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CARDIO-ONCOLOGY (EH YANG, SECTION EDITOR)

Electrophysiologic Toxicity of Chemoradiation

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Abstract

Purpose of Review There is growing awareness of the link between oncology treatments and cardiovascular (CV) complications. This has led to the development of cardio-oncology, a specialty aimed at managing CV risk and disease in cancer patients and survivors. Cardiac arrhythmias are potential adverse CV complications of cancer treatments; however, these cardiotoxicities are often underappreciated due to the uncertain arrhythmogenic mechanisms of various chemotherapeutic agents.

Recent Findings Chemotherapeutic agents can induce arrhythmias via direct electrophysiological effects on ion channels or intracellular signaling pathways, or indirectly from cardiac tissue damage.

Summary As more drugs are being linked to the development of arrhythmias, a deeper understanding of the pathophysiology of their electrophysiological (EP) effects will be necessary. Expanding research in this field has allowed for the identification of novel agents with potential arrhythmogenic properties and the development of preventative measures, early recognition, and closer surveillance of patients more susceptible to these EP side effects.

Keywords Arrhythmias · Chemotherapy · Cardio-oncology · QT prolongation

Introduction

The number of cancer survivors continues to grow as diagnostic modalities improve and the development of more targeted chemotherapies increase [1]. As mortality rates of various malignancies improve and the population ages, the link between cardiovascular disease and various cancer treatments has become more apparent. Historically, the focus has been primarily on the cardiotoxic manifestations of left ventricular dysfunction and heart failure associated with several commonly utilized chemotherapeutics; however, growing awareness of the potential arrhythmogenic properties of many of these therapies has led to increased research in this area [2, 3, 4••].

The exact pathophysiological mechanisms by which chemotherapeutic agents cause electrophysiological (EP) complications are unknown; however, theories have suggested their effects on specific intracellular signaling pathways may lead to "off-target" arrhythmogenic effects on the heart and cardiovascular tissues [4••]. The most common EP complications are atrial fibrillation (AF), supraventricular tachycardia (SVT), and QT prolongation which can lead to ventricular arrhythmias such as torsades de pointes [4••, 5, 6••]. Evaluation and management of these arrhythmias can pose significant and unique challenges in cancer patients given their multiple comorbidities and the complexities of their treatment plans.

In this article, we will review the current data regarding the cancer therapies associated with the development of arrhythmias and various other EP abnormalities as well as potential evaluation and management strategies.

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Section 1: Traditional Chemotherapy

Anthracyclines

Anthracyclines (AC) are a class of chemotherapy agents that function by inhibiting DNA and RNA synthesis and are utilized in the treatment of several malignancies including leukemias, lymphomas, and breast cancer. Examples in this class include daunorubicin, doxorubicin, idarubicin, and epirubicin. There are two means by which anthracyclines have pro-arrhythmic effects: (1) in the setting of cardiomyopathy due to structural changes or (2) through direct toxicity to cardiac myocytes.

One of the more feared complications of AC treatment is the development of a chemotherapy-induced cardiomyopathy (CMO), which increases the risk of arrhythmias due to cardiac structural changes and fibrosis. These abnormalities lead to an arrhythmogenic substrate resulting from territories of conduction block which allow for the development of reentry and uncontrolled impulse propagation [7, 8]. AC has also been linked to a pro-inflammatory response including histamine release and cytokine release syndrome, which can lead to the development of myocarditis, pericarditis, myocardial fibrosis, and hypertrophy [4••]. While reports vary in the literature, the incidence of CMO with the use of AC can be more than 5% at a cumulative dose of 450 mg/m^2 or higher [2, 7, 9, 10]. Recommendations by the American Society of Clinical Oncology suggest patients at the highest risk for cardiac dysfunction include those exposed to high-dose anthracyclines (e.g., doxorubicin ≥ 250 mg/m^2, epirubicin ≥ 600 mg/m^2) as well as those exposed to lower dose protocols who have cardiovascular risk factors or who receive radiation in which the heart is in the treatment field [11].

In a recently published study evaluating arrhythmias in patients with AC-associated CMO and implantable devices, non-sustained ventricular tachycardia (NSVT) was seen in 73.9%, AF in 56.6%, while ventricular fibrillation (VF) was seen in only 30.4% [12••]. There was no statistically significant difference in clinical outcomes including overall mortality or device therapy when comparing the AC-associated CMO group to other cardiomyopathy etiologies [12••]. In a different study, rates and risk of arrhythmias in cancer survivors with chemotherapy-induced cardiomyopathy were similar to patients with other forms of non-ischemic cardiomyopathy [13].

In the absence of left ventricular dysfunction and CMO, there are several mechanisms by which AC can be directly arrhythmogenic. Mechanisms causing arrhythmias are thought to be due to dysregulation of ion channels and buildup of free radical particles [6••, 14]. Doxorubicin has also been shown to widen the QRS complex and prolong the QT interval by inhibition of Purkinje fiber Na^+ and Ca^{2+} exchange in animal models and the formation of reactive oxygen species (ROS) which promote apoptosis [15–17]. In one study, premature ventricular complexes (PVCs) were the most commonly encountered arrhythmias, occurring in 3% of patients at 1-h post-infusion and in 24% of patients 24-h post-infusion, followed by non-sustained VT (up to 6% 24-h post-infusion) and SVT and VT (at 0.5–3%) [18, 19]. Of the SVTs, atrial fibrillation had an incidence of up to 10.3% as a result of AC exposure [5, 18, 19].

Alkylating Agents

Alkylating agents are class of chemotherapy that work by disrupting the structural formation of the double helix of DNA. Examples in this class include cyclophosphamide, busulfan, and melphalan.

Cyclophosphamide is used to treat leukemia, lymphoma, ovarian cancer, breast cancer, and multiple myeloma (MM). There are a wide range of arrhythmias that result in the context of utilizing cyclophosphamide in various chemotherapy regimens. One study demonstrated an 8–10% occurrence rate of atrial and ventricular tachyarrhythmias in patients treated with high-dose cyclophosphamide [20]. These arrhythmias, mainly consisting of SVT, paroxysmal AF, premature ventricular beats, VT, and QT prolongation, occurred 24- to 72-h post-administration and typically resolved 1–7 days post-administration [20]. Other studies illustrated the development of SVT, VT (including VF), and AV block due to high-dose cyclophosphamide treatment in the setting of stem cell transplantation (SCT) [21–24]. There have also been reports of cyclophosphamide-associated ventricular arrhythmias secondary to QT prolongation [20]. Furthermore, when cyclophosphamide is used in combination with busulfan (another alkylating agent) as preconditioning chemotherapy for SCT, the incidence of AF is increased to 6.4% [24].

Melphalan is an alkylating agent used in the treatment of light-chain (AL) amyloidosis, MM, and ovarian cancer and is often administered as induction chemotherapy prior to SCT. In one study, melphalan caused SVT in 11% of BMT recipients [25]. SVT was most common among patients with MM treated with melphalan (72.58%) followed by non-Hodgkin's lymphoma (14.52%) and amyloidosis (4.84%). Significant risk factors associated with the development of SVT after melphalan exposure include advanced age, history of hypertension, history of AF, increased left atrial size, and increased serum creatinine [25].

Antimetabolites

5-Fluorouracil (5-FU) is primarily utilized in the treatment of gastrointestinal and head and neck cancers. 5-FU can cause coronary vasospasm resulting in ischemia [6••]. As a result, ventricular arrhythmias are common ranging from PVCs to sudden cardiac death [26–28]. VT has an incidence rate of

3.7–7.4% [29]. Sinus bradycardia is reported in up to 12% of patients while a minority may develop advanced AV block [29]. Arrhythmias recur in 90% of patients when re-challenged with an antimetabolite confirming a pro-arrhythmic class effect [30–32].

Gemcitabine is used in treatment of bladder cancer, pancreatic cancer, and non-small cell lung cancer. It has a strong association with SVT, especially AF [33]. In one study, 8.2% of patients treated with gemcitabine in combination with vinorelbine developed AF or atrial flutter [34].

Antimicrotubule Agents

Paclitaxel is an antimicrotubule agent used to treat breast cancer, ovarian cancer, lung cancer, and cervical cancer. Paclitaxel results in QTc prolongation, right and left bundle branch blocks, and T wave changes on ECG [6••]. It is associated with transient, asymptomatic sinus bradycardia in about 29% of patients when used as monotherapy and rarely AV block. The arrhythmias typically manifest within 24-h post-infusion and dissipate 48- to 72-h post-infusion; however, patients may experience SVT or PVCs up to 10 days after the final infusion [35–37]. The incidence increases when used with cisplatin. A postulated mechanism of bradycardia is via H1 and H2 receptor stimulation leading to conduction delay through the AV node and Purkinje network [36, 37].

Platinum Compounds

Cisplatin is utilized in treating various cancers including head and neck malignancies and small cell lung cancer. Systemic use of cisplatin can result in sinus bradycardia [6••]. Premature atrial complexes and PVCs have been noted in about 66% of patients; however, incidence of SVT and AF is rare and generally limited to case reports in the literature [38, 39]. Electrolytes should be monitored during treatment as cisplatin-induced hypomagnesemia may predispose to arrhythmias [40]. In contrast, the incidence of arrhythmias is much higher in the setting of direct intrapericardial cisplatin administration (AF: 12–18.8%; NSVT: 8%) [41–43]. These effects were neither dose- nor time-dependent occurring hours to months after treatment [3, 4••, 41–43].

Arsenic Trioxide

Arsenic trioxide is a chemotherapeutic agent with significant efficacy in the treatment of acute promyelocytic leukemia (APL) with studies reporting remission rates between 85 and 93% [5, 44–46]. It is strongly associated with the development of QTc prolongation. In one study evaluating patients from phase 1 and phase 2 trials, the incidence of QT prolongation was 38%, with 26% of subjects demonstrating QT intervals greater than 500 ms [44, 47]. QTc prolongation persisted for up to 5 weeks and typically returned to normal after 8 weeks [44–49]. It is recommended that therapy be discontinued if the QTc exceeds 500 ms and resumed once below 460 ms [47].

Arsenic trioxide has also been shown to cause life-threatening arrhythmias including accelerated idioventricular rhythms and torsades de pointes likely due to preceding QT prolongation within the first 24 h of administration [48, 49]. Arsenic trioxide has also been reported to cause ST-T wave abnormalities, first-degree AV block, PVCs, non-sustained VT, and complete AV block sometimes requiring temporary pacing to allow for continued treatment [44–49].

Section 2: Targeted and Immunotherapies

Tyrosine Kinase Inhibitors

Tyrosine kinase inhibitors (TKIs), which target abnormal signaling pathways, have led to significant advances in the treatment of various malignancies [50]. Unfortunately, these agents have been associated with adverse off-target effects on the cardiovascular system leading to hypertension, acute coronary syndromes, and LV dysfunction. In addition, there is increased recognition of arrhythmias and electrical complications including AF QT prolongation and ventricular arrhythmias associated with these agents (Table 1) [5, 50–53].

Ibrutinib is an inhibitor of Bruton's tyrosine kinase protein (BTK) approved for the treatment of chronic lymphocytic leukemia (CLL), mantle cell lymphoma (MCL), and Waldenstrom's macroglobulinemia with multiple studies ongoing evaluating its role in various other malignancies and disease states [54, 55]. Emerging data suggests a strong link between ibrutinib and the development of atrial fibrillation and other supraventricular arrhythmias [51, 52]. The incidence of AF across various clinical studies has been reported up to 16% [56•]. A recent publication evaluating patients with CLL and MCL in four large randomized controlled studies reported AF incidence in those treated with ibrutinib to be 6.5% [95% confidence interval (CI): 4.8, 8.5] at 16.6 months versus 1.6% (95% CI: 0.8, 2.8) for the comparator group [56•]. At 36-month follow-up, the incidence of ibrutinib-associated arrhythmias was 10.4% (95% CI: 8.4, 12.9) [56•]. Another meta-analysis reported a relative risk of AF with ibrutinib exposure to be 3.86 (95% CI: 1.97–7.54) [57].

The risk of AF with ibrutinib appears to increase with ongoing therapy with a median time to onset of approximately 3 months after initiation. Moreover, independent risk factors for developing AF in this population include older age and prior AF history [50, 56•, 58]. Optimal treatment and management of AF in these patients is of significant importance to avoid discontinuation of the drug. Anticoagulation is often an

Table 1 Tyrosine kinase inhibitors commonly associated with arrhythmias and other electrophysiological abnormalities

Name	TKI subtype	Common electrophysiological abnormalities	Rare electrophysiological abnormalities
Ceritinib	ALK	Sinus bradycardia, QTc prolongation	PACs
Crizotinib	ALK	Sinus bradycardia, QTc prolongation	N/A
Dasatinib	BCR-ABL	SVT	PVCs, VT, QTc prolongation
Ibrutinib	BTK	A.Fib	PVCs, VT
Nilotinib	BCR-ABL	N/A	A.Fib, AVB, SCD, QTc prolongation
Pazopanib	VEGF	N/A	Sinus bradycardia, QTc prolongation
Sorafenib	VEGF	QTc prolongation	Sinus bradycardia, SVT
Sunitinib	VEGF	QTc prolongation	A.Fib, sinus bradycardia
Vandetanib	VEGF	QTc prolongation	SCD, VT
Vemurafenib	BRAF	QTc prolongation	Sinus bradycardia, sinus tachycardia, PACs, PVCs, VT

ALK, anaplastic lymphoma kinase inhibitor; *A.Fib*, atrial fibrillation; *AVB*, atrioventricular block; *BCR-ABL*, tyrosine kinase inhibitor; *BRAF*, kinase inhibitor; *BTK*, Bruton tyrosine kinase inhibitor; *PACs*, premature atrial complexes; *PVCs*, premature ventricular complexes; *QTc*, corrected QT interval; *SCD*, sudden cardiac death; *SVT*, supraventricular tachycardia; *TKI*, tyrosine kinase inhibitor; *VEGF*, vascular endothelial growth factor inhibitor; *VT*, ventricular tachycardia

important component in the treatment algorithm of AF in order to reduce stroke risk. However, ibrutinib is associated with an increased risk of clinically significant bleeding. In particular, intracranial hemorrhage has been reported in patients taking ibrutinib and warfarin. As such, vitamin K antagonists are contraindicated in ibrutinib-treated patients [59, 60]. While there are no specific studies evaluating the safety of direct-acting oral anticoagulants (DOACs) in this population, they may be a safer alternative as multiple phase III trials have demonstrated fewer bleeding events with DOACs in comparison to warfarin in the general population [61, 62].

One possible mechanism by which ibrutinib causes atrial fibrillation is its effects on P13K protein expression in myocytes. A study done by McMullen et al. revealed that there was reduced P13K protein expression and AKT signaling in the myocytes of rats treated with ibrutinib [52]. Further studies have demonstrated that reduced expression of P13K protein in human myocytes could be associated with atrial fibrillation specifically the alpha subunit of the P13K heterodimer which is expressed in both lymphoid tissue and cardiac myocytes [52, 63, 64]. Nevertheless, the second-generation BTK inhibitor, acalabrutinib, has not demonstrated increased rates of arrhythmias as compared to ibrutinib [65].

Emerging data has also linked ibrutinib to development of ventricular arrhythmias. In one recently published article looking at cases of ventricular arrhythmias or sudden death in ibrutinib-treated patients documented in the FDA Adverse Event Reporting System (FAERS), there were seven identified instances of VT/VF and six sudden deaths; 10 of these 13 cases had no prior cardiac history [66]. None of these patients were taking any other medications known to cause arrhythmias [66]. In the HELIOS trial, the number of grade ≥ 3 ventricular arrhythmias, cardiac arrests, and sudden deaths was seven in the ibrutinib-containing arm versus 0 in the placebo-containing arm [67].

Dasatinib and nilotinib are BCR-ABL tyrosine kinase inhibitors used in the treatment of Philadelphia chromosome-positive chronic myeloid leukemia (CML) and have been associated with various conduction disturbances. While the majority of the attention is focused on their effect on the QT interval, SVT and non-sustained VT have been reported [6••, 68]. QTc prolongation is more commonly seen with nilotinib and rarely with dasatinib. The incidence of QT prolongation greater than 30 ms has been reported in up to 26% of patients exposed to nilotinib with one study showing an average QT interval change of 18 ms in healthy volunteers [68–70]. In < 1% of patients, QTc prolongation of > 500 ms has been observed, and in 0.6% of patients, sudden cardiac death (SCD) was reported; thus, nilotinib has a black box warning for SCD and QTc prolongation [69–71].

Ceritinib and crizotinib are anaplastic lymphoma kinase (ALK) inhibitors, used in the treatment of non-small cell lung cancer, and have been associated with sinus bradycardia and QTc prolongation [72, 73]. Bradycardia associated with crizotinib is usually asymptomatic and rarely requires therapy interruption. In one series of patients undergoing therapy with crizotinib, 31% developed a heart rate below 50 beats per minute [72, 74]. QTc prolongation is relatively common with crizotinib and ceritinib with increases > 60 ms from baseline reported in 3.5 and 3% of patients, respectively [72, 73].

TKIs with specific activity against vascular endothelial growth factor (VEGF) signaling pathways are often referred to as VEGF inhibitors. These agents have been linked to significant adverse cardiovascular events, most frequently

hypertension; however, electrophysiology issues including dose-dependent QTc prolongation and atrial and ventricular arrhythmias also occur [4••, 71, 75, 76]. Vandetanib, used for the treatment of medullary thyroid cancer, carries a black box warning for increased risk of QTc prolongation, torsades de pointes, and SCD which commonly results in its discontinuation or dose reduction [69, 71]. Vandetanib's effects are dose-dependent, with an average change in QTc of 14–35 ms. One large meta-analysis reported an incidence of QTc prolongation with vandetanib use of 16–18% and high-grade QTc prolongation of 3.7–12% [69, 75, 76]. Torsades de pointes is less common with an incidence of 0.09–0.16% [50].

Clinical trials have demonstrated that the VEGF inhibitor sunitinib, which is used for the treatment of gastrointestinal stromal tumors and renal cell carcinoma, causes dose-dependent QTc prolongation with the average increase in the QTc of 15.4 ms (90% CI: 8.4–22.4 ms) [77]. QT prolongation greater than 500 ms occurred in less than 2.3% of patients and episodes of torsades de pointes occurred in less than 0.1% in the US FDA database [4••, 53, 77]. Other VEGF inhibitors with significant QT-prolonging effects include vemurafenib (used the treatment of metastatic melanoma) with clinical trials reporting an interval increase of > 60 ms from baseline occurring in 5% of patients with 1.5 to 2.9% developing intervals > 500 ms [78], and pazopanib (used in the treatment of renal cell carcinoma, soft tissue sarcomas, and thyroid cancer) with reported QTc prolongation > 500 ms identified in 2% of patients and torsades de pointes in < 1% of patients [4••, 50].

Sunitinib has also been reported to cause AF although the exact incidence is unknown, as these findings are limited to case reports. Sunitinib-induced arrhythmias may also occur in the setting of heart failure and LV dysfunction which have been reported at rates of up to 15% in the literature [4••, 53, 77, 79, 80]. Sorafenib, used in the treatment of hepatocellular carcinoma and renal cell carcinoma, is more commonly associated with AF with an incidence of about 5.1% if used in conjunction with the antimetabolite 5-fluorouracil [81, 82].

Monoclonal Antibodies

Trastuzumab is a human epidermal growth factor receptor 2 (HER2)/neu inhibitor, used primarily in the treatment of breast cancer. It is most commonly associated with the development of cardiomyopathy and ventricular arrhythmias may occur in this setting [83]. Interestingly, these effects are not dose-dependent and are frequently reversible upon discontinuation of trastuzumab [4••, 83]. Other HER 2/neu receptor inhibitors, such as lapatinib, have been reported to cause significant QTc prolongation with clinical studies reporting QTc > 500 ms in up to 6.2% of patients [4••].

Rituximab has been associated with the development of AF, SVT, VT, and PVCs during or immediately after infusion and often cease upon discontinuation of therapy [84, 85]. In one study comparing the incidence of SVT and cardiac toxicity between patients treated with CHOP chemotherapy, those patients also exposed to rituximab had a higher incidence of arrhythmias than those who were not given this drug (24 vs. 13% respectively) [84].

Cetuximab is an epidermal growth factor receptor inhibitor used primarily in the treatment of head and neck cancers that carries a black box warning for increased risk of cardiopulmonary arrest and SCD [86]. Hypomagnesemia might be the underlying mechanism behind some of these cases [87]. Adverse events are higher in patients treated with concurrent radiation therapy (2 vs. 0% respectively) or in combination with 5-FU (3 vs. 2% respectively) [4••, 86, 87].

Proteasome Inhibitors

Bortezomib and carfilzomib are proteasome inhibitors used in the treatment of multiple myeloma. Both have been associated with development of heart failure and secondary arrhythmias; however, they are more common with carfilzomib [88–90]. Common primary or secondary arrhythmias seen with bortezomib therapy include AF, bradycardia, and complete AV block requiring pacemaker placement [88].

Patients on carfilzomib are at increased risk of cardiomyopathy especially in the setting of prior heart failure or exposure to other cardiotoxic chemotherapy regimens. It has also been associated with development of arrhythmias, most commonly supraventricular tachycardias. Interestingly, the risk of arrhythmias with carfilzomib therapy decreases with subsequent cycles [91]. Among 526 patients with advanced multiple myeloma that took part in one of four phase II studies with single-agent carfilzomib, adverse cardiac events were reported in 112 patients (22.1%) [91]. Of these patients, 73.6% had a past history of cardiac disease and 70% had baseline cardiovascular risk factors. Cardiac arrhythmias were reported in 70 patients (13.3%), with 12 patients having grade 3 or higher arrhythmias and 11 having serious life-threatening arrhythmias. Discontinuation of treatment occurred in 23 patients due to cardiac events and six patients required dose reduction [91].

Another retrospective single-center study of 130 patients treated with carfilzomib reported cardiac adverse events in 26 patients (20%) including hypertension, AF, SVT, and congestive heart failure [92•]. Among the four patients in the study that were hospitalized due to a cardiac arrhythmia, two of them experienced cardiac arrest from the arrhythmia [92•]. Interestingly, in these patients, median ejection fraction dropped from 55 to 33% as assessed by echocardiography [92•]. The pathophysiological mechanism behind carfilzomib's cardiotoxic effects is not well known, although proteasome inhibition has been shown in murine models and

clinical studies to impair cardiac function [92•, 93–95]. Similar adverse cardiovascular event rates have been reported in the phase 3 ENDEAVOR trial comparing carfilzomib and dexamethasone with bortezomib and dexamethasone [96].

Immunomodulatory Agents

Thalidomide and lenalidomide are two agents used in the treatment of multiple myeloma. Thalidomide has been associated with development of mild sinus bradycardia in up to 55% of patients and severe sinus bradycardia in 1–3% of patients possibly through inhibition of both TNF-alpha and the vagus nerve leading to over activity of the parasympathetic nervous system [97, 98]. Bradycardia usually resolves within 12 to 21 days after stopping the agent, but in some cases, pacemaker placement has been necessary [97]. In addition to sinus bradycardia, thalidomide has also been associated with development of atrial fibrillation and sustained VT, although the latter is quite rare [97–99]. Routine cardiac monitoring is recommended in these patients as well as limiting the use of beta-blockers, calcium channel blockers, digoxin, or antiarrhythmic drugs. Lenalidomide has also been implicated in development of atrial fibrillation, and overall incidence in clinical trials has ranged from 4.6 to 7% especially in combination with dexamethasone and bortezomib [97–100].

Histone Deacetylase Inhibitors

Vorinostat, panobinostat, and romidepsin are histone deacetylase inhibitors used in the treatment of various hematological malignancies that have been associated with significant side effects including non-specific ECG changes including ST and T wave abnormalities and QTc prolongation. Various arrhythmias including SVT, AF, and ventricular arrhythmias as well as torsades de pointes have been reported [101].

Romidepsin therapy is associated with frequent ectopy and more seriously sudden cardiac death. In two different studies, 2 out of the 131 patients and 1 out of the 25 patients treated with romidepsin for metastatic neuroendocrine tumors developed SCD with the latter study prematurely terminated because of the high number of electrophysiological events including QTc prolongation and VT [101–104]. Clinical studies have reported up to 38% of patients treated with romidepsin will develop SVT, 14% can develop VT, and PACs and PVCs were seen in 65 and 38%, respectively. In an observational study of 42 patients treated with romidepsin for T cell lymphoma, QTc intervals > 450 and > 500 ms were seen in 28 and 4 patients, respectively [104].

Panobinostat also causes non-specific ECG changes that are usually temporary; however, it can cause significant QTc prolongation which varies depending on the extent and frequency of therapy as well as the dose and route of administration. Observational studies have reported QTc prolongation of > 500 ms ranging up to 28% leading to a black box warning for severe arrhythmias [4••, 101, 105].

Immune Checkpoint Inhibitors

In recent years, immunotherapy has revolutionized the field of oncology, emerging as an effective treatment for various malignancies. While autoimmune side effects are well described, there is increasing data suggesting immunotherapy may also lead to cardiovascular toxicities, particularly myocarditis. Genetic deletion of immune checkpoints on T lymphocytes in mice (e.g., cytotoxic T lymphocyte-associated protein 4 (CTLA-4), programmed cell death protein 1 (PD-1), and programmed death-ligand 1 (PD-L1)) is associated with dilated cardiomyopathy and the development of autoimmune myocarditis suggesting that these checkpoints protect against T cell-mediated myocarditis [106, 107]. Therefore, mechanistically, it is of no surprise that PD-1 and CTLA-4 inhibitors have an increased risk of myopericarditis [106–108].

Pembrolizumab and nivolumab are programmed death receptor-1 inhibitors that are associated with development of myocarditis. Arrhythmias including sinus tachycardia, ventricular bigeminy, AV block, AF, and even SCD have been reported during treatment with these agents likely secondary to myocarditis [109, 110]. Ipilimumab is another checkpoint inhibitor that targets CTLA-4 and has also been associated with likely immune-mediated pericarditis and myocarditis. There have also been limited reports of AF and secondary ventricular arrhythmias with ipilimumab [109, 110]. Among 20,594 patients treated with immune checkpoint inhibitors in the safety databases of Bristol-Myers Squibb, there were 18 reported myocarditis cases with more severe episodes reported in patients who had received combination therapy with nivolumab plus ipilimumab [106, 108]. These episodes were diagnosed at an average of 17 days after the first treatment suggesting early toxicity [106, 108]. These findings also demonstrate that cardiac complications are more frequent with combined immune checkpoint inhibitors as opposed to treatment with single agents.

Chimeric antigen receptor therapy (CAR-T therapy) is a new modality of immunotherapy where T cells are genetically modified to target tumors through the expression of a chimeric antigen receptor. CAR-T cell therapy has been efficacious in the treatment of various hematological malignancies; however, unexpected cardiotoxicities have been observed possibly via off-target effects resulting from low affinities of T cell receptors for the targeted tumor antigens or through harmful immune responses such as the cytokine release syndrome (CRS) [111–113]. CRS is the most prevalent adverse event following CAR-T and involves release of inflammatory cytokines which have been associated with tachycardia, hypotension, and cardiac dysfunction [113]. Other clinical features, including high fevers, renal impairment, hepatic failure, and

disseminated intravascular coagulation, increase the risk for development of arrhythmias including SVT and atrial fibrillation [111–113].

Interleukin-2 Immunotherapy

Interleukin-2 was the first successful immunotherapy agent activating T cell proliferation and differentiation to combat cancer. It is currently utilized in the treatment of metastatic renal cell carcinoma and melanoma. IL-2 therapy has been associated with significant cardiotoxicity including the development of SVT and AF with reported rates as high as 17% [114–116]. The frequency of ventricular arrhythmias is low (0.4–1.1%) [114]. Arrhythmias typically subside upon discontinuation of therapy. Proposed mechanisms of action include direct myocardial toxicity versus coronary artery vasospasm or myocarditis. Capillary leak syndrome commonly occurs with IL-2 therapy leading to hypotension and a reflex increase in heart rate which can also trigger SVT and VT [114–117]. Due to these side effects, IL-2 therapy is not recommended for patients with cardiac or pulmonary disease.

Topoisomerase Inhibitors

Amsacrine, used in the treatment of some lymphomas and acute leukemias, has been reported to cause ECG changes and arrhythmias within minutes to hours after the first course of therapy and typically resolve with discontinuation of the drug. It has been associated with QTc prolongation as well as non-specific ST-T wave abnormalities and tachyarrhythmias including AF or atrial flutter, SVT, PVCs, and even ventricular fibrillation and SCD. The incidence of torsades de pointes in one study was as high as 16% with 90% of patients developing QTc > 470 ms and 65% with QTc > 500 ms [118–120]. The arrhythmic risk may be significantly increased in the setting of amsacrine-induced electrolyte abnormalities; thus, maintaining appropriate electrolyte levels is of extreme importance [118–120].

Section 3: Radiation Induced Rhythm Disturbances

Radiation therapy can cause long-term cardiovascular effects including accelerated coronary artery disease, fibrosis-induced pericarditis, and valvular heart disease which in turn have associated arrhythmic complications. Less commonly, radiation itself can cause direct electrophysiological abnormalities including ECG changes and arrhythmias. Data on the effects of radiation therapy and acute ECG changes is limited primarily to case reports of secondary arrhythmias and non-specific changes such as T wave abnormalities, decreased QRS amplitude, and rarely bundle branch or AV block [121, 122].

In one prospective trial looking at 25 patients receiving > 45 Gray (Gy) to the thorax with pretreatment estimates of > 20 Gy to the heart, 12 patients experienced acute non-specific ECG changes during therapy, including T wave changes, prolonged QTc, and poor R wave progression [121]. Seven of these patients had resolution of their ECG changes on subsequent evaluation, and no patients required any intervention for these findings [121]. There have also been several case reports documenting the development of left bundle branch block in patients receiving radiotherapy as well as the development complete heart block requiring pacemaker implantations, although this is quite rare [121–124].

In addition to increased risk of cardiotoxicity, there have also been documented reports of autonomic dysfunction associated with thoracic and neck radiation therapy [125, 127]. A cohort study looking at Hodgkin's lymphoma survivors who had received thoracic radiation therapy demonstrated increased resting heart rate as well as abnormal heart rate recovery compared to matched control subjects [125]. These patients also had reduced exercise tolerance with exercise treadmill testing and increased all-cause mortality [125]. In addition, radiation therapy patients were more likely to have blunted or abnormal systolic blood pressure responses to exercise compared with the control subjects [125]. A similar study of childhood survivors of Hodgkin's lymphoma also reported an elevated resting heart rate on ambulatory Holter monitoring and a blunted blood pressure and heart rate response to exercise [126].

Autonomic dysfunction has also been reported as a late side effect of neck radiotherapy via baroreceptor failure [127]. In one study, heart rate response to deep breathing and Valsalva ratio were notably lower in patients ≥ 6 months after radiation therapy for nasopharyngeal carcinoma [127]. The findings from these studies suggest possible dose-related injury of the autonomic nervous system as higher doses of radiation therapy had higher predispositions to abnormal heart rate recovery [125–127].

Conclusion

There is increasing awareness of the potential cardiotoxic and arrhythmogenic properties of many different cancer therapeutics. The most common electrophysiological abnormalities include the development of atrial arrhythmias, in particular atrial fibrillation and QTc prolongation with the associated risk of torsades de pointes and sudden cardiac death. While these may be secondary to some other cardiotoxicity such as cardiomyopathy and heart failure, many novel treatments have direct electrophysiological and arrhythmogenic effects. Treating these patients can be challenging and often requires a multidisciplinary approach. Therefore, it is essential for the collaboration between cardiologists and oncologists in the

management of treatment-related arrhythmias in order for patients to continue receiving optimal cancer therapies while minimizing cardiovascular risk. As the field continues to evolve, research is necessary to better understand the etiology and treatment of arrhythmias in this population. The ongoing MADIT-CHIC study (Multicenter Automatic Defibrillator Implantation Trial–Chemotherapy-Induced Cardiomyopathy; NCT02164721) will be the first prospective study evaluating the benefit of cardiac resynchronization therapy defibrillators in AC-associated CMO. The results of this study will improve our understanding of the natural history of this type of CMP as well as provide information about associated arrhythmia burden. Moreover, it is essential to improve our identification of those at the highest risk for the development of arrhythmias. While there are increased rates of AF observed with many cancer therapies, it is not clear if these risks persist once treatment is withdrawn. Ambulatory rhythm monitoring using handheld technology such as with smartphones or using implantable rhythm monitors may be necessary to better quantitate long-term burden. In addition, appropriate stroke risk mitigation strategies must be studied in the setting of cancer-related abnormalities including anemia and thrombocytopenia. As such, there may be increased utility for direct oral anticoagulants or even left atrial appendage closure devices in these patients. With enhanced understanding via investigation, clinicians will be better prepared to effectively manage arrhythmias in cancer patients in the future.

Compliance with Ethical Standards

Conflict of Interest Merna A. Armanious declares that she has no conflict of interest.

Shreya Mishra declares that she has no conflict of interest.

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin. 2016;66:7–30.
2. Yeh ET, Bickford CL. Cardiovascular complications of cancer therapy: incidence, pathogenesis, diagnosis, and management. J Am Coll Cardiol. 2009;53:2231–47.
3. Guglin M, Aljayeh M, Saiyad S, Ali R, Curtis AB. Introducing a new entity: chemotherapy-induced arrhythmia. Europace. 2009;11:1579–86.
4. •• Tamargo J, Caballero R, Delpon E. Cancer chemotherapy and cardiac arrhythmias: a review. Drug Saf. 2015;38:129–52. **This article reviews documented arrhythmias and the electrophysiological pathophysiology associated with multiple chemotherapeutic agents, as well as reports on the relative frequency of various arrhythmias.**
5. Viganego F, Singh R, Fradley M. Arrhythmias and other electrophysiology issues in cancer patients receiving chemotherapy or radiation. Curr Cardiol Rep. 2016;18:52.
6. •• Buza V, Rajagopalan B, Curtis AB. Cancer treatment-induced arrhythmias focus on chemotherapy and targeted therapies. Circ Arrhythm Electrophyisol. 2017;10:e005443. https://doi.org/10.1161/CIRCEP.117.005443. **This review describes the ECG changes and arrhythmias associated with various cancer treatments and provides the available evidence regarding the mechanisms by which cancer therapies cause arrhythmias.**
7. Doxorubicin. FDA Package Insert. Available at https://www.accessdata. fda.gov/drugsatfda_docs/label/2012/062921s022lbl.pdf. Accessed 26 Nov 2017.
8. Wu T, Ong JJC, et al. Characteristics of wave fronts during ventricular fibrillation in human hearts with dilated cardiomyopathy: role of increased fibrosis in the generation of reentry. JACC. 1998;32(1):187–96.
9. Swain SM, Whaley FS, Ewer MS. Congestive heart failure in patients treated with doxorubicin: a retrospective analysis of three trials. Cancer. 2003;97(11):2869–79.
10. Von Hoff DD, Layard MW, Basa P, et al. Risk factors for doxorubicin-induced congestive heart failure. Ann Intern Med. 1979;91(5):710–7.
11. Armenian AH, Lacchetti C, Barac A, et al. Prevention and monitoring of cardiac dysfunction in survivors of adult cancers: American Society of Clinical Oncology (ASCO) Clinical Practice Guidelines. J Clin Oncol. 2017;35(8):893–911. https://doi.org/10.1200/JCO.2016.70.5400.
12. •• Mazur M, Wang F, Hodge DO, et al. Burden of cardiac arrhythmias in patients with anthracycline-related cardiomyopathy. JACC: Clin Electrophysiol. 2016;3(2):139–50. https://doi.org/10.1016/j.jacep.2016.08.009. **This was the first article to evaluate arrhythmia risk and incidence in patients with anthracycline-induced cardiomyopathy using data from implantable cardiac devices.**
13. Fradley MG, Viganego F, Kip K, Martin A, Patel AA, Ismail-Khan R, et al. Rates and risk of arrhythmias in cancer survivors with chemotherapy-induced cardiomyopathy compared with patients with other cardiomyopathies. Open Heart. 2017;4:e000701. https://doi.org/10.1136/openhrt-2017-000701.
14. Hahn VS, Lenihan DJ, Ky B. Cancer therapy-induced cardiotoxicity: basic mechanisms and potential cardioprotective therapies. J Am Heart Assoc. 2014;3(2):e000665.
15. Wang YX, Korth M. Effects of doxorubicin on excitation-contraction coupling in guinea pig ventricular myocardium. Circ Res. 1995;76(4):645–53.
16. Aversano RC, Boor PJ. Acute doxorubicin-induced cardiac arrhythmias during ether anesthesia. Res Commun Chem Pathol Pharmacol. 1983;41(2):345–8.
17. Olson RD, Mushlin PS, Brenner DE, Fleischer S, Cusack BJ, Chang BK, et al. Doxorubicin cardiotoxicity may be caused by its metabolite, doxorubicinol. Proc Natl Acad Sci U S A. 1988;85(10):3585–9.
18. O'Bryan RM, Luce JK, Talley RW, Gottlieb JA, Baker LH, Bonadonna G. Phase II evaluation of adriamycin in human neoplasia. Cancer. 1973;32(1):1–8.

19. Outomuro D, Grana DR, Azzato F, Milei J. Adriamycin-induced myocardial toxicity: new solutions for an old problem? Int J Cardiol. 2007;117(1):6–15.
20. Gottdiener JS, Appelbaum FR, Ferrans VJ, Deisseroth A, Ziegler J. Cardiotoxicity associated with high dose cyclophosphamide therapy. Arch Intern Med. 1981;141(6):758–63.
21. Kupari M, Volin L, Suokas A, Timonen T, Hekali P, Ruutu T, et al. Cardiac involvement in bone marrow transplantation: electrocardiographic changes, arrhythmias, heart failure and autopsy findings. Bone Marrow Transplant. 1990;5(2):91–8.
22. Ando M, Yokozawa T, Sawada J, Takaue Y, Togitani K, Kawahigashi N, et al. Cardiac conduction abnormalities in patients with breast cancer undergoing high-dose chemotherapy and stem cell transplantation. Bone Marrow Transplant. 2000;25(2):185–9.
23. Cazin B, Gorin NC, Laporte JP, Gallet B, Douay L, Lopez M, et al. Cardiac complications after bone marrow transplantation. A report on a series of 63 consecutive transplantations. Cancer. 1986;57(10):2061–9.
24. Ulrickson M, Aldridge J, Kim HT, Hochberg EP, Hammerman P, Dube C, et al. Busulfan and cyclophosphamide (Bu/Cy) as a preparative regimen for autologous stem cell transplantation in patients with non-Hodgkin lymphoma: a single institution experience. Biol Blood Marrow Transplant. 2009;15:1447–54. https://doi.org/10.1016/j.bbmt.2009.07.014.
25. Feliz V, Saiyad S, Ramarao SM, Khan H, Leonelli F, Guglin M. Melphalan induced supraventricular tachycardia: incidence and risk factors. Clin Cardiol. 2011;34(6):356–9.
26. Fradley MG, Barrett CD, Clark JR, Francis SA. Ventricular fibrillation cardiac arrest due to 5-fluorouracil cardiotoxicity. Tex Heart Inst J. 2013;40(4):472–6.
27. Yilmaz U, Oztop I, Ciloglu A, Okan T, Tekin U, Yaren A, et al. 5-fluorouracil increases the number and complexity of premature complexes in the heart: a prospective study using ambulatory ECG monitoring. Int J Clin Pract. 2007;61:795–801. https://doi.org/10.1111/j.1742-1241.2007.01323.x.
28. de Forni M, Malet-Martino MC, Jaillais P, Shubinski RE, Bachaud JM, Lemaire L, et al. Cardiotoxicity of high dose continuous infusion fluorouracil: a prospective clinical study. J Clin Oncol. 1992;10(11):1795–801.
29. Khan MA, Masood N, Husain N, Ahmad B, Aziz T, Naeem A. A retrospective study of cardiotoxicities induced by 5-fluouracil (5-FU) and 5-FU based chemotherapy regimens in Pakistani adult cancer patients at Shaukat Khanum Memorial Cancer Hospital & Research Center. J Pak Med Assoc. 2012;62:430–4.
30. Hrovatin E, Viel E, Lestuzzi C, Tartuferi L, Zardo F, Brieda M, et al. Severe ventricular dysrhythmias and silent ischemia during infusion of the antimetabolite 5-fluorouracil and cisplatin. J Cardiovasc Med (Hagerstown). 2006;7(8):637–40.
31. Keefe DL, Roistacher N, Pierri MK. Clinical cardiotoxicity of 5-fluorouracil. J Clin Pharmacol. 1993;33(11):1060–70.
32. Robben NC, Pippas AW, Moore JO. The syndrome of 5-fluorouracil cardiotoxicity. Cancer. 1993;71(2):493–509.
33. Santini D, Tonini G, Abbate A, Di Cosimo S, Gravante G, Vincenzi B, et al. Gemcitabine induced atrial fibrillation: a hitherto unreported manifestation of drug toxicity. Ann Oncol. 2000;11(4):479–81.
34. Gridelli C, Cigolari S, Gallo C, Manzione L, Ianniello GP, Frontini L, et al. Activity and toxicity of gemcitabine and gemcitabine + vinorelbine in advanced non-small cell lung cancer elderly patients: phase II data from the Multicenter Italian Lung cancer in the Elderly Study (MILES) randomized trial. Lung Cancer. 2001;31:277–84.
35. McGuire WP, Rowinsky EK, Rosenshein NB, Grumbine FC, Ettinger DS, Armstrong DK, et al. Taxol: a unique antineoplastic agent with significant activity in advanced ovarian epithelial neoplasms. Ann Intern Med. 1989;111:273–9.
36. Arbuck SG, Strauss H, Rowinsky E, Christian M, Suffness M, Adams J, et al. A reassessment of cardiac toxicity associated with Taxol. J Natl Cancer Inst. 1992;15:117–30.
37. Rowinsky EK, Eisenhauer EA, Chaudhry V, Arbuck SG, Donehower RC. Clinical toxicities encountered with paclitaxel (Taxol). Semin Oncol. 1993;20(4 Suppl 3):1–15.
38. Raja W, Mir MH, Dar I, Bandey MA, Ahmad I. Cisplatin induced paroxysmal supraventricular tachycardia. Indian J Med Paediatr Oncol. 2013;34(4):330–2. https://doi.org/10.4103/0971-5851.125262.
39. Yavaş O, Aytemir K, Celik I. The prevalence of silent arrhythmia inpatients receiving cisplatin-based chemotherapy. Turkish J Cancer. 2008;38:12–5.
40. Thix CA, Königsrainer I, Kind R, Wied P, Schroeder TH. Ventricular tachycardia during hyperthermic intraperitoneal chemotherapy. Anaesthesia. 2009;64:1134–6. https://doi.org/10.1111/j.1365-2044.2009.05993.x.
41. Tomkowski WZ, Wiśniewska J, Szturmowicz M, Kuca P, Burakowski J, Kober J, et al. Evaluation of intrapericardial cisplatin administration in cases with recurrent malignant pericardial effusion and cardiac tamponade. Support Care Cancer. 2004;12(1):53–7.
42. Bischiniotis TS, Lafaras CT, Platogiannis DN, Moldovan L, Barbetakis NG, Katseas GP. Intrapericardial cisplatin administration after pericardiocentesis in patients with lung adenocarcinoma and malignant cardiac tamponade. Hell J Cardiol. 2005;46(5):324–9.
43. Richards WG, Zellos L, Bueno R, Jaklitsch MT, Jänne PA, Chirieac LR, et al. Phase I to II study of pleurectomy/decortication and intraoperative intracavitary hyperthermic cisplatin lavage for mesothelioma. J Clin Oncol. 2006;24(10):1561–7.
44. Roboz GJ, Ritchie EK, Carlin RF, Samuel M, Gale L, Provenzano-Gober JL, et al. Prevalence, management, and clinical consequences of QT interval prolongation during treatment with arsenic trioxide. J Clin Oncol. 2014;32:3723–3723-3728. https://doi.org/10.1200/JCO.2013.51.2913.
45. Hu J, Shen ZX, Sun GL, Chen SJ, Wang ZY, Chen Z. Long-term survival and prognostic study in acute promyelocytic leukemia treated with all-trans-retinoic acid, chemotherapy, and As2O3: an experience of 120 patients at a single institution. Int J Hematol. 1999;70:248–60.
46. Soignet SL, Frankel SR, Douer D, Tallman MS, Kantarjian H, Calleja E, et al. United States multicenter study of arsenic trioxide in relapsed acute promyelocytic leukemia. J Clin Oncol. 2001;19:3852–60.
47. Barbey JT, Pezzullo JC, Soignet SL. Effect of arsenic trioxide on QT interval in patients with advanced malignancies. J Clin Oncol. 2003;21:3609–15.
48. Beer TM, Tangen CM, Nichols CR, Margolin KA, Dreicer R, Stephenson WT, et al. Southwest oncology group phase II study of arsenic trioxide in patients with refractory germ cell malignancies. Cancer. 2006;106(12):2624–9.
49. Westervelt P, Brown RA, Adkins DR, Khoury H, Curtin P, Hurd D, et al. Sudden death among patients with acute promyelocytic leukemia treated with arsenic trioxide. Blood. 2001;98(2):266–71.
50. Krause DS, Van Etten RA. Tyrosine kinases as targets for cancer therapy. N Engl J Med. 2005;353:172–87.
51. Xu Z, Cang S, Yang T, Liu D. Cardiotoxicity of tyrosine kinase inhibitors in chronic myelogenous leukemia therapy. Hematol Rev. 2009;1:17–21.
52. McMullen JR, Boey EJ, Ooi JY, et al. Ibrutinib increases the risk of atrial fibrillation, potentially through inhibition of cardiac PI3K-Akt signaling. Blood. 2014;124:3829–30.

53. Chu TF, Rupnick MA, Kerkela R, Dallabrida SM, Zurakowski D, Nguyen L, et al. Cardiotoxicity associated with tyrosine kinase inhibitor sunitinib. Lancet. 2007;370:2011–9.
54. Miklos D, Cutler CS, Arora M, Waller EK, Jagasia M, Pusic I, et al. Ibrutinib for chronic graft-versus-host disease after failure of prior therapy. Blood. 2017;130(21):2243–50. https://doi.org/10.1182/blood-2017-07-793786.
55. Byrd JC, Brown JR, O'Brien S, et al. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. N Engl J Med. 2014;371:213–23.
56.• Brown JR, Moslehi J, O'Brien S, et al. Characterization of atrial fibrillation adverse events reported in ibrutinib randomized controlled registration trials. Haematologica. 2017;102(10):1796–805. https://doi.org/10.3324/haematol.2017.171041. **This study pooled data from randomized controlled studies to report on atrial fibrillation incidence with ibrutinib treatment, identify risk factor, and discuss management.**
57. Leong DP, Caron F, illis C, Duan A, Healey JS, Fraser G, et al. The risk of atrial fibrillation with ibrutinib use: a systematic review and meta-analysis. Blood. 2016;128:138–40. https://doi.org/10.1182/blood-2016-05-712828.
58. Wang ML, Blum KA, Martin P, Goy A, Auer R, Kahl BS, et al. Long-term follow-up of MCL patients treated with single-agent ibrutinib: updated safety and efficacy results. Blood. 2015;126:739–45.
59. Shatzel JJ, Olson SR, Tao DL, McCarty OJT, Danilov AV, DeLoughery TG. Ibrutinib-associated bleeding: pathogenesis, management and risk reduction strategies. J Thromb Haemost. 2017;15(5):835–47. https://doi.org/10.1111/jth.13651.
60. Wang ML, Rule S, Martin P, Goy A, Auer R, Kahl BS, et al. Targeting BTK with ibrutinib in relapsed or refractory mantle-cell lymphoma. N Engl J Med. 2013;369(6):507–16.
61. Chai-Adisaksopha C, Crowther M, Isayama T, Lim W. The impact of bleeding complications in patients receiving target-specific oral anticoagulants: a systematic review and meta-analysis. Blood. 2014;124:2450–8.
62. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus warfarin in patients with atrial fibrillation (ARISTOTLE). N Engl J Med. 2011;365(11):981–2. https://doi.org/10.1056/NEJMoa1107039.
63. Pretorius L, Du XJ, Woodcock EA, et al. Reduced phosphoinositide 3-kinase (p110alpha) activation increases the susceptibility to atrial fibrillation. Am J Pathol. 2009;175:998–1009.
64. Lannutti BJ, Meados SA, Herman SE, et al. CAL-101, a p110delta selective phosphatidylinositol-3-kinase inhibitor for the treatment of B-cell malignancies, inhibits PI3K signaling and cellular viability. Blood. 2011;117:591–4.
65. Byrd JC, Harrington B, O'Brien S, Jones JA, Schuh A, Devereux S, et al. Acalabrutinib (ACP-196) in relapsed chronic lymphocytic leukemia. N Engl J Med. 2016;374:323–32. https://doi.org/10.1056/NEJMoa1509981.
66. Lampson BL, Yu L, Glynn RJ, et al. Ventricular arrhythmias and sudden death in patients taking ibrutinib. Blood J. 2017; https://doi.org/10.1182/blood-2016-10-742437.
67. Chanan-Khan A, Cramer P, Demirkan F, Fraser G, Silva RS, Grosicki S, et al. Ibrutinib combined with bendamustine and rituximab compared with placebo, bendamustine, and rituximab for previously treated chronic lymphocytic leukaemia or small lymphocytic lymphoma (HELIOS): a randomised, double-blind, phase 3 study. Lancet Oncol. 2016;17(2):200–11.
68. Steinberg M. Dasatinib: a tyrosine kinase inhibitor for the treatment of chronic myelogenous leukemia and Philadelphia chromosome-positive acute lymphoblastic leukemia. Clin Ther. 2007;29:2289–308. https://doi.org/10.1016/j.clinthera.2007.11.005.
69. Locatelli M, Criscitiello C, Esposito A, Minchella I, Goldhirsch A, Cipolla C, et al. QTc prolongation induced by targeted biotherapies used in clinical practice and under investigation: a comprehensive review. Target Oncol. 2015;10:27–43.
70. Larsan RA, Hochhaus A, Saglio G, et al. Cardiac safety profile of imatinib and nilotinib in patients with newly diagnosed chronic myeloid leukemia in chronic phase (CML-CP): results from ENESTnd. Blood. 2010;116:2291.
71. Fradley MG, Moslehi J. QT prolongation and oncology drug development. Card Electrophysiol Clin. 2015;7:341–55.
72. Tartarone A, Gallucci G, Lazzari C, Lerose R, Lombardi L, Aieta M. Crizotinib-induced cardiotoxicity: the importance of a proactive monitoring and management. Future Oncol. 2015;11:2043–8. https://doi.org/10.2217/fon.15.47.
73. Khozin S, Blumenthal GM, Zhang L, Tang S, Brower M, Fox E, et al. FDA approval: ceritinib for the treatment of metastatic anaplastic lymphoma kinase-positive non-small cell lung cancer. Clin Cancer Res. 2015;21:2436–9. https://doi.org/10.1158/1078-0432.CCR-14-3157.
74. Ou SH, Tang Y, Polli A, Wilner KD, Schnell P. Factors associated with sinus bradycardia during crizotinib treatment: a retrospective analysis of two large-scale multinational trials (PROFILE 1005 and 1007). Cancer Med. 2016;5:617–22. https://doi.org/10.1002/cam4.622.
75. Shah RR, Morganroth J, Shah DR. Cardiovascular safety of tyrosine kinase inhibitors: with a special focus on cardiac repolarization (QT interval). Drug Saf. 2013;36:295–316.
76. Fradley MG, Pinilla-Ibarz J. Arrhythmic complications of tyrosine kinase inhibitors. Futur Cardiol. 2015;11(4):395–9.
77. Bello CL, Mulay M, Huang X, Patyna S, Dinolfo M, Levine S, et al. Electrocardiographic characterization of the QTc interval in patients with advanced solid tumors: pharmacokinetic-pharmacodynamic evaluation of sunitinib. Clin Cancer Res. 2009;15:7045–52. https://doi.org/10.1158/1078-0432.CCR-09-1521.
78. Flaherty L, Hamid O, Linette G, et al. A single-arm, open-label, expanded access study of vemurafenib in patients with metastatic melanoma in the United States. Cancer J. 2014;20:18–24. https://doi.org/10.1097/PPO.0000000000000024.
79. Hall PS, Harshman LC, Srinivas S, Witteles RM. The frequency and severity of cardiovascular toxicity from targeted therapy in advanced renal cell carcinoma patients. JACC Heart Fail. 2013;1(1):72–8. https://doi.org/10.1016/j.jchf.2012.09.001.
80. Telli ML, Witteles RM, Fisher GA, Srinivas S. Cardiotoxicity associated with the cancer therapeutic agent sunitinib malate. Ann Oncol. 2008;19:1613–8.
81. Tolcer AW, Appleman LJ, Shapiro GI, et al. A phase I open-label study evaluating the cardiovascular safety of sorafenib in patients with advanced cancer. Cancer Chemother Pharmacol. 2011;67:751–64. https://doi.org/10.1007/s00280-010-1372-3.
82. Petrini I, Lencioni M, Ricasoli M, Iannopollo M, Orlandini C, Oliveri F, et al. Phase II trial of sorafenib in combination with 5-fluorouracil infusion in advanced hepatocellular carcinoma. Cancer Chemother Pharmacol. 2012;69:773–80. https://doi.org/10.1007/s00280-011-1753-2.
83. Piotrowski G, Gawor R, Slomka R, et al. Cardioverter-defibrillator in the treatment of arrhythmia induced by trastuzumab used in the adjuvant setting in a patient with positive human epidermal growth factor receptor type-2 breast cancer. Kardiol Pol. 2012;70:756–7.
84. Coiffier B, Lepage E, Briere J, Herbrecht R, Tilly H, Bouabdallah R, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. N Engl J Med. 2002;346(4):235–42.
85. Arai Y, Tadokoro J, Mitani K. Ventricular tachycardia associated with infusion of rituximab in mantle cell lymphoma. Am J Hematol. 2005;78(4):317–8.

86. Cetuximab. FDA package insert. https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/125084s262lbl.pdf.
87. Kordelas L, Bauer S, Schuler M, et al. Successful resuscitation of a patient with ventricular fibrillation due to hypomagnesemia under cetuximab therapy. Tumor Diagn Ther. 2014;35:25–7.
88. Orcioulo E, Buda G, Cecconi N, Galimberi S, Versari D, Cervetti G, et al. Unexpected cardiotoxicity in haematological bortezomib treated patients. Br J Haematol. 2007;138(3):396–403.
89. Berenson JR, Jagannath S, Barlogie B, Siegel DT, Alexanian R, Richardson PG, et al. Safety of prolonged therapy with bortezomib in relapsed or refractory multiple myeloma. Cancer. 2005;104(10):2141–8.
90. Xiao Y, Yin J, Wei J, Shang Z. Incidence and risk of cardiotoxicity associated with bortezomib in the treatment of cancer: a systematic review and meta-analysis. PLoS One. 2014;9(1):e87671.
91. Siegel D, Martin T, Nooka A, Harvey RD, Vij R, Niesvizky R, et al. Integrated safety profile of single-agent carfilzomib: experience from 526 patients enrolled in 4 phase II clinical studies. Haematologica. 2013;98:1753–61. https://doi.org/10.3324/haematol.2013.089334.
92.• Atrash S, Tullos A, Panozzo S, et al. Cardiac complications in relapsed and refractory multiple myeloma patients treated with carfilzomib. Blood Cancer J. 2015;5:e272. https://doi.org/10.1038/bcj.2014.93. **This study reports data on patients who developed significant cardiovascular adverse events necessitating hospitalization during the first two cycles of therapy with carfilzomib either alone or with dexamethasone. It also reviews echocardiogram findings before and after treatment as well as BNP measurements.**
93. Papandreou CN, Daliani DD, Nix D, Yang H, Madden T, Wang X, et al. Phase I trial of the proteasome inhibitor bortezomib in patients with advanced solid tumors with observations in androgen-independent prostate cancer. J Clin Oncol. 2004;22:2108–21.
94. Honton B, Despas F, Dumonteil N, Rouvellat C, Roussel M, Carrie D, et al. Bortezomib and heart failure: case-report and review of the French Pharmacovigilance database. Fundam Clin Pharmacol. 2014;28:349–52.
95. Enrico O, Gabriele B, Nadia C, Sara G, Daniele V, Giulia C, et al. Unexpected cardiotoxicity in haematological bortezomib treated patients. Br J Haematol. 2007;138:396–7.
96. Phase 3 study with carfilzomib and dexamethasone versus bortezomib and dexamethasone for relapsed multiple myeloma patients (ENDEAVOR). (http://clinicaltrials.gov/show/NCT01568866).
97. Fahdi IE, Gaddam V, Saucedo JF, Kishan CV, Vyas K, Deneke MG, et al. Bradycardia during therapy for multiple myeloma with thalidomide. Am J Cardiol. 2004;93(8):1052–5.
98. Kaur A, Yu SS, Lee AJ, Chiao TB. Thalidomide-induced sinus bradycardia. Ann Pharmacother. 2003;37:1040–3.
99. Rajkumar SV, Rosinol L, Hussein M, et al. Multicenter, randomized, double-blind, placebo-controlled study of thalidomide plus dexamethasone compared with dexamethasone as initial therapy for newly diagnosed multiple myeloma. J Clin Oncol. 2008;26:2171–7. https://doi.org/10.1200/JCO.2007.14.1853.
100. Lenalidomide. FDA package insert. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021880s049lbl.pdf. Accessed 2 May 2017.
101. Shah MH, Binkley P, Chan K, Xiao J, Arbogast D, Collamore M, et al. Cardiotoxicity of histone deacetylase inhibitor depsipeptide in patients with metastatic neuroendocrine tumors. Clin Cancer Res. 2006;12:3997–4003.
102. Noonan AM, Eisch RA, Liewehr DJ, Sissung TM, Venzon DJ, Flagg TP, et al. Electrocardiographic studies of romidepsin demonstrate its safety and identify a potential role for K(ATP) channel. Clin Cancer Res. 2013;19:3095–104. https://doi.org/10.1158/1078-0432.CCR-13-0109.
103. Piekarz RL, Frye AR, Wright JJ, Steinberg SM, Liewehr DJ, Rosing DR, et al. Cardiac studies in patients treated with depsipeptide FK229, in a phase II trial for T-cell lymphoma. Clin Cancer Res. 2006;12(12):3762–73.
104. Sandor V, Bakke S, Robey RW, Kang MH, Blagosklonny MV, Bender J, et al. Phase I trial of the histone deactylase inhibitor, depsipeptide (FR901228, NSC 630176), in patients with refractory neoplasms. Clin Cancer Res. 2002;8(3):718–28.
105. Rathkopf DE, Picus J, Hussain A, Ellard S, Chi KN, Nydam T, et al. A phase 2 study of intravenous panobinostat in patients with castration-resistant prostate cancer. Cancer Chemother Pharmacol. 2013;72:537–44. https://doi.org/10.1007/s00280-013-2224-8.
106. Varricchi G, Galdiero MR, Tocchetti CG. Cardiac toxicity of immune checkpoint inhibitors: cardio-oncology meets immunology. Circulation. 2017;136(21):1989–92. https://doi.org/10.1161/CIRCULATIONAHA.117.029626.
107. Nishimura H, Okazaki T, Tanaka Y, Nakatani K, Hara M, Matsumori A, et al. Autoimmune dilated cardiomyopathy in PD-1 receptor-deficient mice. Science. 2001;291:319–22. https://doi.org/10.1126/science.291.5502.319.
108. Johnson DB, Balko JM, Compton ML, Chalkias S, Gorham J, Xu Y, et al. Fulminant myocarditis with combination immune checkpoint blockade. N Engl J Med. 2016;375:1749–55. https://doi.org/10.1056/NEJMoa1609214.
109. Heinzerling L, Ott PA, Hodi FS, Husain AN, Tajmir-Riahi A, Tawbi H, et al. Cardiotoxicity associated with CTLA4 and PD1 blocking immunotherapy. J Immunother Cancer. 2016;4:50. https://doi.org/10.1186/s40425-016-0152-y.
110. Behling J, Kaes J, Munzel T, et al. New-onset third-degree atrioventricular block because of autoimmune-induced myositis under treatment with anti-programmed cell death-1 (nivolumab) for metastatic melanoma. Melanoma Res. 2017;27:155–8.
111. Zheng PP, Li J, Kros JM. Breakthroughs in modern cancer therapy and elusive cardiotoxicity: critical research-practic gaps, challenges, and insights. Med Res Rev. 2018;38(1):325–76. https://doi.org/10.1002/med.21463.
112. Linette GP, Stadtmauer EA, Maus MV, Rapoport AP, Levine BL, Emery L, et al. Cardiovascular toxicity and titin cross-reactivity of affinity-enhanced T cells in myeloma and melanoma. Blood. 2013;122(6):863–71. https://doi.org/10.1182/blood-2013-03-490565.
113. Bonifant CL, Jackson HJ, Brentjens RJ, Curran KJ. Toxicity and management in CAR T-cell therapy. Mol Ther Oncolytics. 2016;3:16011. https://doi.org/10.1038/mto.2016.11.
114. Siegel JP, Puri RK. Interleukin-2 toxicity. J Clin Oncol. 1991;9:694–704.
115. Rosenberg SA, Lotze MT, Muul LM, Chang AE, Avis FP, Leitman S, et al. A progress report on the treatment of 157 patients with advanced cancer using lymphokine-activated killer cells and interleukin-2 or high-dose interleukin-2 alone. N Engl J Med. 1987;316:889–97.
116. Margolin KA, Rayner AA, Hawkins MJ, Atkins MB, Dutcher JP, Fisher RI, et al. Interleukin-2 and lymphokine-activated killer cell therapy of solid tumors: analysis of toxicity and management guidelines. J Clin Oncol. 1989;7:486–98.
117. Atkins MB, Lotze MT, Dutcher JP, Fisher RI, Weiss G, Margolin K, et al. High-dose recombinant interleukin 2 therapy for patients with metastatic melanoma: analysis of 270 patients treated between 1985 and 1993. J Clin Oncol. 1999;17:2105–16. https://doi.org/10.1200/JCO.1999.17.7.2105.
118. Weiss RB, Grillo-Lopez AJ, Marsoni S, et al. Amsacrine-associated cardiotoxicity: an analysis of 82 cases. J Clin Oncol. 1986;4:918–28. https://doi.org/10.1200/JCO.1986.4.6.918.
119. Arlin ZA, Feldman EJ, Mittelman A, Ahmed T, Puccio C, Chun HG, et al. Amsacrine is safe and effective therapy for patients with

myocardial dysfunction and acute leukemia. Cancer. 1991;68: 1198–200.
120. Shinar E, Hasin Y. Acute electrocardiographic changes induced by amsacrine. Cancer Treat Rep. 1984;68(9):1169–72.
121. Gomez DR, Yusuf SW, Munsell M, et al. A prospective exploratory analysis of cardiac biomarkers and electrocardiogram abnormalities in patients receiving thoracic radiation therapy with high-dose heart exposure. J Thorac Oncol. 2014;9(10):1554–60.
122. Adams MJ, Lipshultz SE, Schwartz C, et al. Radiation-associated cardiovascular disease: manifestations and management. Semin Radiat Oncol. 2003;13:346–56.
123. Vasic N, Stevic R, Pesut D, Jovanovic D. Acute left bundle branch block as a complication of brachytherapy for lung cancer. Respir Med. 2011;105(Suppl 1):S78–80. https://doi.org/10.1016/S0954-6111(11)70016-6.
124. Tsagalou EP, Kanakakis J, Anastasiou-Nana MI. Complete heart block after mediastinal irradiation in a patient with the Wolff-Parkinson-White syndrome. Int J Cardiol. 2005;104(1): 108–10.
125. Groarke JD, Tanquturi VK, Hainer J, et al. Abnormal exercise response in long-term survivors of Hodgkin's lymphoma treated with thoracic irradiation: evidence of cardiac autonomic dysfunction and impact on outcomes. J Am Coll Cardiol. 2015;65(6):573–83. https://doi.org/10.1016/j.jacc.2014.11.035.
126. Adams MJ, Lipsitz SR, Colan SD, Tarbell NJ, Treves ST, Diller L, et al. Cardiovascular status in long-term survivors of Hodgkin's disease treated with chest radiotherapy. J Clin Oncol. 2004;22(15): 3139–48.
127. Huang CC, Huang TL, Hsu HC, Chen HC, Lin HC, Chien CY, et al. Long-term effects of neck irradiation on cardiovascular autonomic function: a study in nasopharyngeal carcinoma patients after radiotherapy. Muscle Nerve. 2013;47(3):344–50. https://doi.org/10.1002/mus.23530.