolarization.¹ Therefore, drugs that modulate these pharmacological targets are also more likely to alter the electrophysiological characteristics of the human heart, including action potential duration and QT interval. Whereas drugs acting at the hERG channel affect IKr current within minutes or hours, drugs that prolong QT interval by impairing the trafficking of the hERG channel may not manifest their full QT-prolonging effect until 2–3 days after repeated administration. Both oncologists and regulators expect sponsors of oncology drugs to investigate them for their ECG effects with a special focus on the effect on QTc interval. Not surprisingly, therefore, the US National Cancer Institute (NCI) has now added QTc interval to its list of Common Terminology Criteria for Adverse Events (CTCAE.v3) (shown in **Table 2**); QTc interval should not only be studied, graded, and reported according to its severity

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Table 1 Oncology drugs reported to affect cardiac repolarization

<i>Histone deacetylase inhibitors</i>
Depsipeptide (FK228)
LBH589
LAQ824
Vorinostat
<i>Multitargeted tyrosine kinase inhibitors</i>
Sunitinib
ZD6474
ZL647
<i>Vascular disruption agents</i>
Combretastatin A4 phosphate
5,6-Dimethylxanthenone-4-acetic acid
<i>Farnesyl protein transferase inhibitors</i>
L-778123
Lonafarnib
<i>Src and/or Abl kinase inhibitors</i>
Dasatinib (BMS-354825)
Nilotinib (AMN107)
<i>Protein kinase C inhibitors</i>
Enzastaurin
<i>Aurora receptor tyrosine kinase inhibitors</i>
VX-680
<i>Multidrug resistance modulators</i>
S9788
<i>DNA-binding cytotoxic agents</i>
SR271425
502U83
<i>Topoisomerase II inhibitors</i>
Aclarubicin
<i>ErbB-1/-2 receptors inhibitors</i>
Lapatinib
<i>Mammalian target of rapamycin inhibitors</i>
Temsirolimus
<i>Microtubule-stabilizing agents</i>
Ixabepilone
<i>Proteasome inhibitors</i>
Bortezomib (PS-341)
<i>Miscellaneous</i>
Acodazole (NSC 305884)
Arsenic trioxide

and consequences but also be used to determine patient eligibility, dose modification, retreatment, and/or discontinuation of a patient from a clinical trial involving cytotoxic and other drugs used for treating malignancies.

The US Food and Drug Administration's Division of Oncology Drug Products recently presented a review of new drug applications submitted during 2006–2007 for QT

Table 2 QTc interval–related toxicity grading

QTc prolongation grade	Definition
1	QTc >450 but ≤470 ms
2	QTc >470 but ≤500 ms and/or an increase of ≥60 ms from baseline QTc
3	QTc >500 ms
4	QTc >500 ms with life-threatening signs or symptoms (i.e., arrhythmia, CHF, hypotension, shock, syncope, TdP)
5	Death

CHF, congestive heart failure; QTc, rate-corrected QT interval; TdP, torsade de pointes. Data from the National Cancer Institute Cancer Therapy Evaluation Program, 9 August 2006 <<http://ctep.cancer.gov/protocoldevelopment/>>.

evaluation.² The study design, analysis methods, and labeling implications were compared across submissions. Eight of the nine new drug applications submitted contained QT evaluations. Of the submissions with QT data, two contained dedicated QT studies, but neither of these studies met the criteria for a thorough QT/QTc trial (TQT) study as defined by the International Conference on Harmonisation (ICH) E14 guideline. Time-matched concentrations and ECGs providing a pharmacokinetic–pharmacodynamic (PK/PD) model of exposure vs. QTc effect were available in seven of the submissions. Of the six approved submissions, five were found to prolong the QT interval and were labeled accordingly. It was concluded that QT evaluation is now expected to be routine in oncology development.

A number of researchers have advocated various strategies for evaluating the QT liability of an investigational drug in early-phase oncology programs, and the reader is referred to these reviews for further details.^{3–8} The impact of the disease, together with comorbidities and comedications, on patients with cancer is such that they are unable to tolerate excessive testing. Therefore, the search for a precise characterization of the ECG effects of the drug must be carefully balanced against the feasibility of arriving at such precision. This is especially important given that the duration of the QTc interval is a less-than-perfect marker of the risk for proarrhythmia. Therefore, in this article we describe the broad principles relating to intensive ECG monitoring in early-phase oncology trials without compromising either the welfare of the study patients or the scientific objective of gathering the required cardiac safety data. We also consider a number of exclusion criteria (related to baseline QTc interval and to cardiac comorbidity) that can be pragmatically applied during these trials until such time as the ECG-related effects of the new agent are defined. This approach will ensure patients' safety without compromising their access to novel drugs. We also discuss the potential need for an E14-type intense study to define the ECG-related effects (especially the QT effects) in the target population, the level of intensity of ECG monitoring that can be carried out in late-phase trials, and the management of QTc-related effects that may emerge. These recommendations should be adapted to suit individual drugs and their treatment regimens.

ICH GUIDELINES AND ONCOLOGY DRUGS

In May 2005, the Steering Committee of the ICH adopted two QT-related guidelines:

ICH S7B, “The Nonclinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals”;⁹

ICH E14, “The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-antiarrhythmic Drugs”.¹⁰

ICH E14¹⁰ is a broadly applicable guideline that provides only a general framework for investigation of, and regulatory approach to, a drug’s potential to prolong the QTc interval. It does not exempt any drug with systemic bioavailability from scrutiny of its QT-related liability. The central element of ICH E14 is the requirement for a TQT, typically conducted in healthy volunteers, as the primary method of evaluating the QT liability of non-antiarrhythmic agents during their development. Depending on nonclinical data and information from early-phase clinical pharmacology studies, sponsors generally undertake TQT after early clinical pharmacology and dose-ranging phase II studies but prior to pivotal phase III studies, because the result of the TQT drives the intensity of ECG monitoring in phase III clinical trials. ICH E14 recommends that the investigational approach used for a particular drug be individualized, depending on the PD, PK, and safety characteristics of the product, as well as on its proposed clinical use. However, it does not provide any guidance regarding products that cannot be studied in healthy volunteers but that may be studied only in the intended patient populations, which may be atypical in their needs, such as patients with oncologic or orphan diseases. Products intended exclusively for the pediatric population, with a wide range of age categories, also present challenges because of the current regulatory initiatives and requirements for studies specifically in this population.

Clinical trials with drugs used in the treatment of malignant disorders will continue to present many unique challenges, given the widely divergent PD properties of the individual drugs, the variability in the characteristics of the patients enrolled, and the nature of the disease under investigation. ICH E14 acknowledges that there are some drugs that cannot be studied in healthy volunteers because of safety or tolerability concerns (e.g., cytotoxic cancer drugs). In such cases, a TQT in healthy volunteers can be substituted, when feasible, with an intense ECG trial in the target patient population. Clearly, when ethically possible, a TQT in healthy volunteers is the preferred approach to a clinical quantification of the effects of a new oncology drug on cardiac safety. According to ICH E14, when a TQT study is not possible, an intense ECG trial will provide an alternative means of detecting and modifying the proarrhythmic risk. The approach in an intense trial often includes intensive collection and evaluation of ECGs at multiple time points under tightly controlled settings that target a broad range of doses early in development, as well as an evaluation of the relationship between concentration and QT/QTc effects of the drug. We refer to this approach as an “intense ECG (QT) study.”

EVALUATING ECGs IN EARLY-PHASE ONCOLOGY TRIALS

In practice, the paradigm of drug development programs for non-oncology drugs, typically divided into three widely accepted discrete phases (I, II, and III) with well-defined objectives for each phase, can hardly ever be applied in the development of oncology drugs. For these drugs, studies in (usually) small numbers of patients progressively merge from one phase to the next (phases I–II), culminating in larger late-phase studies (phases II–III). Studies qualifying for regulatory approval may be accomplished in phase II or, more commonly, phase III trials.

Although the debate over the predictive value of nonclinical data will never cease, it is now generally acknowledged that nonclinical studies—when conducted in compliance with good laboratory practice and modern standards and techniques—have much to offer. This is especially the case if these studies include investigating the effect of the drug not only on the hERG channel *in vitro* and in dogs *in vivo* but also, where appropriate, on hERG trafficking^{8,11,12} in proarrhythmia models^{13,14} as well as on transmural dispersion of repolarization¹⁵ and triangulation of action potential profile.¹⁶ Studies using more than one assay are obviously more informative.¹⁷ Nowhere is this more true than in the development of the many oncology drugs that cannot be administered safely to healthy volunteers or, at high doses, even to patients. These nonclinical studies are especially helpful in guiding the design of the first-in-human early-phase single ascending-dose studies and multiple-dose clinical pharmacology studies. The current regulatory view in North America is that nonclinical studies have a high predictive value when positive, but negative results are inadequate to reliably exclude a clinical QT risk.⁸ Therefore, every available opportunity should be seized to characterize the ECG-related effects of a new drug as early as possible. Early clinical pharmacology studies, including single and multiple ascending-dose studies and food- and drug-interaction studies, provide an ideal opportunity for investigating the ECG-related effects and the QT liability of the drug in a suitably controlled setting.¹⁸

Evaluating ECG-related effects in early clinical studies

The objectives of first-in-human oncology studies are to ascertain early evidence of potential therapeutic activity, characterize the PK profile, determine dose-limiting toxicities, and define the maximum tolerated dose. Typically such studies are conducted across a very wide range of doses in a number of cohorts. The exploration of dose range in these studies provides the earliest, and often the most robust, opportunity to investigate the potential ECG-related effects and QT liability of the drug.

Because early-phase oncologic drug trials rarely employ control agents and almost never involve a placebo, and the QTc duration has a marked spontaneous variability, the determination of a drug effect requires comparing the change in QTc duration across a wide variety of drug doses and, even more usefully, across a range of exposures (plasma concentration levels). We therefore suggest that all patients enrolled in early clinical studies receive intense ECG monitoring until a data set adequate to assess the effect of the new drug on QTc interval has been obtained. The number of patients required will be inversely related to the

magnitude of the effect on QTc interval, but a minimum data set from 50–100 patients (in the aggregate) from the program should be anticipated in the clinical effective dose range.

There are certain prerequisites to obtaining reliable ECG data in these trials:

- Standardized, centrally calibrated ECG machines should be provided to investigational sites.
- Multiple ECGs should be recorded at baseline (usually at least three, with more precision achieved with six) to obtain more precise point estimates of the ECG parameters measured, in light of the large spontaneous variability in QT, and given that all results are defined by the “change from baseline” analysis.
- The concentration–effect relationship should be measured at several time points after the dose, appropriate to the pharmacology of the drug and the demands that can be tolerated by patients.
- A central core ECG laboratory should be used for standardized, digital morphology analysis and measurements of the cardiac intervals.
- Each patient should be assessed for significant changes in QTcF interval (QT interval corrected by the Fridericia method) at relevant time intervals so as to ensure patient safety.

Each dose–cohort of the new drug should be assessed for a mean change from baseline in QTcF duration to determine the potential for QTc liability and its magnitude.

In terms of a basic framework and design issues, intense evaluation should be undertaken within a single clinical trial; however, if different patient populations are being studied, data from more than one trial may be integrated into one data set, provided the approaches to ECG monitoring across the different trials are broadly similar. ECGs are recorded at baseline; then, at a number of time points after drug administration, ECGs are recorded and plasma concentrations of the drug and/or its metabolites are measured to determine the magnitude of ECG change from baseline and to establish concentration–effect relationships.

Because the primary evaluation is a change from baseline, and also because the intraindividual baseline QTc duration varies by 75 ms on average,¹⁹ we recommend that at least three (preferably six) ECGs, separated by 5–20 min, be obtained at baseline. The mean QTcF interval, computed from baseline ECGs, should be used for comparison with on-therapy values, because the Fridericia correction tends to be more reliable/accurate than the Bazett correction when compensating for changes in heart rate induced by a drug or by clinical conditions. This is especially so when the heart rate increases during therapy as compared with baseline.

After the first dose on day 1, serial ECGs, followed immediately by plasma sampling, are generally required at four to eight postdose time points over 24 h. This time period encompasses the peak plasma concentration (C_{max}) and also allows for the lag in ECG effects due to hysteresis (time taken by a

drug to effect changes in the cardiac ion channels in response to its changing concentrations). However, the choice of time points should be adapted to the individual pharmacology of each drug. These investigations should be undertaken not only on day 1 of cycle 1 ($C1D_1$) after the first dose but also at steady state ($C1D_{SS}$). In addition, at a minimum, single ECGs should be recorded (although a set of three may be more reliable), preferably predose and at C_{max} , on 3–5 additional days of cycle 1. Depending on the clinical setting and the effects observed at steady state, ECGs may be recorded at the end of the cycle to confirm the full time course of ECG effects; however, this step is not absolutely essential. It is estimated that for a 28-day cycle, this approach will entail ECG recording and plasma sampling at no more than a total of 35 time points per subject. If QTc changes or abnormal ECGs are noted, these should be reviewed and evaluated by a cardiology consultant who is experienced in evaluating drug-induced ECG effects, before any further dose escalation is considered. This will allow for a determination of whether other comorbid conditions, events, or new concomitant medications may have complicated the assessment of the drug's effect in an individual patient.

During subsequent cycles, ECG recordings may, in general, be reduced, typically to a single ECG recording before the dose and another at C_{max} on 2–4 days per cycle. However, depending on how reliable the results from cycle 1 are and their level of consistency with nonclinical findings, it may become necessary to repeat the ECG recordings and PK evaluation described for cycle 1 in one or possibly two more cycles. Data from this intense evaluation can then be used to determine the intensity of ECG monitoring required in late-phase clinical trials to further document these effects and their clinical relevance and to safeguard patients in such trials. A careful prespecified statistical plan for analyzing the ECG data and the PK/PD modeling should be developed before generating any trial data.

We believe that, in addition to analyzing central tendency effects of the drug under investigation, an outlier analysis may also be helpful in evaluating its QT liability. Before any conclusions are drawn from outlier analysis, each outlier must be carefully scrutinized for any confounding effect of risk factors such as electrolyte imbalance, comorbidities, and comedications. A compound is considered likely to have a positive QTc effect if, in an evaluation of a minimum of 50 patients, any of these criteria are met:

- ≥ 10 ms change from baseline in QTcF by central tendency analysis or by estimated C_{max} analysis using a PK/PD model;
- >60 ms change from baseline QTcF in $>15\%$ of patients;
- New absolute QTcF >500 ms in $>5\%$ of patients.

Subsequent impact of the QTc effects of a new agent

When the drug under development has a toxicity that precludes its administration to healthy volunteers, we believe that intense evaluation of the ECG effects as described earlier in this article should be adequate to characterize the ECG effects of the investigational oncology agent with sufficient precision and to

define the intensity of ECG monitoring required in late-phase pivotal clinical trials.

We are in agreement with Sarapa and Britto⁷ when they caution that, for a drug that may manifest a modest effect on cardiac repolarization, the use of placebo and positive controls is needed for adequate interpretation of the QTc effect of the drug. In anticipation of increasing regulatory requirements—even for oncology drugs—for a study that is broadly in compliance with a TQT study in healthy volunteers, they propose a thorough QTc assessment in a stand-alone study, which they style as a “dedicated QT study,” in patient populations. They recommend that all dedicated QT studies include single doses of placebo and positive control in a fixed treatment sequence prior to the start of repeat dosing with nonadjuvant anticancer agents. As a matter of principle, one cannot disagree with these recommendations, but we believe that, apart from the ethical constraints (which Sarapa and Britto fully acknowledge) and the practical difficulties of recruiting relatively drug-naïve patients, the extra precision resulting from a thorough QT study in patients would probably not influence subsequent clinical trials, regulatory evaluation of the drug, or its label. Given the potential for unavoidable interactions with comorbidity and comedications in late-phase pivotal trials, we believe that, even when the QTc effect computed from the above intense evaluation is only modest, the subsequent development of the drug should proceed as if the QTc effect is clinically relevant or “positive.”

It has been suggested that a dedicated QT study for a nonadjuvant anticancer agent is negative if the upper 95% confidence interval of placebo-corrected maximum change from baseline excludes 20 ms.⁷ In our opinion, the designation of a study as positive or negative by adapting the threshold for a particular class of drugs is not as important as the more relevant issue of knowing the magnitude of the risk arising from the observed effect on QTc interval and applying this risk–benefit assessment. Stated differently, whereas a non-oncology drug may be deemed nonapprovable if the upper 95% confidence interval of its placebo-corrected maximum change from baseline includes even 10 ms, approval of an oncologic agent that has benefit will be probable irrespective of the magnitude of the QTc change. This is an important point to emphasize because if a 20 ms QTc effect is noted, the mere designation of this change as negative does not relieve the sponsor of the requirement to conduct a more intense evaluation of ECGs in late-phase clinical trials to safeguard patients. After all, this 20 ms threshold is well in excess of the effect of moxifloxacin, a drug known to induce proarrhythmia in patients with risk factors. Given that many patients with malignant disorders are elderly, they are more likely to have cardiovascular and other risk factors related to comorbidities and comedications, which may render them more susceptible to proarrhythmia. Hence, our recommendation is that a QTc liability of <20 ms should not be termed “negative”; we recommend that a 10–20 ms QTc change be considered clinically relevant and that patients in this range, especially those with QT-related risk factors, be safeguarded with careful ECG assessment during treatment. If the upper

95% confidence interval of placebo-corrected maximum change from baseline excludes a value as high as 20 ms, and the study is declared “negative” for QT-related risk on the basis of this, the level of safeguard or protection for the patient will clearly be lower than if a study is declared negative on the basis of more stringent criteria. The purpose of correctly defining a new oncologic agent’s quantitative effect on QTc interval duration as early as possible in the drug development process is to define the cardiac safety-related ECG monitoring needed in future trials and to provide data that will help with the regulatory risk–benefit assessment.

When the drug concerned has no toxicity that precludes its administration to healthy volunteers, we believe that:

- If early-phase intense ECG data from patients demonstrate a clear effect on QTc interval (a mean change from baseline of ≥ 14 ms), a TQT study is not required because this is clearly a positive effect on cardiac repolarization. However, in this scenario, a more intense preapproval scrutiny of the risk–benefit assessment of the drug and a QT warning on the label should be anticipated.
- If early-phase data are equivocal (6–13 ms change from baseline), a TQT study is required in order to rule out a clinically relevant QTc effect. A QT-related warning on the label is likely if the sponsor elects to omit this study from the development program. If a TQT study is not performed, there is a high probability that the Food and Drug Administration and/or the European Medicines Agency will require that it be conducted before the drug is considered for approval.
- If early-phase data demonstrate no relevant effect on QTc interval (≤ 5 ms), an E14-compliant TQT study is advisable so as to fully satisfy regulatory authorities that, in correspondence with nonclinical data, the drug indeed does not prolong the QT interval. If a TQT study is not performed, there is a high probability that the Food and Drug Administration and/or the European Medicines Agency will require that it be carried out either before the drug is considered for approval or, exceptionally, as a postapproval commitment.

Clinical trial exclusion criteria related to baseline QTc interval
ICH E14 suggests three QT-related criteria for exclusion of patients from early-phase clinical trials in general until the effects of the drug on the QT/QTc interval have been characterized. Consistent with the ICH E14 recommendation, many sponsors have used the following exclusion criteria at study entry:

- Prolongation of QT/QTc interval (e.g., repeated demonstration of a QTc interval >450 ms, although we recommend a slightly greater latitude in this respect; please see below) as defined by a screening ECG and preferably determined by a core ECG laboratory using validated digital techniques rather than by the automatic algorithm analysis determined by the ECG recorder;

- History of additional risk factors for torsade de pointes (e.g., hypokalemia, a family history of long QT syndrome or sudden unexpected death, congestive heart failure, and atrial fibrillation);
- Use of concomitant medications that prolong the QT/QTc interval or inhibit the elimination of the agent under investigation.

Strevel *et al.*⁴ have emphasized that the validity of (ICH E14) QT-related exclusion criteria have not been rigorously studied; this has led to concerns that cancer patients may be inappropriately disqualified from trials of promising new agents. A number of other investigators with considerable experience in the treatment of cancer patients have considered the upper limit of 450 ms QTc duration for inclusion to be too restrictive. Available evidence suggests that patients with malignancies have a higher baseline QTc interval as compared to a matched control population with no malignancies. For example, in one report of studies in which prolongation of QTc interval was not an exclusion criteria, ~10% of the male patients and 13% of the female patients with cancer had a machine-read baseline QTc interval >450 ms.²⁰ Sarapa *et al.* also reported that the mean machine-read QTc intervals at baseline were 415.1 (\pm 16.6) ms in 160 cancer patients and 400.6 (\pm 16.9) ms in 41 healthy subjects participating in PK studies.²¹ The maximum QTc intervals were 490 ms in patients and 440 ms in healthy volunteers. Overall, 17 of 160 cancer patients (10.6%) had baseline QTc readings above the upper limit of normal, and this would have excluded them from enrollment if eligibility criteria typical of healthy volunteer trials had been used.

Rock *et al.*⁸ have suggested that, ideally, there should be a minimum difference of 50–60 ms between the upper limit of eligibility and the lower limit of discontinuation or treatment modification. We interpret this to mean an upper limit of eligibility of 450 ms if the lower limit of discontinuation or treatment modification is set at the proarrhythmic threshold of 500 ms.

In an effort to ensure that an otherwise eligible patient is not denied access to promising new treatments, it has been proposed that, for oncology drugs with and without a previous signal for QTc prolongation, QTc interval thresholds for exclusion at screening and prior to dosing be set at 470 and 500 ms, respectively.⁷ We would, however, urge caution with implementation of thresholds of >470 ms for exclusion, and suggest that the possible benefit for a few patients be weighed against the potential risks to the wider patient community arising from what may turn out to be a spurious effect. Many of these patients will have been heavily pretreated prior to randomization, and previous treatment with anthracycline is a significant risk factor for torsade de pointes.²² Furthermore, the normally observed small effect of a drug on QTc interval may be amplified in genetically compromised patients with clinically silent mutation of cardiac ion channels. Factors such as diurnal variation, a very mild QT-prolonging activity of the investigational drug, or *de novo* appearance of electrolyte imbalance could very easily convert a patient's baseline QTc interval from just short of 500 ms (CTCAE grade 2 toxicity) to one >500 ms (CTCAE grade 3 toxicity). In turn, this may lead to adverse

safety-related effects being inaccurately attributed to the drug. Therefore, although the suggestion appears appealing at first, this proposal likely carries certain consequential risks of inappropriate restrictive labeling. To maintain the validity of the data from early-phase clinical trials for quantifying the true effect of the drug on QTc interval, it is preferable that patients who have baseline QTc intervals >470 ms not be enrolled in these early-phase trials. If these patients are otherwise appropriate candidates for a novel therapy, they are best treated in a separate trial on a compassionate use basis but within the intense cardiac safety monitoring program. This approach is also more likely to generate additional data of clinical value in a subset of the population with higher baseline QTc interval values. A comparison of the effect in this subset with that in the main study population will also serve to validate QT-related baseline exclusion criteria.

Exclusion criteria in oncology trials should be individually modified to take into account a number of factors, such as the intensity of signal from nonclinical studies, anticipated baseline QTc intervals in the target patient population (further stratified by gender), the inevitable presence of comorbidities, and the pattern of comedication usage, so as to allow patients to have access to a novel medicine while ensuring their safety. To avoid stifling fair access to a new drug, compromising the safety of subjects randomized to study groups, or risking the ability to quantify the true QTc-prolonging effect of the drug, we recommend the following QT-related exclusion criteria:

- QTc interval duration >470 ms on screening ECG (see above);
- Congenital long QT syndrome;
- Family history of sudden unexpected death from cardiac-related causes, if indicative of a pathogenic mutation of cardiac ion channels;
- Inability to measure QT interval for technical reasons (e.g., 60-cycle interference);
- Obligate use of a cardiac pacemaker;
- Complete left bundle branch block;
- Right bundle branch block and left anterior hemiblock (bifascicular block);
- Coadministration of a medication known to be a potent inhibitor or inducer of the metabolism of the study drug;
- Coadministration of a medication known to affect cardiac repolarization.

The 470 ms threshold for exclusion in early clinical pharmacology and ECG-intensive clinical trials can be adapted upward (<480 ms) or downward (<450 ms), depending on the intensity of the nonclinical signal. According to NCI-CTCAE.v3, all patients with a baseline QTc interval >450 ms can be considered to have already developed grade 1 QT toxicity. The inclusion of patients with CTCAE grade 1 QTc effect is consistent with inclusion of patients with other CTCAE grade 1 effects such as hepatic, renal, or bone marrow dysfunction. However, we emphasize that, in the absence of any risk factor, there are at present no hard data to clearly demonstrate an increased safety

margin with a baseline QTc interval of <450 ms as compared to higher baseline values.

If supported by the QT/QTc interval data from early clinical studies, later clinical trials could expand the eligibility criteria to include a broader spectrum of patients who are likely to receive the drug once approved.

Exclusion criteria related to cardiac comorbidity

Often, because of advanced age, cancer patients are likely to have cardiovascular disease that is not clinically manifest. The presence of cardiac disease is associated with greater prolongation of QTc interval after the administration of a QT-prolonging drug.^{23,24} Previous therapy with anthracycline²² or the presence of malignancy per se may confer an enhanced susceptibility to QT interval prolongation.

The following conditions, which either constitute additional risk factors or interfere with measurement of QT interval, should be included as additional exclusion criteria in early clinical trials until results from the intense ECG (QT) study are known:

- Left ventricular ejection fraction <45% as determined by multigated acquisition scan or echocardiogram;
- Myocardial infarction, angina pectoris, or major cardiac surgery within the 3 months prior to study enrollment;
- Clinically significant bradycardia (typically defined as a heart rate of <50 beats per min);
- History or presence of ventricular tachyarrhythmias;
- Presence of unstable atrial fibrillation (ventricular response >100 bpm);
- Uncontrolled hypertension (>150 mm Hg systolic or >100 mm Hg diastolic blood pressure);
- Other clinically significant heart diseases (e.g., cardiomyopathy).

MONITORING ECGs IN LATE-PHASE ONCOLOGY TRIALS

In accordance with the ICH E14 guidance, the degree of ECG monitoring in late-phase pivotal clinical trials with non-oncology drugs depends on the outcome of a TQT. Similarly, the data from early oncology trials that include intensive ECG monitoring are also expected to influence the intensity of ECG monitoring in late-phase pivotal clinical trials. The absence of an effect on QT interval allows the sponsor to collect on-therapy ECGs in accordance with the current practices in each therapeutic area, and these will constitute sufficient evaluation; however, evidence of a positive effect on QT interval requires the sponsor to implement expanded ECG safety evaluation. Unfortunately, there is at present no generally accepted guidance or consensus on what constitutes expanded or current-practice ECG monitoring in any therapeutic area. The goal is to characterize the magnitude of clinical risk arising from the observed QTc effect of the drug. Neither is there any guidance on the management of patients with certain categories of QT-related response while on therapy.

As stated above, we recommend intensive ECG monitoring in late-phase oncology trials if a compound meets any of the following criteria in early-phase trials conducted with a minimum of 50 evaluable patients:

- ≥ 10 ms change from baseline in QTcF by central tendency analysis or by estimated C_{max} analysis using a PK/PD model;
- >60 ms change from baseline QTcF in >15% of patients;
- New absolute QTcF >500 ms in >5% of patients.

Exclusion criteria in late-phase oncology trials

The exclusion criteria applied in late-phase oncology trials depend on the results of early-phase clinical trials. The selection of these criteria is critical to determining the final label and accessibility to the new drug once it has been approved.

When there is evidence of a QT liability in early-phase clinical trials (per the QTcF-related findings mentioned above), all QTc-related exclusion criteria implemented in early-phase clinical trial should be retained, whereas most of the other cardiac-related exclusion criteria can be eliminated, provided no other cardiac toxicity has been observed. When there is no evidence of a QT liability in early-phase clinical trials (again, as defined above), all QTc-related exclusion criteria should be eliminated in late-phase clinical trials. Other cardiac-related exclusion criteria implemented in early-phase trials should also be eliminated, provided no other cardiac toxicity has been observed.

ECG monitoring for drugs with early-phase evidence of QTc effect

It has been recommended that, when coupled with one or more additional risk factors, a large effect in early-phase clinical trials may warrant more intensive ECG monitoring in the pivotal late-phase studies.⁷ The relevant effect size is defined as the upper 90% confidence interval of >20 ms for a mean increase in QTc interval from baseline, particularly if observed at the likely therapeutic doses. Accordingly, intensive ECG monitoring might include at least triplicate ECG measurement at baseline followed by similar ECG measurements at a minimum of four other time points after the dosing in successive treatment cycles, either in all patients enrolled or in a subset of those particularly susceptible to proarrhythmia. These measurements should be accompanied by measurement of plasma concentrations of the drug and its metabolites. Analysis of the data should include concentration–effect relationship and categorical analysis based on CTCAE QT-toxicity grades.

We are broadly in agreement with this general approach, except that we would recommend intensive ECG monitoring in late-phase oncology trials if a compound meets any of the criteria set out above. As for the intensity of ECG monitoring, we would recommend the following basic approach:

1. Multiple baseline ECGs (minimum of three but six is preferred) should be followed in cycles 1 (C1) and 2 (C2) by:
 - ECGs on days of dosing or once weekly, whichever is less;
 - ECG recordings at the time of maximal QTc effect as determined from early-phase studies, at the end of dosing, and at two to four other time points as warranted.

2. For cycle 3 and thereafter, monitoring of ECGs should be individualized and determined on the basis of the QT-related response of each patient during the first two cycles:
 - If there was no significant QTc effect (such as a QTc interval increase of >60 ms from baseline or new absolute QTcF >500 ms), one ECG per cycle may be recorded.
 - If a significant QTc effect was observed, ECG monitoring as in cycle 1 should be continued for two additional cycles. The duration of monitoring should be individualized depending on the compound and on a consideration of risk vs. benefit.

ECG monitoring for drugs with no early-phase evidence of QTc effect

Multiple baseline ECGs (a minimum of three, but six would yield more robust data) should be followed by one or two ECGs per patient per cycle or whenever routine blood tests are performed to evaluate toxicity in other organs. For intermittent dosing schedules, ECGs recorded at C_{max} are preferred, but for dosing schedules requiring continuous uninterrupted therapy, ECGs may be obtained at any time after steady state is achieved. For the convenience of patients, ECGs should be scheduled to coincide with the days of blood collection for hematologic or biochemical analyses.

MANAGING QT-RELATED OUTCOMES IN LATE-PHASE ONCOLOGY TRIALS

For the ethical reasons discussed earlier and issues related to intraindividual variability in QTc interval, the management of individual patients who develop prespecified categories of responses in oncology clinical trials presents challenges to the sponsor and the investigator alike. We suggest the following approach.

No QTcF change from baseline >60 ms:

- Maintain dose level.
- Reduce ECG monitoring in subsequent cycles.

QTcF change from baseline >60 ms (but absolute QTcF <500 ms):

- Check electrolytes and correct any abnormalities.
- Check concomitant medications for any medications that may be contributing to QTc prolongation.
- Maintain dose level.
- Perform ECG monitoring per cycle 1 (C1) for cycles 2 and 3 (C2 and C3) as well.
- Reduce ECG monitoring in subsequent cycles if there is no aggravation of the effect on QTcF interval.

Appearance of an absolute QTcF interval >500 ms (based on ECG reading at site) that is not associated with symptoms suggestive of a ventricular tachyarrhythmia:

- Repeat ECGs twice within 30 min to confirm the value of the QTcF interval.
- Suspend dosing and obtain immediate evaluation of ECG by the central laboratory.

- Arrange for the patient to be monitored by the investigator with hourly ECGs until QTcF <470 or <30 ms from baseline, whichever is lower.
- Check electrolytes and correct any abnormalities.
- Check concomitant medications for any medications that may be contributing to QTc prolongation.
- Obtain plasma sample for measurement of drug levels and, if the patient consents, blood for pharmacogenetic testing.
- After resolution of the problem, the patient should be retreated at a reduced dose, ECGs should be monitored as in cycle 1 for the first cycle after dose reduction, and:
 - If there is no QTcF change from baseline >60 ms, reduced ECG monitoring in subsequent cycles may be adequate.
 - If there is a QTcF change from baseline >60 ms (but absolute QTcF <500 ms) cycle 1 ECG monitoring should be maintained for all subsequent cycles.
 - If a QTcF interval >500 ms re-emerges after dose reduction, the patient should be discontinued from the trial.
- If QTcF ≥500 ms is not confirmed by the central laboratory and if there is no evidence of drug-related abnormal ECG findings, the study drug may be restarted at the pre-event dose level.

Appearance of an absolute QTcF interval >500 ms (based on ECG reading at site) that is associated with symptoms suggestive of a ventricular tachyarrhythmia:

- Suspend dosing and obtain immediate evaluation of ECG by the central laboratory.
- Hospitalize the patient for rhythm monitoring and hourly ECGs until the QTcF is <470 ms or <30 ms from baseline, whichever is lower.
- Check electrolytes and correct any abnormalities.
- Check concomitant medications for any medications that may be contributing to QTc prolongation.
- Obtain plasma sample for measurement of drug levels and, if the patient consents, blood for pharmacogenetic testing.
- If a QTcF ≥500 ms is confirmed by the central laboratory, and if the cardiac/electrophysiology evaluation confirms that the symptoms are the consequence of a drug-induced QTc interval prolongation, discontinue the patient from the trial.
- In exceptional cases, after the study drug has been interrupted, it may be restarted at a lower dose if the QTcF interval is confirmed by the central laboratory to be <460 ms or <30 ms from baseline, whichever is lower.

CONCLUSIONS

Given the prognoses associated with the diseases under treatment, regulatory authorities have shown considerable pragmatism in their approach to the issue of granting approval for oncology drugs. Arsenic trioxide is a good example of this pragmatism.

However, an increasing number of oncology drugs are now known to prolong QTc interval, a concentration-related toxic effect that can be readily investigated before the drug is approved. Nonclinical data are expected to contribute significantly to this assessment. A thorough QT study provides the ultimate clinical evidence of the level of risk and should be conducted whenever possible. When this is not feasible, the gathering of data on QT effects of the drug should commence as early as possible during its clinical development, preferably with first-in-human administration.¹⁸ In such circumstances, risk assessment requires an integrated assessment of nonclinical data and data from early-phase clinical trials, intensive ECG study, and PK/PD analysis.

In the final analysis, QTc interval is an imperfect marker of the risk that matters most, namely, a potentially fatal proarrhythmia. Therefore, although it is important to determine as precisely as possible the QTc liability of an oncology drug, this requirement should take into account the capabilities and tolerance of the patients. A more collaborative approach, involving the sponsor of the new drug, regulatory agencies, oncologists, and cardiologists, is called for when developing these much-needed drugs.²⁵ Regulatory appraisal of the risk–benefit assessment of the drug, its approvability, and prescribing restrictions requires a delicate and balanced evaluation of the benefits of the drug on the one hand (in relation to the available therapeutic alternatives) and the perceived drug-related risk on the other (risk of torsade de pointes, typically very small), given the prognosis of the condition under treatment.

CONFLICT OF INTEREST

J.M. is the chief scientist of eResearchTechnology and clinical professor of medicine at the University of Pennsylvania School of Medicine and provides expert consultancy services on cardiac safety of new drugs to a number of pharmaceutical companies. R.R.S. was formerly a senior clinical assessor at the Medicines and Healthcare products Regulatory Agency, London, UK, and now provides expert consultancy services on cardiac safety of new drugs to a number of pharmaceutical companies. J.W.S. declared no conflict of interest. The views expressed in this article are those of the authors and do not necessarily reflect the views or opinions of any regulatory authorities, any of their advisory bodies, or any of the sponsor pharmaceutical companies.

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