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Anticancer drug-induced cardiac rhythm disorders: Current knowledge and basic underlying mechanisms☆

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ABSTRACT

Significant advances in cancer treatment have resulted in decreased cancer related mortality for many malignancies with some cancer types now considered chronic diseases. Despite these improvements, there is increasing recognition that many cancer patients or cancer survivors can develop cardiovascular diseases, either due to the cancer itself or as a result of anticancer therapy. Much attention has focused on heart failure; however, other cardiotoxicities, notably cardiac rhythm disorders, can occur without underlying cardiomyopathy.

Supraventricular tachycardias occur in cancer patients treated with cytotoxic chemotherapy (anthracyclines, gemcitabine, cisplatin and alkylating-agents) or kinase-inhibitors (KIs) such as ibrutinib. Ventricular arrhythmias, with a subset of them being torsades-de-pointes (TdP) favored by QTc prolongation have been reported: this may be the result of direct hERG-channel inhibition or a more recently-described mechanism of phosphoinositide-3-kinase inhibition. The major anticancer drugs responsible for QTc prolongation in this context are KIs, arsenic trioxide, anthracyclines, histone deacetylase inhibitors, and selective estrogen receptor modulators.

Anticancer drug-induced cardiac rhythm disorders remain an underappreciated complication even by experienced clinicians. Moreover, the causal relationship of a particular anticancer drug with cardiac arrhythmia occurrence remains challenging due in part to patient comorbidities and complex treatment regimens. For example, any cancer patient may also be diagnosed with common diseases such as hypertension, diabetes or heart failure which increase an individual's arrhythmia susceptibility. Further, anticancer drugs are generally usually used in combination, increasing the challenge around establishing causation.

Thus, arrhythmias appear to be an underappreciated adverse effect of anticancer agents and the incidence, significance and underlying mechanisms are now being investigated.

Contents

Abbreviations: 5-FU, 5-fluorouracil; AF, atrial fibrillation; ALK, anaplastic lymphoma kinase; APD, action potential duration; APL, acute promyelocytic leukemia; BCR-ABL, breakpoint cluster region-Abelson; BTK, Bruton tyrosine kinase; CD20, cluster of differentiation 20; CDK, cyclin-dependent kinase; CLL, chronic lymphocytic leukemia; CTLA4, cytotoxic T-lymphocyte–associated antigen 4; CYP17, 17α-hydroxylase/C17,20-lyase; DAMPs, damage-associated molecular pattern molecules; EGFR, epidermal growth factor receptor; EMA, European Medicines Agency; FDA, Food and Drug Administration; GnRH, gonadotrophin releasing hormone; HDIs, histone deacetylases inhibitors; HER2, human epidermal growth factor receptor 2; ICD, implantable cardioverter defibrillator; IL-2, interleukin-2; KIs, kinase inhibitors; LGE, late gadolinium enhancement; LV, left ventricular; MEK, mitogen-activated extracellular signal-regulated kinase; NAC, *N*-acetyl-cysteine; NFκB, nuclear factor kappa B; PD-1, programmed death 1; PDL-1, programmed death-ligand 1; PI3K, phosphoinositide 3-kinase; RAF, rat fibrosarcoma; ROS, reactive oxygen species; RyR2, cardiac ryanodine receptor; SERM, selective estrogen receptor modulator; TdP, torsades de pointes; Tec, tyrosine kinase expressed in hepatocellular carcinoma; TLRs, toll-like receptors; VEGFR, vascular endothelial growth factor receptor; VT, ventricular tachycardia.

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1. Introduction

Therapeutic innovations have led to improved survival of patients with cancer, but this also has led to concerns about medium and long-term complications of therapy (Buza, Rajagopalan, and Curtis, 2017; Chang, Moudgil, Scarabelli, Okwuosa, and Yeh, 2017; Chang, Okwuosa, Scarabelli, Moudgil, and Yeh, 2017). Some cancers that were historically associated with poor short-term survival now have improved rates of cure or delayed disease progression, changing the view of malignancy to a more chronic disease. Additionally, the average life expectancy has risen and more patients may experience adverse effects of anticancer treatment that are magnified by the comorbid cardiovascular risk factors of an aging population. Resultant cardiovascular diseases are increasingly recognized complication of anticancer therapies, and there are growing concerns that these complications may lead to premature morbidity and death among cancer survivors (Bellinger et al., 2015; Ewer and Ewer, 2015; Moslehi, 2016). While there has been much focus on therapy-induced cardiomyopathy, there is increasing recognition of therapy-induced rhythm disturbances in cancer patients that may occur without any underlying cardiomyopathy. Anticancer drug-induced arrhythmias result from a combination of "on-target" and "off-target" effects that lead to direct and acute modifications of specific molecular pathways critically-linked to arrhythmogenesis (such as I_{Kr} inhibition prolonging the QTc interval and causing Torsades de Pointes) or indirect actions that lead to medium or long-term effects by creating a structural arrhythmia substrate (such as myocardial damage/modification through inflammation, fibrosis, apoptosis or ischemia) (Buza et al., 2017).

The precise incidence of anticancer drug-induced arrhythmias is not known as most clinical trials are underpowered to detect real-world side effects, exclude patients with preexisting cardiac disease (which represent the most vulnerable population for cardiac arrhythmias) and have not intensively monitored cardiac side effects (Groarke, Cheng, and Moslehi, 2013). This problem appears to be more prominent with older drugs like anthracyclines because most incidence data is inferred from uncontrolled clinical studies. The evidence for drug-induced QTc changes is better reported than arrhythmia events because collecting detailed data on repolarization has been a focus of both the Food and Drug Administration (FDA) and European Medicines Agency (EMA) for decades. Moreover, there is a lack of consensus guidelines for anticancer drug-induced cardiotoxicity management; therefore practices of oncologists are disparate and this has motivated the development of personalized cardio-oncology programs (Jovenaux et al., 2017). Establishing a causal relationship between anticancer agents and cardiac arrhythmias remains challenging. The diagnosis of cancer alone can predispose to increased arrhythmia burden and occurs in as many as 16–36% of patients either treated for cancer (Tamargo, Caballero, and Delpón, 2015; Yeh and Bickford, 2009) and can even precede cancer diagnoses (Ostenfeld et al., 2014). Cardiac arrhythmia in cancer patients can be exacerbated by underlying heart disease, by the direct effects of the tumor, or by cancer treatment (Ewer and Ewer, 2015). The underlying propensity for the development of arrhythmia is increased by the stresses induced by malignancy and may be related to prior organ injury, immune reaction, systemic inflammation, electrolyte or endocrine abnormalities, impaired oxygenation, or metabolic alterations (Ewer and Ewer, 2015). Chemotherapy can influence many of these factors and, therefore, may also contribute proarrhythmic effects.

Atrial fibrillation (AF) and ventricular tachycardia (VT) related, or not, to prolonged QTc interval are particularly frequent and associated with significant mortality (Zamorano et al., 2016). We review here cardiac arrhythmias related to anticancer drugs, with a focus on AF, VT, and QTc prolongation, and their characteristics with an overview of underlying basic mechanisms, epidemiological evidence, and clinical data. When available, we selected references to randomized trials (including QTc studies) or observational studies using standard doses of anticancer drugs (as specified in their FDA labels). In the absence of such information, references including high drug doses (greater than those specified in labels) were selected.

2. Atrial fibrillation and other supraventricular tachycardias

2.1. Anthracyclines

Anthracyclines have been cornerstone chemotherapeutics for a variety of cancers including breast cancers, sarcomas, leukaemias, and lymphomas. Although left ventricular (LV) dysfunction and cardiomyopathy are the classical cardiotoxicities associated with anthracycline exposure, cardiac arrhythmias are also common even in the absence of LV dysfunction (Amioka et al., 2016). In 249 patients with lymphoma who had no baseline cardiomyopathy and who received anthracyclines, fifteen patients (6%) developed new AF after the chemotherapy (mean follow-up of 34 months). Among these 15 patients who developed AF, 11 developed subsequent heart failure and 4 developed AF without clinical heart failure. In the case of patients presenting with both AF and heart failure, the onset of AF always preceded the development of heart failure suggesting that new-onset AF might be an indicator of anthracycline-induced cardiomyopathy (Amioka et al., 2016). At standard doses, anthracyclines induce both acute and reversible AF (more often paroxysmal AF, occurring during or within several hours after the infusion) and delayed AF (more often persistent AF, several months/years after administration) (Amioka et al., 2016; Ando et al., 2000; Guglin, Aljayeh, Saiyad, Ali, and Curtis, 2009; Kilickap et al., 2007). AF frequency was reported to be between 7.7 and 10.3% in non-randomized and small trials (Table 1) (Ando et al., 2000; Guglin et al., 2009; Kilickap et al., 2007). Persistent AF seems to be more frequent (80%) with the first AF episode occurring between 8 and 36 months after starting anthracycline therapy (Amioka et al., 2016). AF occurrence is not a benign event in the patient course since AF is associated with a higher risk of developing acute heart failure (hazard ratio 12.78; $p < 0.001$) and a greater risk of all-cause mortality (hazard ratio 4.77; $p < 0.001$), regardless of the cumulative anthracycline dose (Amioka et al., 2016).

The mechanisms by which anthracyclines induce AF are not established (Fig. 1); hypotheses include direct and indirect effects on cardiac ion channels, accumulation of reactive oxygen species, and activation of pro-inflammatory pathways which can cause both acute and long-term cardiac side effects (Binah, Cohen, and Rosen, 1983; Tamargo et al., 2015). It is notable that cytokine release mediated by activation of the innate immune system is believed to be involved in the pathogenesis of anthracyclines-induced cardiotoxicity (Nozaki, Shishido, Takeishi, and Kubota, 2004). Toll-like receptors (TLRs) are important receptors involved in the activation of the innate immune system and their role in anthracycline-induced cardiomyopathy has recently been investigated in mice (Riad et al., 2008). TLR4 is the most common TLR isoform expressed in the heart with expression on the cell surface of multiple cell types, including cardiomyocytes, smooth muscle cells, endothelial cells, and cardiac fibroblasts (Topkara et al., 2011). TLR4 activation, resulting from a variety of ligands such as damage-associated molecular pattern molecules (DAMPs), may lead to a pro-inflammatory response in the heart that has recently been associated with AF (Topkara et al., 2011). Anthracyclines also increase mitochondrial ROS production and induce mitochondrial dysfunction

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