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Editorial Comment

QTc prolongation and/or oncology drug development: Who's in danger?

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Over recent years, several non-oncological agents were removed from the market based on cardiac toxicity due to prolongation of the cardiac repolarisation, defined as prolongation of the QTc interval on the ECG, observed post registration. This resulted in enhanced regulatory attention on cardiac safety monitoring during drug development and, in May 2005, the implementation by the FDA of the E14 'Clinical evaluation of QT/QTC interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs'.[1] These guidelines have been written in the light of drug development in non-oncological areas and do not take into consideration the differences in the patient population, in study design or the risk-benefit balancing relative to potential QT-liability and potential anticancer efficacy.

During the development of new drugs a continuous benefit and risk assessment takes place. The involved considerations will be different and dependent on the patient population targeted. In oncology the nature and severity of the disease is such that most patients with metastatic disease will still succumb to their disease. Balancing the need for novel treatment in this area against the risks of the medical products will result in accepting more toxicity compared to other indications, as is presently the case for many standard therapeutic options in oncology. Also, the intense lobbying of patient representatives for early access to experimental drugs indicates the willingness of this patient population to accept more risks than the regulatory community.[2]

Cardiotoxicity is a well-known side effect of oncology drugs. Anthracyclines induce a cumulative dose related risk of developing cardiac heart failure. Also, treatment with trastuzumab is associated with cardiac dysfunction.[3] Another chemotherapeutic agent causing cardiac toxicity is paclitaxel, resulting in cardiac rhythm disturbances, mainly bradycardia.[4] Despite these cardiac toxicities all three agents are accepted as the standard of care since their benefits outweigh the risks of treatment.

Recently, concerns have been raised about the prolongation of the cardiac repolarisation by hormones, targeted agents and cytotoxics with the potential risk of development of life-threatening cardiac arrhythmia, although the likelihood of clinical morbidity due to arrhythmia is small.

In this issue of the EJC, Curigliano et al. propose a strategy to translate the guidelines of the FDA to assess the proarrhythmic risk of cytotoxic agents in early phase I and II studies and elaborate on the challenges it imposes on oncologic drug development.[5] The electrophysiological measurement of QT/QTc, assessed by electrocardiogram, is used as a biomarker for predicting the risk of a potentially fatal arrhythmia although the QTc-interval is not highly correlated with the risk of torsades de pointes.[6] Notwithstanding, the latter is used in human clinical trials. The definition of the normal

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QT/QTc interval is based on data derived from healthy drug-free volunteers, men and women aged between 18 and 45 years.[6] Several studies indicate that in cancer patients, possibly due to increasing age, co-morbidities, prior cancer therapy and the use of co-medication, more than 10% of the patients had a prolonged QTc interval as defined by these criteria, thereby excluding these patients from access to new anticancer drugs if patients with prolonged QTc time at baseline are excluded.[7,8] Patients are also required to have normal values for potassium, sodium, magnesium, phosphate and calcium at entry and during the study since changes in these ions may impose an increased risk of QT/QTc prolongation. However, in our experience, this will limit the eligibility of patients considerably and will also have a major impact on drug delivery once on trial. Also, the use of many co-medications, a.o. 5HT3 antagonists, is restricted at base line and during the study because of the possible effect on the QTc interval. However, these restrictions are not consistent with conventional care of patients with advanced cancer and, as such, are not feasible.

As discussed by Curigliano, there are several methods to define the QTc time.[5] The Bazett and the Fridericia formulas are commonly used for correction of the QT/QTc interval for heart rate. In the phase I study of combretastatin A4 phosphate, calculation of QT/QTc by both the Bazett formula and the Frediricia formula resulted in a mean difference of 30.8 versus 17.5 msec, respectively, compared with the baseline QT/QTc indicating the implications of lack of uniformity in defining QT/QTc .[8–10] Also, the relatively small number of patients in phase I studies, the lack of time-matched controls in a placebo group and the lack of a positive control group during oncology trials will result in QT/QTc data that will be difficult to interpret.[11] Of even greater importance are the growing inconsistencies in technical approaches. Inadequate acquisition or measurement of ECG data may bring about an incorrect assessment of the ECG effects of a drug.[6] Properly centralised ECG laboratory methods and digital processes are required. Meanwhile, the implementation of all these additional examinations will have a major impact on the costs of drug development and will put a tremendous logistical and financial burden on clinical research resources.[12]

Risk-benefit assessments might be relatively straightforward in non-oncological studies and are provided in the ICH E14 document. In principle, risk-benefit must be interpreted in the context of the nature and severity of the disease and conservative approaches will delay or prevent patient access to innovative treatment. Currently, different criteria are used in defining which prolongation of the QT-QTc time or change over baseline is feasible. The use of uniform thresholds to describe changes of concern for all protocol applications can simplify study conduct and subsequent data collection.[9] As suggested by Curigliano et al., grading according to the Common Toxicities Adverse Events version 3 (CTCAE v3) might be considered a uniform guideline in which grade 3 QT-QTc prolongation is defined as a value exceeding 500 msec.[5] In oncology trials, treatment related events of grade 3 or higher are often considered for decision making and dosing decisions. Asymptomatic prolongation of the QT-QTc time exceeding 60 msec over baseline may be too sensitive to guide dosing in oncological studies, since these changes can already be observed as a diurnal variation, even in healthy volunteers, and might even be larger in oncological patients.[9,11]

Of utmost importance is that the data generated in oncological studies are pooled to provide additional information on the Qt/QTc interval in cancer patients and to guide us to broaden the eligibility criteria of studies in the oncologic setting, to implement the concomitant use of for oncology relevant medication, to standardise dose-modification and discontinuation criteria, to search for alternatives in study design and result in timely approval of drugs by the regulatory authorities providing access for patients to promising new anti-cancer agents.[11]

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