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Review

Drug-induced QTc interval prolongation: A proposal towards an efficient and safe anticancer drug development

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ABSTRACT

The goal of drug development is to define potential risks and benefits of new therapies. Assessment of new drugs for their potential to alter cardiac repolarisation, prolong QTc interval and induce potentially fatal proarrhythmias such as 'torsade de pointes' is now one of the major goals during phase I–II studies. The results from these early phase clinical studies can profoundly influence 'go, no-go' decisions as well as decisions on the selection of optimal dose regimen for subsequent development, its delivery and conduct of pivotal clinical studies, including eligibility of patients. Increasingly, anticancer drugs are now also attracting attention with regard to their proarrhythmic safety. Unfortunately, regulatory guidelines focus essentially on non-cytotoxic drugs and there is no clear guidance available for evaluation of the potential of cytotoxic drugs to alter cardiac repolarisation during their development. We propose a strategy to assess the QT-liability of a cytotoxic agent in early phase I–II studies without compromising the objectives of these studies or patient access to potentially beneficial novel agents. A pragmatic and thoughtful strategy for the assessment of this proarrhythmic risk and its management, involving close collaboration between drug developers, regulatory agencies, oncologists and cardiologists, is essential for the development of these oncology agents.

1. Introduction

Prolongation of the QT interval can lead to a life-threatening cardiac arrhythmia known as 'torsade de pointes' (TdP). Although prolongation of QT interval is not the best predictor of this proarrhythmic risk, it represents the principal clinical surrogate marker by which to evaluate the torsadogenic risk of a drug and it has been a common cause of withdrawal from the market for several drugs.[1,2]

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Anticancer drugs are a special problem as they are designed to treat a fatal disease. For this reason, assessment of cardiac safety and risk/benefit is more complicated in the field of oncology. The decision of a regulatory agency to approve a promising anticancer agent, and the physician to administer it, is based on the assumption that the benefits of therapy outweigh the risks. Thus, although clinicians, regulatory bodies and drug developers may be able to predict that a given drug may carry some risks due to QTc prolongation, precise determination of the risk/benefit remains difficult if not elusive for the development and clinical use of many anticancer agents.

The first regulatory document addressing the evaluation of non-cardiovascular drugs to alter cardiac repolarisation in humans was published in 1997.[3] Subsequently, the International Conference on Harmonisation (ICH) adopted a tripartite harmonised guidance (ICH E14) document entitled: 'The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs' that was accepted by the regulatory authorities in the United States, the European Union and Japan in 2005.[4]

In addition to conventional new molecular entities, recent experiences have raised concerns about direct or indirect actions of other agents, including biologicals and hormones, to prolong the QTc and/or to induce arrhythmias. Multiple factors have been implicated in causing QT interval prolongation and inducing TdP. Amongst these, inappropriate use of QT-prolonging medications deserves special attention.[5,6] To reduce the risk of TdP, clinicians from all therapeutic areas should understand the fundamentals of drug-induced QTc prolongation, including congenital syndromes associated with QT interval prolongation.[7–10] Data gathered by clinicians, basic electrophysiologists and geneticists have collectively contributed greatly to our understanding of the mechanisms whereby drugs may cause this type of arrhythmia.[11]

2. What is QT interval?

The QT interval on the surface ECG is measured from the beginning of the QRS complex to the end of the T wave (Fig. 1). It is the electrocardiographic manifestation of ventricular depolarisation and repolarisation. These electrical processes in cardiac myocytes are mediated through channels, complex molecular structures within the myocardial cell membrane that regulate the flow of ions in and out of cardiac cells in a well-synchronised sequence. The ventricular action potential proceeds through five phases. The initial upstroke (phase 0—depolarisation) occurs through the opening and closing of Na^+ channels. The repolarisation process begins with the rapid transient outflow of K^+ ions (phase 1). This is followed by a relatively more sustained flow of outward current through two components of delayed rectifier K^+ channels (IK_s and IK_r) and of inward current through Ca^{2+} channels, constituting phase 2 or the plateau phase of repolarisation. Increasing conductance of the rapid delayed rectifier (IK_r) and inward rectifier (IK_i) currents completes repolarisation (phase 3). Phase 4 represents a return of the action potential to baseline. The rapid inflow of positively charged ions (sodium and calcium) results in normal myocardial depolarisation. When this inflow is exceeded by outflow of potassium ions, myocardial repolarisation occurs. Malfunction of ion channels that leads to sustained inward flow of positively charged sodium ions or to impaired outward flow of potassium ions results in prolongation of QT interval. QT interval prolongation can result from drugs, electrolyte abnormalities or other factors. Almost all drugs that prolong the QT interval have been shown to impair the function of IKr channel. At a sub-molecular level, the effect of a drug on IKr current is recapitulated by its effect on hERG (human ether-a-go-go) subunit that is encoded by the *KCNH2* gene. Table 1 summarises the risk factors which could provoke TdP.

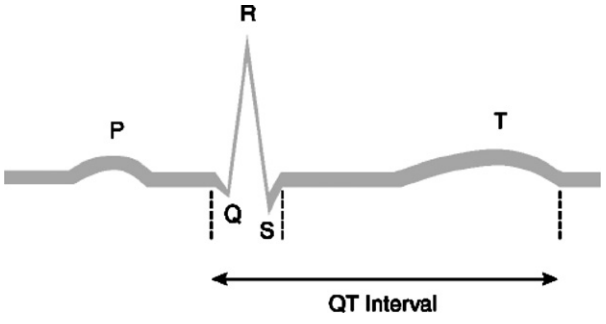

Fig. 1 – ECG representation and QT interval.

Table 1 – Risk factors for 'torsade de pointes' in case of QTc prolongation

Risk factors
Female sex
Age >65 years
Bradycardia (especially recent heart-rate slowing)
Congestive heart failure or cardiac hypertrophy
Clinical or subclinical congenital LQTS
Ion-channel polymorphisms
Baseline ECG that shows prolonged QT or T-wave lability
Post-exposure ECG that shows: QT prolongation, pathological TU morphology and marked post-extrasystolic QTU changes
Mitral valve prolapse?
Diuretic use (independent of electrolyte serum concentrations)
Pro-rhythmic drugs
Hypokalaemia, hypomagnasaemia
High drug concentrations
Anorexia nervosa, 'liquid proteins diets, major gastrointestinal by-pass'
Nervous system injuries (subarachonoid haemorrhage, righ neck dissection, pheochromocytoma)
AIDS?

Modified from Sami Viskin. Long QT syndromes and torsade de pointes. The Lancet 1999; 354(6):1625–33.

3. Measurement and interpretation of the QT interval

The duration of QT interval varies with the heart rate. Thus, a drug can influence the duration of QT interval not only by an inhibitory effect on IKr but also indirectly by an effect on heart rate or autonomic factors. Changes through these indirect factors can easily occur as a result of therapeutic consequences, such as reduction of fever caused by infection, relief of psychological stress or an effect on tumour progression. Because QT interval is prolonged at slower heart rates and shortened at faster heart rates, the measured QT interval

Table 2 – QT correction formulae

Reference	Formula	Advantages	Disadvantages
Nonlinear formulae			
Bazett	$QTcB = (HR/60)^{1/2} = QT\ (RR)^{-1/2}$	The most used; simple limited number of ECG records; more corrections at HR < 60 bpm	Non subjective variable; less correction with long QT
Fridericia	$QTcFri = (HR/60)^{1/3} = QT\ (RR)^{-1/3}$	More correction at HR < 100 bpm	Non-subjective variable; less correction with short QT
Malik	$QT_{ij} = QT_{ij}1000^{\beta j}/RR^{\beta j}$	Subjective variable	Require an high ECG records; applicable only with on drug off drug model
Linear formulae			
Framingham	QTcFr = QT + 154 (1 – HR/60) = QT + 0.154 (1000 – RR)	Expresses in Mses, more correction with long QT, adaptable for men and women	Less correction with short QT
Hodges	QTcH = QT + 1.75 (HR – 60) = QT + 105 (1/RR – 1)	Expresses in s, fits globally the ECGs database; works well with wide populations	Less correction with HR < 60 bpm

QT = QT interval; QTc = QT correction; RR = RR interval; HR = heart rate; B = Bazett; Fri = Fridericia; i = subject variable; β = treatment variable; Fr = Framingham; H = Hodges.

requires a correction for heart rate (to derive heart-rate corrected QTc interval) to standardise it to a heart rate, usually 60 beats per minute, to isolate the effect due to the drug. Dozens of formulae have been proposed for this correction (Table 2). Yet differences of opinion exist regarding the most useful correction for heart rate.[12] None of these corrections has been thoroughly evaluated and compared to each other in patients to determine the most effective formula in predicting which patients are at the greatest risk of the actual clinical risk, namely TdP. One of the commonly used formulae is the Bazett formula, in which the measured QT interval is corrected for heart rate by dividing it by the square root of the R–R interval to yield rate-corrected QTcB interval. However, this formula has been criticised for over- and under-estimating the real effect on QT interval at fast or slow heart rates. Other formulae are the Fridericia cube-root correction (QT interval divided by the cube root of the R–R interval to yield QTcF interval) and the Framingham linear regression equation. From an epidemiological perspective, the Framingham approach is widely used because it is based on empirical data from a large population sample rather than on hypothetical reasoning. For the evaluation of drug effects, however, analyses of drug effect using the Fridericia correction (QTcF interval) have been considered generally satisfactory in studies that are conducted in patients. Correction of the measured QT interval by a subject-specific exponent, when it is possible to compute this exponent, provides a more robust approach to heart rate correction (QTcI interval) and is particularly valuable when the effect is of borderline regulatory concern. Unfortunately, to compute this exponent, a large number of baseline ECGs covering a wide range of heart rates, are required.

4. ICH, QTc interval prolongation and new drugs: non-clinical assessment

4.1. *ICH S7B guideline*

S7B is an ICH guideline that deals with non-clinical evaluation of the potential for delayed ventricular repolarisation by human pharmaceuticals. It promotes a concept of integrated risk assessment, based on the chemical and pharmacological class of the drug together with data from two core tests – *in vitro* IKr or hERG assay and *in vivo* studies in a suitable species. Although a great progress has been made over the last 10 years or so, no single non-clinical assay has an absolute positive and/or negative predictive value or can be considered a gold standard.[13] Therefore, the use of several *in vitro* assays and/or *in vivo* models facilitates accurate decision-making and is recommended by most experts in the field.[14] The sensitivity of non-clinical tests (i.e. their ability to label as positive those drugs with a real risk of inducing QT prolongation in humans) is sufficiently good, but their specificity (i.e. their ability to label as negative those drugs carrying no risk) has been challenged. Although S7B does not refer to it, transmural dispersion of repolarisation seems to be another marker of the torsadogenic potential of a compound.[15] This parameter is a measure of the radial dispersion of repolarisation across the ventricular wall and is the interval from the first repolarisation of the specialised M cells located in the midmyocardial layer to the epicardial cells.[16] This radial dispersion of repolarisation generates local electrical gradients and appears to provide the electrophysiologic substrate necessary for the induction of TdP. Consequently, transmural dispersion of repolarisation, rather than QTc interval prolongation, is thought to be more predictive of the potential risk of developing TdP.[17,18]

5. QTc interval prolongation and new drugs: clinical assessment

5.1. *ICH E14 guideline*

New drugs present a special problem, because clinical experience with each drug is limited at the time of their evaluation by regulatory authorities such as the US Food and Drug Administration (FDA) or the European Medicines Agency (EMEA). Many new agents may be shown to produce a small degree of QTc interval prolongation but with limited rigorous

data on effects at high exposures that are likely to occur in some patients post-approval. As a result, ICH E14 focuses on a more systematic clinical evaluation of a drug for its effect on QTc interval in man. According to ICH E14, drugs are expected to receive a clinical electrocardiographic evaluation, beginning early in clinical development, typically including a single trial dedicated to evaluating their effect on cardiac repolarisation ('thorough QT/QTc study' or TQTS).

5.2. *'Thorough QT/QTc study' or TQTS*

The TQTS is an *in vivo* bioassay designed to evaluate precisely the propensity of a drug to prolong the QT interval in humans. Normal healthy volunteers receive in a randomised crossover sequence or in parallel groups: placebo, a positive control that slightly prolongs the QT interval, the study drug at therapeutic dose and the study drug at a supratherapeutic dose. Other important features of a TQTS include digital ECG data collection with rigorous methodology, ECG readings manually by experts with suitable training, application of appropriate heart rate corrections of measured QT interval, analysis of an effect of the drug on central tendency (mean study population-based effect) and categorical analysis (data on individuals with pre-specified changes of concern from baseline) and characterisation of concentration–effect relationship by simultaneous measurement of plasma concentrations of the drug and its metabolites and recording the pharmacodynamic ECG effect on QTc interval. The positive control is intended to ensure the sensitivity of the study to detect small effects on QTc interval whereas the placebo arm compensates for other variables and allows determination of the true effect of the drug *per se*.

The guidance recommends that subject enrollment for a given trial would be influenced by the clinical and non-clinical information available on the effects of the drug on cardiac repolarisation. Until the effects of the drug on the QT/QTc interval have been characterised, the following exclusion criteria are suggested:

- A marked baseline prolongation of QT/QTc interval (e.g. repeated demonstration of a QTc interval >450 milliseconds (ms)).
- A history of additional risk factors for TdP (e.g. heart failure, hypokalaemia, family history of Long QT Syndrome).
- The use of concomitant medications that prolong the QT/QTc interval.

If supported by the QT/QTc interval data from the 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.

5.3. *Applying TQTS principles to phase I oncology trials*

ICH E14 acknowledges that there are some drugs that cannot be studied in a TQTS in healthy volunteers due to safety or tolerability concerns (e.g. cytotoxic cancer drugs). In such cases, the TQTS can often be conducted in patient populations. However, as discussed below, the TQTS design is not ideally suited to cytotoxics or other similar oncology products even when conducted in patients, given the clinical history of this population. Therefore, for the development of cytotoxic oncology products, discussions continue between regulators and other stakeholders about the most optimal methods for gathering data on their QT-liability.

Cardiac safety in its broad terms is often evaluated in oncology in phase I studies, conducted in patients with advanced malignancy. Patients with cancers are in general elderly with multiple co-medications and co-morbidities. Pre-existing clinical features in these patients comprise some of the above exclusion criteria suggested in ICH E14, including the presence of significant cardiovascular diseases. It is frequently not possible to discontinue co-medications, even if these carry a mild degree of QT-liability. Administrations of a positive control or placebo are equally indefensible. Oncology phase I studies are not commonly randomised (crossover or parallel) with placebo groups, and they often lack the internal controls, rigor and eligibility requirements recommended for the TQTS.

There are several other concerns that need to be highlighted when designing Phase I trials in oncology. These are probably unique to oncology and may be different from other therapeutic areas.

Patient capabilities and compliance in tolerating trial demands must be considered. The timing of ECG collection is usually concomitant with pharmacokinetic blood sampling and requires an outstanding level of compliance from patients enrolled into the study. Because of concomitant medications, rapid assessment and decision making during administration of the drug with a significant risk of QTc prolongation can induce psychological distress that needs to be mitigated through education and preparation including the informed consent process.

Another level of concerns is related to protocol issues. Trial protocols described in ICH E14 have many features feasible in healthy volunteers or in patients from many therapeutic areas, but are not suitable for conventional care of patients with advanced malignancy.

Oncology trial issues can be divided into design issues and technical ECG issues. The trial design issues originate from defining the purpose of the study and how the potential QT evaluation will affect the trial. Definition of clinical trial inclusion criteria is an important consideration. In two phase II studies, the appropriate reference values of QTc interval for adult patients with haematological or solid tumours, enrolled across various programmes were evaluated.[19,20] Data indicated that the distribution of QTc interval duration was greater in these patients when compared with results from a trial with similar ECG methods conducted in healthy volunteers. This implies that if exclusion criteria of 450 ms were considered for oncology trials, more than 10% of patients would be excluded from phase I or phase II studies because of marginally prolonged QTc interval at baseline.

It is also necessary to emphasise that the QTc threshold for exclusion as well as other exclusion criteria should also be driven by non-clinical data. In view of the major difficulties encountered in conducting a formal TQTS for a cytotoxic oncology product, it is not appropriate or ethical to exclude all patients with prolonged QTc at baseline. Such exclusions also raise significant clinical dilemmas for investigators, pa-

tients and caregivers alike because phase I studies offer access to new agents that can provide perhaps the only opportunity for disease control. In addition, and perhaps more importantly, the risk and the frequency of QTc prolongation do not correlate well with the risk and the frequency of significant arrhythmia or other adverse clinical outcomes. Therefore, the quest for precise characterisation of a new investigational cytotoxic agent for its potential to prolong the QTc interval should not obscure the more desirable objectives of phase I clinical trials to define the relative benefits and risks of treatment alternatives.

There is also a need to make many protocol decisions related to the technical aspects of capturing ECGs. Although these issues can be approached essentially in the same manner in oncology trials as in trials in any other therapeutic area, the special needs of oncology patients must be recognised. These special needs are related to the performance status of the patients: a rapid disease progression or a symptomatic disease could affect compliance of the patient with an 'intensive' cardiac monitoring protocol. ICH E14 addresses these technical issues in very general terms only but more details are provided in other publications.[21]

6. QT assessment in phase I trials with anticancer agents

There is little doubt that cytotoxic drugs, like drugs in other therapeutic areas, need characterisation of their QT-liability. Therefore, for the development of anticancer and other special agents, designs of clinical study protocols to characterise QTc prolongation remain an area of active research and discussion amongst the pharmaceutical industry, the investigators and the regulators.

Although there are no specific recommendations in E14 that apply to special drugs such as those in oncology, it is acknowledged therein that certain factors could reduce the need for a TQTS. These include the inability to conduct the study in healthy volunteers or patients, how the drug is studied and used (e.g. administered under continuous monitoring), as well as non-clinical data.[4] Therefore, when a TQTS is not possible even in patients, ICH E14 emphasises that 'the importance of detecting and modifying this safety risk means that other ways of detecting effects on the QT/QTc interval need to be developed. These might include the collection of ECGs at multiple time points under tightly controlled settings that target a broad range of doses early in development'. At the heart of the guidance is the concept of the TQTS but we believe that this wording from E14 is the key to investigating difficult drugs.

With regard to non-clinical data, the technology and methodology for non-clinical testing of drugs have improved greatly over the last 5 years and sponsors of new drugs now use a battery of standardised non-clinical tests. In a recent survey, non-clinical models used to evaluate changes in cardiac repolarisation included hERG assay (93% of the respondents) action potential duration (APD) (68%) and *in vivo* QT study (100%).[18] Non-clinical studies, conducted in compliance of ICHS7B, provide information that is of particular value to the development of cytotoxic agents since other approaches are formidable or prohibitive in oncology. Not only are these studies helpful in guiding the initial dosing regiment that can be tested safely from cardiac viewpoint but they also provide corroborative evidence to support the conclusions from ECG studies in patients.

Usually a well-conducted early phase I study with robust ECG monitoring in a sizeable subset of patients could achieve an acceptable dataset well within the spirit of TQTS for adequate assessment of the QT-prolonging potential of an anticancer drug. The decision to develop or approve an anticancer agent with QTc liability ultimately rests on an estimate of the perceived risk relative to the expected benefits for patients and society. Estimates of benefit are specific to particular indications, but they also include an assessment of morbidity or mortality associated with the disease under treatment, the expected favourable impact of a new treatment and consideration of efficacy and toxicity of other available alternative therapies.

To comply as much as possible with the principles that underpin a TQTS, we propose collecting detailed data on factors that can potentially induce QTc prolongation (such as concomitant medications, cardiac disease and other factors known to prolong the QTc interval) during the screening period (drug-off phase). The design of the study should be tailored to gather appropriate cardiologic data (with robust monitoring of ECG) before and after treatment administration (drug-on phase). This 'crossover' study design could be employed ethically without significant clinical burden for the patient. Even for drugs with long half-life or with active metabolites and/or for schedules consisting of multiple doses, it is usually not appropriate to use a 'parallel group'. The limitations arising from this pharmacokinetic or dosing issue could be overcome by adapting cardiac monitoring to the pharmacokinetic profile of the drug, including plasma concentration profile. In addition, other variables that could influence the assessment of ECG effects of the drug (such as meal composition and schedules, activity level and environmental factors) should be recorded and equalised between drug-off and drug-on periods. ECG collection methodology should also be standardised and requires a well-equipped clinical pharmacology unit with trained and experienced staff.

If there is no known QT prolongation risk due to the drug, then routine recordings of ECGs can be undertaken at baseline, at peak drug concentrations and at a pre-defined timepoints after the dosing in case there is QT-liability related to a metabolite or tissue accumulation. Digital data collection and a centralised review of ECGs by a cardiologist with an expertise in measuring ECG intervals are essential and this could be implemented, as for non-oncology drugs, to achieve the desired objective of such a study. The proposed 'drug-off drug-on' design could be compromised by a large degree of spontaneous QTc variability observed within a single patient and we do not dismiss the difficulties of assessing a mean change in drug-induced QTc prolongation as the primary endpoint in this sub-study nested within the phase I study. However, the practice of defining dose-limiting toxicities (DLTs) is central in Phase I oncology trials. One can use the version 3 of Common Toxicities Adverse Events (CTCAE.v3) definition of grade 3 QT prolongation as a general guideline (QTc >500 ms documented by three repeated ECG over 5–10 min, without life-threatening arrhythmias). This approach would be con-

sistent with the analysis of data by categorical responses as recommended in ICH E14 for the TQTS. Therefore, another complementary approach would be to establish the duration of QTc interval prolongation that constitute grade 2 (e.g. >470 ms or a change of >60 ms above baseline) and grade 3 toxicities (e.g. >500 ms) and to document the frequency of these 'ECG events', without trying to characterise small changes in mean QTc interval from baseline.

7. PK/PD analysis

We believe that evaluation of a cytotoxic drug to affect cardiac repolarisation requires an integrated assessment of non-clinical data, clinical data from early phase 1 clinical trials and the relationship between concentration and effect. The dataset on a range of concentrations of the drug can be enriched by further integrating robust ECG monitoring in phase 2 studies investigating various dose schedules of the investigational drug.

Regulatory authorities such as the FDA have gathered extensive PK/PD data on a large number of drugs and developed considerable expertise and experience in understanding the significance of this relationship with respect to drug-induced QTc interval prolongation. Evaluation of data on concentration-QTc effect generated during early phase clinical studies has been used not only to absolve the need for a TQTS when these data are indicative of a risk but also to determine dose schedules that might be appropriate for safe use of the drug and to determine dosing regimes in patients with comorbidities such as hepatic impairment.

If the dataset is large enough, it may also be possible to determine interactions between the investigational drug and other factors that influence the risk of QTc interval prolongation.

8. Conclusions

Clinicians in oncology are increasingly faced with both older and new anticancer agents with potential to prolong the QTc interval, a laboratory finding that is associated with an ill-defined risk of significant cardiac arrhythmias. As more sensitive methods for electrocardiographic testing are applied, an increasing number of anticancer agents or treatments for supportive care will likely be described with some risk for QTc prolongation. For many agents, the frequency of QTc prolongation may be common whilst the risk of clinical arrhythmia (TdP) may be very rare. To enable the development and application of future treatments, detailed analyses and publication of arrhythmic events (including TdP), observed in cancer treatment settings, should continue to support rational strategies for risk management with broad relevance. Oncologists have demonstrated their abilities to identify and manage complicated cardiac risks in clinical investigations and general practices.

Arsenic trioxide (ATO) is a particularly interesting example of successful risk management, supporting the decision for a patient to accept, or a physician to administer an anticancer drug with established risk of QTc prolongation and TdP. Although this drug is known to provoke TdP[22] it is also uniquely effective in an otherwise fatal disease, relapsed acute promyelocytic leukaemia.[23] Therefore, until alternative therapy becomes available, arsenic trioxide remains a drug of choice, despite its potential for causing arrhythmia. In patients receiving multiple courses, QTc intervals may return to pre-treatment levels before the second course, signifying that serial ATO administration does not permanently prolong the QTc interval; however, documented episodes of TdP have been diagnosed beyond the first month of treatment, presumed due to drug accumulation in cardiac tissue.[24] Given appropriate ECG monitoring, identification of contributory factors, and management of electrolytes and concomitant medications, ATO can be safely administered.[25–27]

Across many geographic regions, successful risk management is exemplified by the published experiences with ATO, highlighting the value of systematic ECG testing and attention to concomitant medications, electrolyte abnormalities and co-morbidities, all likely contributing to low frequency of clinical cardiac toxicities reported post-approval. Lately a systematic review has reported that QT interval prolongation is also associated with several novel oncology non-cytotoxic therapies (e.g. histone deacetylase inhibitors, tyrosine kinase inhibitors, vascular disruption agents and farnesyl protein transferase inhibitors).[28] Given the growing introduction of these promising agents, designed to fulfill unmet medical needs, efforts are needed to promote strategies for risk detection and management, avoiding unintended consequences that can impede development, regulatory approval and patient access. More research is needed to assess and manage cardiovascular safety of patients treated with anticancer agents, beginning with a well-organised collaboration between oncologists and cardiologists, and these efforts should have broad relevance to therapeutics designed for treatment or supportive care in oncology.

Conflicts of interest statement

None declared.

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