Assessing Cardiac Safety in Oncological Drug Development

Advances in the development of anti-cancer drugs, including immuno- and targeted therapies, have decreased mortality rates for many cancers and increased patient survival. However, despite these improvements, concerns have been raised about possible medium- and long-term adverse effects of these new anti-cancer agents, including, specifically, the risk of cardiovascular toxicity. Cardiovascular diseases are increasingly being recognised as an adverse effect of anti-cancer therapies. Attention has mostly focused on heart failure, but other types of cardiotoxicity, including cardiac rhythm disorders, can occur in patients with no underlying cardiomyopathy.

This article reviews the main mechanisms of cardiotoxicity for older and more recently developed drugs in cancer patients, focusing particularly on atrial fibrillation (AF), ventricular tachycardia (VT), and QTc prolongation, and their characteristics. We also advocate for the establishment of advanced cardiovascular safety assessments during the development of new drugs, to mitigate these risks.

Cardiac Toxicity of Anti-cancer Drugs

There is no universal definition of cardiotoxicity. The definitions used in clinical trials differ, but all define cardiotoxicity on the basis of various criteria relating to coronary artery disease, cardiac arrhythmias, conduction abnormalities or heart failure (HF).

Cardiac arrhythmia in cancer patients can be worsened by a combination of multiple concomitant factors, such as underlying heart disease, direct effects of the tumour on the cardiovascular system, and the cardiotoxicity of the anti-cancer treatment. Myriad mechanisms may contribute to this process, including immune system modulation, systemic inflammation, electrolyte or endocrine abnormalities, impaired oxygenation, and direct cardiac metabolic alterations, potentially leading to death. Arrhythmias appear to be an underappreciated adverse effect of anti-cancer agents, and their incidence, significance and underlying mechanisms are currently under investigation.

In the context of anti-cancer treatment, arrhythmias seem to result from a combination of effects leading to direct and acute modifications of specific molecular pathways critically linked to arrhythmogenesis (such as IKr inhibition prolonging the QTc interval) or indirect mechanisms with effects in the medium-to-long term, due to the creation of a substrate for structural arrhythmia (such as myocardial damage/modification through inflammation, fibrosis, apoptosis or ischemia).

Many drugs have been shown to produce a small, but reproducible effect on prolonging QTc interval. In particular circumstances, this marked prolongation of the QTc interval may trigger the form of polymorphic ventricular tachycardia known as 'torsades de pointes' (TdP) (generally through direct hERG-channel inhibition and/or by phosphoinositide-3-kinase pathway inhibition for anti-cancer drugs), which may cause syncope or sudden cardiac death.

Cancer patients seem to be particularly at risk of having multiple factors precipitating TdP (e.g. prolonged baseline QTc duration, hypokalemia, bradycardia, and the co-administration of drugs blocking IKr). This is because both the cancer itself, and the drugs used to treat it can induce hypokalemia (by causing vomiting and diarrhoea) and cancer patients often present comorbid conditions that can increase the risk of QTc prolongation (e.g. hypocalcemia or hypomagnesemia). Most, but not all, ventricular arrhythmias induced by anti-cancer agents are, therefore, related to QTc prolongation.

As summarised in Table 1, the major anti-cancer drugs responsible for QTc prolongation in this context are kinase inhibitors, arsenic trioxide, anthracyclines, histone deacetylase inhibitors, anti-androgens and selective oestrogen receptor modulators.

Pharmacological class	Known risk	Main anticancer drugs	Specific comments
Anthracyclines	Acute: **any form of arrhythmia, QTc prolongation, TdP, sudden death** Delayed: **AF** (with or without heart failure)	Doxorubicin Epirubicin	**Dose-independent effects are presumed** **No FDA statement**
Other **cytotoxic agents**	Acute: **QTc prolongation, TdP, Sudden death, AF, VT** Delayed: **AF**	Gemcitabine Cisplatin Melphalan, cyclophosphamide Arsenic trioxide	**Intra-class variability** concerning risk of arrhythmic side effects **Dose-dependent effects** regarding QTc prolongation induced by arsenic trioxide **FDA boxed warning**: QTc prolongation (arsenic trioxide)
Kinase inhibitors	Acute: **QTc prolongation, TdP, Sudden death** Delayed: **AF, VT without any QTc prolongation**	Anti ALK: ceritinib, crizotinib Anti BCR-ABL: bosutinib, imatinib, nilotinib, ponatinib (+ anti-VEGFR) Anti BTK: acalabrutinib, ibrutinib Anti CDK: ribociclib Anti EGFR/HER2: afatinib, lapatinib Anti RAF/MEK: dabrafenib, regorafenib (+anti-VEGFR), sorafenib (+ anti-VEGFR), trametinib, vemurafenib Anti VEGFR: cabozantinib, lenvatinib, nintedanib, Pazopanib, sunitinib, vandetanib	**Intra-class variability** concerning risk of arrhythmic side effects **Dose-dependent effects** regarding QTc prolongation **FDA boxed warning**: QTc prolongation for vandetanib and nilotinib **FDA warning and cautions**: AF for ibrutinib, QTc prolongation for several KIs (sunitinib, lapatinib, crizotinib, vemurafenib, sorafenib, ceritinib, pazopanib, ribociclib, dasatinib, bosutinib and lenvatinib)
Histone deacetylase inhibitors	Acute: **QTc prolongation, TdP, sudden death**	Depsipeptide, panobinostat, romidepsin, vorinostat	**Dose-dependent effects** regarding QTc prolongation **FDA boxed warning**: QTc prolongation
Selective estrogen modulators	Acute: **QTc prolongation, TdP, sudden death**	Tamoxifen, toremifene	**FDA boxed warning**: QTc prolongation for Toremifene
Androgen deprivation therapy (anti-androgenics)	Acute: **QTc prolongation, AF, TdP, sudden death**	Anti-CYP17: abiraterone GnRH agonists: leuprolide, goserelin GnRH antagonists: degarelix	**Intra-class variability** concerning risk of arrhythmic side effects **FDA warning and cautions**: QTc prolongation (leuprolide, goserelin, degarelix)
Immune Checkpoint inhibitors (anti-CTLA4, anti PD-1/PDL-1)	Acute: **any form of arrhythmia** (revealing, or not, a myocarditis	Anti CTLA4: pembrolizumab Anti-PD-1: nivolumab Anti-PDL-1: atezolizumab, avelumab, durvalumab	**Dose-independent effects** **No FDA statement**
Other immunotherapies	Acute: **AF, sudden death**	Cytokine: interleukin-2 Anti-CD20: rituximab Anti-EGFR: cetuximab, necitumumab	**Intra-class variability** concerning risk of arrhythmic side effects **FDA boxed warning**: sudden death with cetuximab and necitumumab

Source: Courtes of Joe-Elie Salem, MD, PhD and J. Alexandre et al. / Pharmacolo & Therapeutics 1892018 89–103

Table 1 Cancer therapies and associated arrhythmia profiles

Recent studies focusing on anti-cancer drugs leading to QT prolongation have revealed new pathways of drug-induced QT prolongation, in addition to the well-known effects involving direct IKr blockade. The identification of non-IKr-dependent pathways leading to QT prolongation will be important for risk assessment, not only for anti-cancer therapies, but also for other QT-prolonging drugs. The identification of these new pathways, most of which are mediated by phosphoinositide-3-kinase pathway inhibition, will shed light on the importance of new signalling pathways modulating QT duration and the associated risk of arrhythmia.

Many cancer therapies, especially kinase inhibitors, require QT monitoring, and warnings are clearly printed on the FDA label (see Table 1). For example, ribociclib (Kisqali, Novartis) is a recently approved kinase inhibitor (CDK4/6 inhibitor) for breast cancer. The FDA label recommends monitoring QT at baseline and during the first two cycles of treatment. Anti-androgenic therapy, used in prostate cancer, has also been associated with a QT prolongation of 10 to 20 milliseconds. QT prolongation has also been observed in early clinical trials for luteinising hormone agonists (leuprolide, goserelin) and antagonists (degarelix), prompting the FDA to issue warnings for these therapies.

In addition to QT prolongation, cytotoxic chemotherapy (anthracyclines, gemcitabine, cisplatin and alkylating-agents) or kinase-inhibitors (KIs), such as ibrutinib, can also drive supraventricular tachycardia, mostly involving atrial fibrillation. Heart failure on anthracyclines, trastuzumab and other agents is also of particular importance in adjuvant therapy for breast cancer patients, in whom life expectancy may be more severely affected by serious cardiovascular events than by cancer prognosis.

Is Cardiotoxicity Adequately Assessed in Current Trials?

Despite growing concern about the cardiotoxic side-effects of new anti-cancer agents, a surprisingly small number of ongoing trials include cardiac end points in their design. According to the clinicaltrials.gov website, current cancer-related trial designs are heterogeneous and non-standardised in terms of the methods used to assess cardiotoxicity. Few of these studies include cardiac safety among their primary or secondary endpoints.

Cardiovascular risk factors are often considered in the inclusion criteria for these trials, but population-based impacts (e.g. age, comorbid conditions) should also be taken into consideration during the management of patients receiving these new therapies, to prevent the creation of arrhythmogenic substrates.

Establishing a causal relationship between anti-cancer agents and cardiac arrhythmia remains challenging, due to interference from the following factors:

- Comorbid conditions in the patients: cancer patients often have concomitant common diseases, such as hypertension, diabetes or heart failure, which may increase their susceptibility to arrhythmia,
- Complex treatment regimens: anti-cancer drugs are usually used in combinations, making the establishment of causality more challenging.

Risk stratification is therefore important in these studies, and requires greater collaboration between cardiologists and oncologists.

Along with greater standardisation in the use of traditional endpoints, such as the monitoring of left ventricular function (LVEF), there is a need for the prospective validation and integration of novel endpoints and means of diagnosis, such as diastolic dysfunction and serum biomarkers. New initiatives are advocating new definitions of cardiac toxicity and proposing standard designs and strategies, to increase the efficiency of cardiotoxicity evaluation for novel anti-cancer agents.

QT Interval Assessment

The QT interval of the electrocardiogram corrected for heart rate (QTc) remains the gold standard (despite its well-recognised limitations) method for measuring the duration of ventricular repolarisation in human studies. It is still widely used as a surrogate marker of ventricular arrhythmia risk.

Bazett's correction (QTcB = QT/RR^0.5) has been widely used, but Fridericia's correction (QTcF = QT/RR^0.33) is currently preferred, in accordance with the E14 ICH Guideline adopted by the FDA and EMA in 2005, as this correction is generally more accurate.

Standard guidelines provide a classification and severity grading system for drugs considered to have a clinically significant QTc interval-prolonging effect: a QTc >500 ms and, to a greater extent, a QTc >550 ms, are associated with at least a two- to three-fold increase in the risk of TdP (Priori *et al.*, 2003; Sauer *et al.*, 2007).

QT interval varies between individuals and is influenced by diverse physiological and pathophysiological factors, including sex, age, heart rate, electrolyte concentrations, concomitant cardiac disease, and other diseases, such as diabetes.

Evaluation of Cardiac Function in Patients on Anti-cancer Drugs

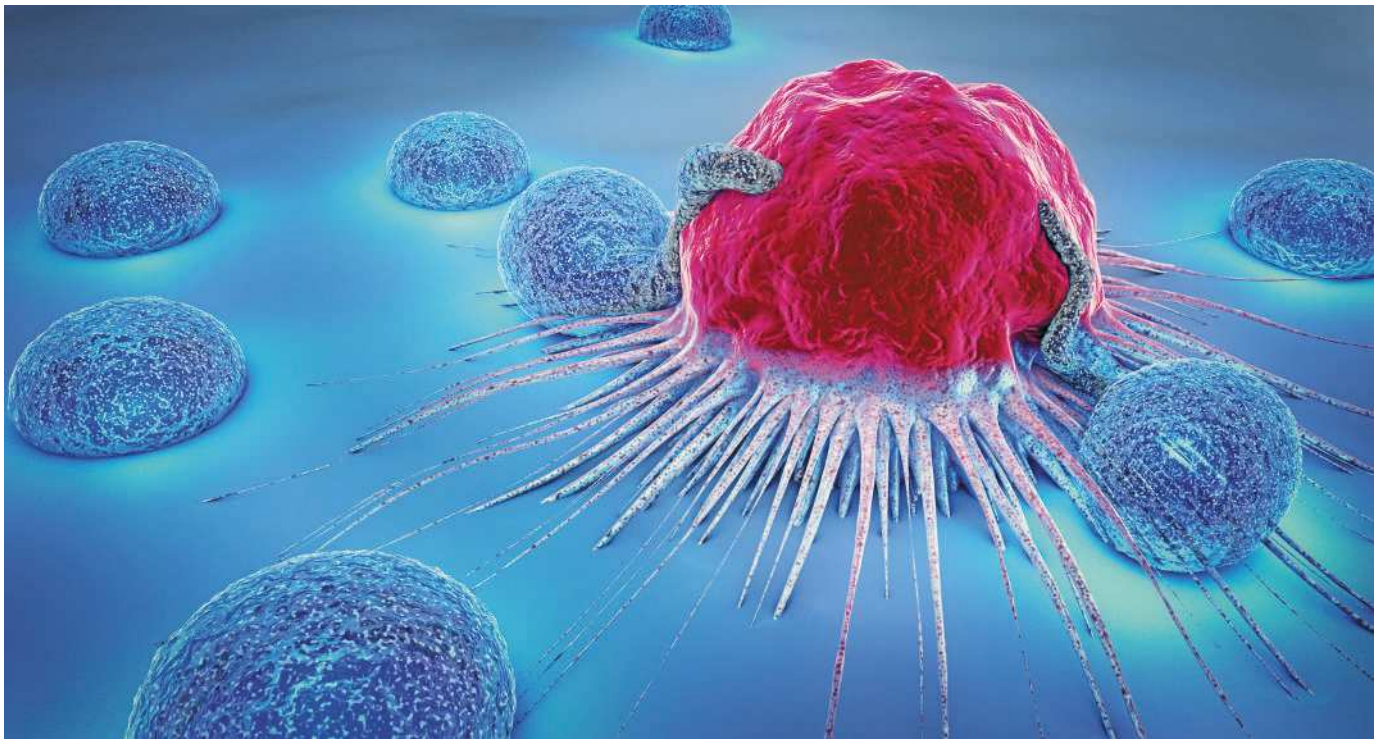
There is also controversy regarding the best method and mode of LVEF monitoring during cancer treatment. It is important to note that the various modes of LVEF monitoring generally used to assess cardiac function have different normal reference values.

MUGA scan is one mode of LVEF monitoring. Its inter- and intra-observer variabilities are low (<5%), and the values obtained are strongly correlated with the findings of cardiac magnetic resonance imaging (cMRI) and 3D echocardiography. The principal disadvantage of this method is the need for repeated exposure to radiation at each time point.

However, the use of MUGA in trials does not reflect the current preference for cardiac ultrasound, which has increased in popularity at many centres. 3D echocardiography is more accurate and reproducible than 2D echocardiography for the measurement of LVEF, and has the best temporal reproducibility during cancer therapy. Echocardiography with estimation of diastolic dysfunction is also being investigated as a more sensitive method for measuring early cardiac damage.

Cardiac ultrasound and scintigraphy remain the most frequently used techniques for estimating LVEF, but they lack consistency in the degree of reduction from baseline or absolute values considered to indicate cardiotoxicity. The recent position paper from the European Society of Cardiology defined cancer therapeutics-related cardiac dysfunction (CTRCD) as a decrease in LVEF of > 10 percentage points, to a value < 50%. This position paper considers transthoracic echocardiography (TTE) to be the method of choice for the detection of CTRCD, before, during and after cancer therapy.

Other types of imaging can also be used to follow LVEF, but radiation exposure during radionuclide angiography and the low



availability and high cost of cardiac magnetic resonance imaging have limited the use of these techniques.

Whatever the approach used, the bottom line is that the mode of diagnosis used must be accurate and reproducible enough to identify a real change in cardiac function reliability. The same technique should be used for baseline assessment and follow-up studies, during and after cancer treatment.

Biological Markers

In addition to clinical and echocardiographic variables, biological markers of myocardial necrosis (troponin I and T) and natriuretic peptides have emerged as possible prognostic factors identifying subclinical myocardial stress and potentially predicting major cardiovascular events, including heart failure.

Several studies have demonstrated the prognostic value of the serum troponin assay performed immediately before or after anthracycline exposure. Some studies have suggested that 30–35% of patients treated with anthracyclines display significant increases in troponin levels. These increases precede LVEF deterioration by three to four months, and the troponin peak seems to be correlated with the severity of left ventricular systolic dysfunction (LVSD).

Conclusion

Recent advances in cancer treatment, including many targeted therapies, have greatly improved the prognosis of cancer patients. Arrhythmia is a common side-effect of several major classes of antineoplastic agents, but the true incidence and significance of this condition has not been adequately characterised. In the future, oncological clinical trials should monitor cardiovascular endpoints with a standardised approach, to characterise possible ECG alterations and the development of cardiac rhythm disorders.

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