Cancer Treatment–Induced Arrhythmias
Focus on Chemotherapy and Targeted Therapies

Vitaly Buza, MD, PhD; Bharath Rajagopalan, MBBS; Anne B. Curtis, MD

With the development of newer drugs and improvements in established treatment protocols, prognosis for many types of cancer has improved dramatically. Some cancers that were historically associated with high fatality rates now have high cure rates or successful palliation, turning the malignancy into a chronic disease. Given this improved prognosis, more patients will face the adverse effects of cancer treatment. Cancer therapy can result in cardiac toxicity, such as cardiomyopathy. Cardiotoxicity with chemotherapeutic agents in the form of cardiomyopathy was first described in 1966 in patients receiving anthracyclines.[1] However, cancer treatment–induced arrhythmia (CTIA) has not attracted specific attention until recently.[2]

CTIA is a complex entity with multiple factors involved in its pathogenesis. It can be divided into primary CTIA (caused by a drug disrupting specific molecular pathways critical for the development of a specific arrhythmia) and secondary CTIA (caused by damage to the endocardium/myocardium/pericardium through ischemia, inflammation, or radiation therapy (RT), with arrhythmia as a secondary phenomenon). Secondary CTIA is much more common. The distinction between primary and secondary CTIA is not well defined, with many contributing and confounding factors, and the exact mechanisms for many drugs are still to be elucidated (Figure).

The incidence of CTIA with many chemotherapeutic agents is yet to be firmly established as most chemotherapy trials have not had adequate numbers of patients enrolled to study this problem. In addition, most cancer treatment trials have excluded patients with preexisting cardiac disease, which is the most vulnerable population for CTIA. The National Cancer Institute has developed Common Terminology Criteria for Adverse Events, which is used for adjudication of cardiac toxicity with chemotherapeutic agents in clinical trials.[4]

Establishing a causal relationship of a certain chemotherapeutic agent to a specific CTIA can be challenging. First of all, cancer itself can predispose to arrhythmia. One example is atrial fibrillation/flutter (AF/AFL), with the overt manifestation of the arrhythmia sometimes preceding the diagnosis of the malignancy.[5] Chronic inflammation, metabolic changes induced by cancer, and the presence of common risk factors, such as obesity and alcohol use, are the most plausible explanations for this association. The absence of cardiac monitoring prior to chemotherapy in most trials makes it difficult to determine whether there was a preexisting undiagnosed arrhythmia, rather than one related to the chemotherapy. Second, most chemotherapy protocols include multidrug regimens, which make the identification of the exact causative agent difficult. In addition, a synergistic effect of multiple drugs on the cardiac toxicity profile cannot be ruled out. Many patients also have a history of prior treatment for cancer, which makes it difficult to determine whether the arrhythmia is secondary to the current regimen or a chronic effect of past therapy. Third, CTIAs in clinical trials are often described as symptoms, and the exact diagnosis of the underlying arrhythmia is often not available. It has been noted that the National Cancer Institute Common Terminology Criteria for Adverse Events for cardiotoxicity is often used incorrectly in oncology trials.[6]

Besides arrhythmias, chemotherapeutic agents can also contribute to various ECG changes, such as QTc interval prolongation and conduction abnormalities. QTc prolongation is most commonly related to effects on hERG (human Ether-à-go-go-Related Gene) potassium channels and the rapid component of the delayed rectifier potassium current I_{Kr}.[7] While QTc prolongation is common with many chemotherapeutic agents, the incidence of clinically significant arrhythmias like torsades de pointes is less frequent. Though rare, the clinical implications of torsades de pointes are extremely important given the life-threatening nature of this arrhythmia. To quantify the risk for torsades de pointes, QTc interval is the best surrogate marker that is readily available and well established in clinical trials.

In this review, we will describe the ECG changes and arrhythmias associated with individual cancer chemotherapeutic agents using the classification in Table 1. The mechanisms by which chemotherapeutic agents cause arrhythmias are in many cases still poorly understood, but we provide what evidence is available. We have left out isolated case reports and rare observations of arrhythmias with various chemotherapeutic agents both because it is more difficult to assess cause and effect and also that, given their rarity, they are less likely to be meaningful to clinicians. Tables 2 and 3 summarize the relative frequency of the various arrhythmias associated with different classes of anticancer drugs.

Anthracyclines

Anthracyclines are commonly used in the treatment of breast cancer, acute leukemia, lymphomas, and childhood solid tumors. Cardiomyopathy is the most common cardiac toxicity of anthracyclines, but they can often cause primary CTIA,

Received May 14, 2017; accepted July 7, 2017.
From the Department of Medicine, University at Buffalo, NY.
Correspondence to Anne B. Curtis, MD, Department of Medicine, University at Buffalo, D2-76, 100 High St, Buffalo, NY 14203. E-mail abcurtis@buffalo.edu
(*Circ Arrhythm Electrophysiol*. 2017;10:e005443. DOI: 10.1161/CIRCEP.117.005443.)

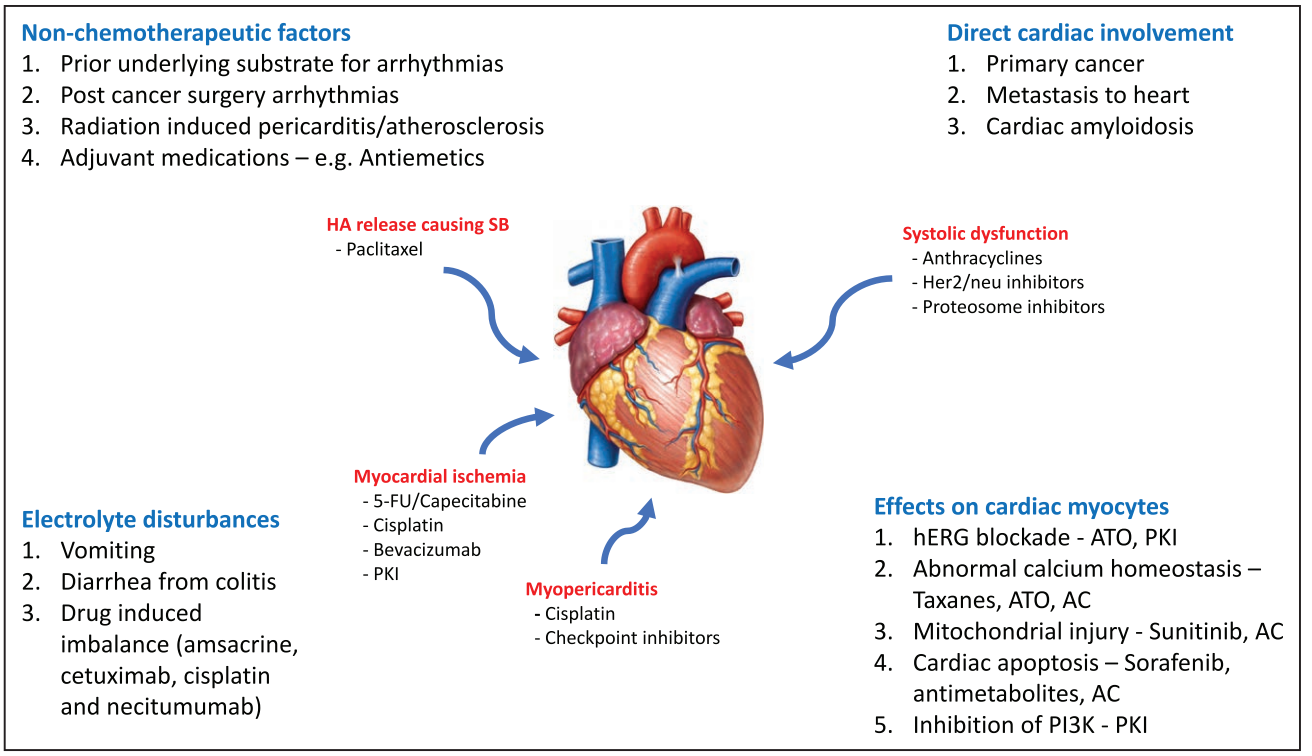

Figure. Mechanisms of arrhythmias in cancer patients. AC indicates anthracyclines; ATO, arsenic trioxide; HA, histamine; hERG, human *Ether-à-go-go*-Related Gene; PI3K, phosphotidyl inositol 3–kinase; PKI, protein kinase inhibitors; SB, sinus bradycardia; and 5-FU, 5-fluorouracil. Heart image reprinted with permission from Marieb and Hoehn.[3] Copyright © 2013, Pearson Education, Inc.

as well as CTIA secondary to cardiomyopathy. Cardiomyopathy associated with anthracyclines is usually dose dependent (5%–8% incidence at 450 mg/m^2 cumulative dose) and not reversible.[8]

Various ECG changes and arrhythmias can be seen even during the first infusion of anthracyclines. They are usually nonspecific and include ST-T segment changes, QRS voltage lowering, T-wave flattening, and QTc interval prolongation. They may be found in ≤30.3% of patients.[9] In contrast to cardiomyopathy, ECG changes induced by anthracyclines seem to be dose independent.

QTc interval prolongation is common with anthracyclines, with QTc>450 ms seen after the first cycle of chemotherapy in 11.5% patients.[10] The incidence can increase with subsequent cycles of anthracyclines, with marked prolongation of QTc sometimes leading to ventricular arrhythmias.[11] Administration of dexrazoxane, an EDTA analog approved by

Table 1. Classification of Chemotherapeutic Agents

Class	Medications
Anthracyclines	Daunorubicin, doxorubicin, epirubicin, idarubicin, aclarubicin, mitoxantrone
Alkylating agents	Cyclophosphamide, busulfan, ifosfamide, melphalan
Antimetabolites	Capecitabine, clofarabine, cytarabine, fludarabine, 5-fluorouracil, gemcitabine, pentostatin
Antimicrotubule agents	Docetaxel, paclitaxel, vinblastine, vincristine
Histone deacetylase inhibitors	Panobinostat, romidepsin, vorinostat
Immunomodulatory drugs	Lenalidomide, thalidomide
Platinum compounds	Carboplatin, cisplatin, oxaliplatin
Proteasome inhibitors	Bortezomib, carfilzomib
HER2 inhibitors	Lapatinib, pertuzumab, trastuzumab
Immune checkpoint inhibitors	Ipilimumab, nivolumab, pembrolizumab
Multitargeted TK inhibitors	Alectinib, ceritinib, crizotinib, dasatinib, ibrutinib, nilotinib, ponatinib
VEGF signaling pathway inhibitors	Axitinib, cabozantinib, lenvatinib, sorafenib, pazopanib, regorafenib, sunitinib, vandetanib, vemurafenib
Other monoclonal antibodies	Alemtuzumab, cetuximab, necitumumab, rituximab
Miscellaneous agents	All-trans retinoic acid, amsacrine, arsenic trioxide, IL-2, interferons

HER2 indicates human epidermal growth factor receptor 2; IL-2, interleukin-2; TK, tyrosine kinase; and VEGF, vascular endothelial growth factor.

Table 2. Arrhythmias Associated With Various Conventional Classes of Chemotherapy

Class	ST	SB	CAVB	PAC	SVT	AF	PVC	VT	QTc/TdP	SCD
Alkylating agents										
Cyclophosphamide	+++	c	c	++	++	++	++	c	c/–	–
Ifosfamide	c	c	–	c	c	c	c	c	–/–	c
Melphalan	c	–	–	c	++	+++	c	c	–/–	–
Busulfan	c	–	c	–	c	++*	c	–	–/–	c
Amsacrine	c	c	–	–	c	c	c	c	c	c
Anthracyclines	+++	++	c	+++	++	+++	+++	++	+++/c	+
Antimetabolites										
Capecitabine	+++	++	c	++	c	++	++	c	+++/c	+
Clofarabine	c	c	–	–	c	+++†	c	–	c/–	–
Cytarabine	–	c	–	–	–	c	–	–	–	–
Fludarabine	–	c	–	–	++	–	–	–	–	–
5-FU	c	+++	c	c	c	++	+++	++	c	++
Gemcitabine	–	–	–	–	c	++‡	–	c	–	c
Pentostatin	–	c	–	–	–	–	c	–	–	c
Antimicrotubule agents										
Docetaxel	c	–	–	–	c	c	–	–	–	c
Paclitaxel	+++	+++	c	c	c	+	c	+	–	c
Vincristine	–	–	–	–	–	c	c	–	–	–
Arsenic trioxide	+++	–	c§	–	–	c	+++	+++	+++§/++§	++
ATRA	–	c	c	–	–	–	–	–	–	–
HDAC inhibitors										
Panobinostat	c	c	–	c	c	c	c	c	+++§/c	c
Romidepsin	c	c	–	–	++	++	–	c	–/–	++
Vorinostat	–	c	–	–	–	c	c	–	++/c	c
IL-2	c	c	c	c	+++	++	++	+	–	+
Immunomodulatory drugs										
Lenalidomide	–	c	–	–	c	++	–	c	–	c
Thalidomide	–	+++	c	–	c	++	c	c	–	c
Interferons	c	–	c	c	c	c	c	c	–	c
Platinum compounds										
Cisplatin	–	c	c	c	c	c/+++‖	c	c/++‖	c/–	–
Proteasome inhibitors										
Bortezomib	c	c	c	c	c	c	c	c	c	c
Carfilzomib	–	c	c	c	++	c	–	–	–	c

– indicates not available; +, uncommon (<1%); ++, common (1% to 10%); +++, very common (>10%); 5-FU, 5-fluorouracil; AF, atrial fibrillation; c, case reports; CAVB, complete atrioventricular block; HDAC, histone deacetylase; IL, interleukin; PAC, premature atrial complexes; PVC, premature ventricular complexes; SB, sinus bradycardia; SCD, sudden cardiac death; ST, sinus tachycardia; SVT, supraventricular tachycardia; TdP, torsades de pointes; and VT, ventricular tachycardia.

*If combined with cyclophosphamide.

†If combined with cytarabine.

‡If combined with vinorelbine.

§Included in FDA black-box warning.

‖For intracavitary use.

the Food and Drug Administration to prevent anthracycline-induced cardiomyopathy, has been shown to reduce the QTc prolongation associated with anthracyclines.[12]

Studies using Holter monitoring have shown an association between anthracycline administration and a broad range of arrhythmias, including sinus bradycardia and tachycardia,

Table 3. Arrhythmias Associated With Various Classes of Novel Targeted Therapies

Class	ST	SB	CAVB	PAC	SVT	AF	PVC	VT	QTc/TdP	SCD
HER2 inhibitors										
Trastuzumab	c	c	–	–	–	–	–	c	–	c
Pertuzumab	+	+	–	–	+	c	c	+	–	+
Lapatinib	c	–	–	–	c	c	–	–	++/–	c
Immune checkpoint inhibitors										
Ipilimumab	–	–	–	–	–	c	–	c	–	c
Nivolumab	–	–	c	–	–	–	–	+	–	c
Pembrolizumab	c	–	–	–	–	c	c	c	–	c
Multitargeted TK inhibitors										
Alectinib	–	++	–	–	–	–	–	–	c/–	–
Ceritinib	–	++	–	c	–	–	–	–	++/–	–
Crizotinib	–	+++	–	–	–	–	–	–	++/–	–
Dasatinib	–	–	–	–	++	–	c	+	++/–	c
Ibrutinib	–	–	–	–	–	++	c	c	–	c
Nilotinib	–	–	c	–	–	c	–	–	++*/–	+*
Ponatinib	–	+	+	–	+	++	–	–	c/–	–
Other monoclonal antibodies										
Alemtuzumab	–	+	–	–	–	+	–	c	–	+
Cetuximab	c	c	–	–	–	c	–	–	c/–	++*
Necitumumab	++	–	–	–	–	–	–	–	–	++*
Rituximab	c	c	c	–	+	++	c	c	c/c	c
VEGF pathway inhibitors										
Sorafenib	–	c	c	–	c	++†	–	–	–	–
Sunitinib	c	c	–	–	–	c	–	–	++/+	c
Vandetanib	–	–	–	–	–	–	–	c	++*/+	+*
Vemurafenib	+	+	–	c	+	++	+	–	++/c	–

– indicates not available; +, uncommon (<1%); ++, common (1% to 10%); +++, very common (>10%); 5-FU, 5-fluorouracil; AF, atrial fibrillation; c, case reports; CAVB, complete atrioventricular block; HER2, human epidermal growth factor receptor 2; PAC, premature atrial complexes; PVC, premature ventricular complexes; SB, sinus bradycardia; SCD, sudden cardiac death; ST, sinus tachycardia; SVT, supraventricular tachycardia; TdP, torsades de pointes; VEGF, vascular endothelial growth factor; and VT, ventricular tachycardia.

*Included in FDA black boxed warning.

†If combined with 5-FU.

premature atrial complexes, supraventricular tachycardia (SVT), premature ventricular complexes (PVCs), and ventricular tachycardia (VT). Even during the first cycle of therapy, arrhythmias have been detected in ≤65.5% of patients.[13] In one study, the frequency of arrhythmia was low (3%) in the first hour postinfusion but increased significantly (24%) from 1 to 24 hours,[14] with most of them being benign arrhythmias. Most of the studies lacked baseline arrhythmia monitoring prior to anthracycline administration, which makes it difficult to determine the true incidence of these arrhythmias that are secondary to anthracycline administration.

While most anthracycline-induced arrhythmias are benign, AF has been a common complication of treatment, with one study showing up to an incidence of 10.3%.[13] In a recent study from the Mayo Clinic, episodes of nonsustained VT, AF, and sustained VT or ventricular fibrillation were seen in 73.9%, 56.6%, and 30.4% of patients with anthracycline-related cardiomyopathy who had implantable cardioverter defibrillators. The prevalence of arrhythmias was similar to that in patients with implantable cardioverter defibrillators implanted for noncancer-related cardiomyopathy.[15] While most arrhythmias associated with anthracyclines may be secondary to cardiomyopathy, rare malignant ventricular arrhythmias can occur during administration of anthracyclines or during the early phase of chemotherapy treatment before the onset of left ventricular systolic dysfunction.[16] Severe hypokalemia can aggravate these arrhythmias,[17] underscoring the importance of maintaining electrolyte balance during treatment with anthracyclines. Bradyarrhythmias including atrioventricular (AV) block have also been reported.

Alkylating Agents

Cyclophosphamide is commonly used in the treatment of breast cancer, lymphomas, leukemia, multiple myeloma, and

ovarian cancer. CTIA is one of the most common manifestations of cardiotoxicity caused by cyclophosphamide. In a series of patients treated with cyclophosphamide before bone marrow transplantation, ECG changes, including ST-segment or T-wave changes, QTc interval prolongation, and arrhythmias were found in 33% of the patients, with 27% developing an early decrease in total QRS voltage.[18]

A broad range of arrhythmias has been documented in patients treated with cyclophosphamide, including premature atrial complexes, PVCs, SVT, AF, ventricular arrhythmias with preceding QTc interval prolongation, and AV block, the latter occasionally requiring pacemaker placement.[19]

Melphalan is an alkylating agent used in the treatment of multiple myeloma, light-chain amyloidosis, and ovarian cancer. CTIA is among the most frequent side effects of melphalan treatment, with AF being the most frequent manifestation. It occurs in 6.6% to 22.5% of patients, particularly elderly patients.[20,21] In a large database of 438 patients receiving melphalan with bone marrow transplantation, supraventricular arrhythmias, including AF and SVT, were seen in 11% of patients in comparison to an incidence of 0% to 2% with other chemotherapeutic regimens.[22]

Busulfan is another nonspecific alkylating agent used prior to bone marrow transplantation for leukemia that is also associated with AF, with an incidence ≤6.4% when used in combination with cyclophosphamide.[23]

Antimetabolites

5-Fluorouracil (5-FU) is commonly used in gastrointestinal cancers and breast cancer. CTIA is the second most common cardiotoxicity of 5-FU after angina and myocardial infarction.[24]

5-FU has been shown to induce ECG changes, with most of them being secondary to ischemia, because this drug can cause coronary vasospasm.[25] Commonly observed ECG changes include prolonged P-wave duration, increased P-wave dispersion, ST–T wave changes, diffusely decreased QRS voltage, QTc prolongation, and increased QT dispersion.[26]

Supraventricular arrhythmias are rare in patients treated with 5-FU monotherapy. On the contrary, 5-FU can cause a wide spectrum of ventricular arrhythmias from frequent PVCs to sudden cardiac death (SCD).[27] The incidence of VT can be as high as 3.7 to 7.4% and often occurs in the setting of myocardial ischemia, and thus, it is secondary CTIA.[28] 5-FU can also cause sinus bradycardia in ≤11.96% of patients in addition to AV block and intraventricular conduction delays.[28]

Gemcitabine is commonly used in the treatment of bladder cancer, pancreatic cancer, and non–small cell lung cancer. Its use is associated with the development of SVT, especially AF. The association of gemcitabine with AF is strong and can occur even after the first dose. In a series of 49 patients treated with a combination of gemcitabine and vinorelbine, AF/AFL occurred in 8.2% of the patients.[29]

Clofarabine is Food and Drug Administration–approved for the treatment of acute lymphoblastic leukemia. The most common arrhythmia associated with clofarabine treatment is AF. The frequency of AF/AFL with clofarabine ranges from 7.4% to 19% depending on treatment schedule and whether it is used as monotherapy or in combination with cytarabine.[30,31] Much less common are ventricular arrhythmias (3% when used in combination with cytarabine),[32] sinus bradycardia, and sinus tachycardia.

Antimicrotubule Agents

Paclitaxel is an anticancer agent from the Pacific yew tree (Taxus brevifolia) used commonly in the treatment of breast cancer, ovarian cancer, lung cancer, and cervical cancer. Before it was introduced as an anticancer drug, cases of VT and SCD because of Taxus poisoning were reported.[33] ECG changes associated with paclitaxel use include T-wave changes, QTc interval prolongation, right bundle branch block, and left bundle branch block.[34]

The most common arrhythmia associated with paclitaxel use is sinus bradycardia, which occurs in 29% of patients if paclitaxel is used as monotherapy[35] and more commonly when combined with cisplatin. Sinus bradycardia is usually mild, transient, and asymptomatic. Rare cases of transient AV block have also been reported.[36]

Histone Deacetylase Inhibitors

Vorinosat is a histone deacetylase inhibitor used in the treatment of cutaneous T-cell lymphoma. It can cause nonspecific ECG changes (ST-T segment, P- and T-wave abnormalities, QTc prolongation).[37]

Panobinostat is used in the treatment of refractory multiple myeloma. It also causes frequent but usually temporary and nonspecific ECG changes. More importantly, panobinostat can cause significant QTc prolongation, with the frequency and extent depending on dose, route, and schedule. The reported incidence of QTc interval prolongation >60 or >500 ms has ranged from 8.6% to 28%. Based on this observation, panobinostat carries black box warning concerning severe arrhythmias and EKG changes.[38]

Romidepsin is a histone deacetylase inhibitor used in the treatment of cutaneous T-cell lymphoma that also commonly causes nonspecific ECG changes. In contrast to panobinostat, romidepsin-induced QTc interval prolongation is usually mild.[39] Romidepsin use is also associated with different supraventricular arrhythmias, although the baseline frequency of ectopy in the studied population of patients is high. More serious is the fact that SCD has been reported with romidepsin. Two of 131 patients in one study[40] and 1 out of 25 in another study had SCD, with the latter study having been terminated prematurely because of an unexpectedly high number of cardiovascular adverse events (QTc interval prolongation and VT in addition to SCD).[41]

Immunomodulatory Drugs

Thalidomide is used in the treatment of multiple myeloma. It is known to cause bradyarrhythmias, including complete AV block, both in monotherapy and in combination with other chemotherapeutic agents. Sinus bradycardia has been observed in 26% to 53% of patients and is usually a primary CTIA.[42] Although sinus bradycardia usually resolves within 12 to 21 days after discontinuation of thalidomide, in some cases, temporary pacing or permanent pacemaker insertion has been necessary.[43]

Thalidomide use has also been associated with the development of AF (4.7% of patients versus 3.4% in the placebo arm)[44] and, rarely, sustained VT or SCD. Given the high incidence of arrhythmias with thalidomide, cardiac monitoring is recommended in these patients.

Lenalidomide is used in treatment of multiple myeloma and myelodysplastic syndrome. It has been associated with the development of AF when used in combination with dexamethasone in the presence or absence of bortezomib. The overall incidence of AF in clinical trials ranged from 4.6% to 7%.[45]

Platinum Compounds

Cisplatin is widely used in the treatment of multiple cancers, including metastatic gonadal tumors and advanced bladder cancer. It can be used systemically or locally. Systemic use of cisplatin is often associated with sinus bradycardia, which can start immediately during infusion. Cases of SVT and AF have also been reported, and they can recur with rechallenge. Premature atrial complexes and PVCs are common during Holter monitoring and have been found in up to two-thirds of the patients.[46] Cisplatin-induced hypomagnesemia has been speculated to be responsible for some CTIA, including AF, asystole, and pulseless VT, even after local use.[47]

Cisplatin can be delivered locally by instillation into serous cavities. If used intrapericardially, the risk of AF ranges from 12% to 18.8%, with an 8% incidence of nonsustained VT. The risk of AF is even higher (23.9%–66 %) if hyperthermic cisplatin lavage is used for instillation into the abdominal and pleural cavities in patients undergoing pleurectomy.[48]

Proteasome Inhibitors

Bortezomib is a proteasome inhibitor used in the treatment of multiple myeloma and mantle cell lymphoma. Heart failure is the most common cardiotoxicity associated with bortezomib and can result in secondary arrhythmias. Isolated cases of SVT and AF have been reported with bortezomib use. Rarely, bradyarrhythmias, including complete AV block, requiring permanent pacemaker implantation have been documented.[49]

Carfilzomib is a proteasome inhibitor used in the treatment of relapsed or refractory multiple myeloma. Similar to bortezomib, carfilzomib has been shown to increase the risk of heart failure. In a pooled safety analysis of 4 phase-2 studies with a total of 526 patients treated with carfilzomib, arrhythmias occurred in 13.3% of patients, most of which were mild supraventricular arrhythmias that likely represented secondary CTIA. The incidence of cardiac arrhythmias was much lower during subsequent cycles of carfilzomib.[50]

Targeted Cancer Therapy

These agents have revolutionized the treatment of many types of cancers. The main concerns with their use are related to QT interval prolongation associated with torsades de pointes and SCD.[51–53] The data on the relevant agents are summarized in Table 4. Some agents with distinct proarrhythmic profiles will be discussed later.

Multitargeted Tyrosine Kinase Inhibitors

Alectinib is approved for the treatment of metastatic non–small cell lung cancer. Bradycardia is the most common cardiac side effect of alectinib and was reported in clinical trials in 7.9% of patients, with sinus bradycardia being documented in 5.1% of them; it is likely a primary CTIA. Moreover, an analysis of the ECGs in this trial demonstrated that 20% of patients had heart rates <50 beats per minute at least once. The mean decrease in heart rate was 11 to 13 beats per minute. Bradycardia associated with alectinib is usually asymptomatic, reversible, and rarely requires interruption of therapy. The effect of alectinib on the QTc interval is mild (mean QTc change 5.3 ms), and only 1 in 221 of the patients has a QTc >500 ms.[54]

Ceritinib inhibits anaplastic lymphoma kinase and is used in the treatment of advanced or metastatic non–small cell lung carcinoma. It can cause sinus bradycardia and QTc interval prolongation.[55] QTc interval prolongation has been reported in 4% of patients, with 3% of them having an increase in QTc interval >60 ms. Only 0.3% of patients developed a QTc interval >500 ms.[56]

Crizotinib is an anaplastic lymphoma kinase inhibitor used in the treatment of advanced or metastatic non–small cell lung carcinoma. Crizotinib has a CTIA profile similar to ceritinib and is associated with sinus bradycardia (likely a primary CTIA) and QTc interval prolongation. The mean observed decrease in heart rate in one series of patients was ≈25 beats per minute, with 31% of patients developing a heart rate <50 beats per minute. A pretreatment heart rate <70 beats per minute was the only significant risk factor for developing sinus bradycardia.[57] QTc interval prolongation is also relatively common, with a QTc interval >500 ms or an increase from baseline QTc >60 ms occurring in 1.3% and 3.5% of patients, respectively.[58]

Dasatinib is a BCR-ABL (breakpoint cluster region-Abelson) tyrosine kinase inhibitor used in the treatment of Philadelphia chromosome–positive chronic myeloid leukemia and acute lymphoblastic leukemia. Its use is associated with the development of SVT and nonsustained VT, with the overall incidence of arrhythmias in clinical trials reaching 11%.[59] Some of the arrhythmias may be secondary to the development of cardiomyopathy. Dasatinib causes only mild prolongation of the QTc interval (mean change of only 3–6 ms), though around 1% of the patients in clinical trials experienced QTc prolongation of >500 ms.

Ibrutinib is a Bruton's kinase inhibitor used in the treatment of chronic lymphoid leukemia, mantle cell lymphoma, and Waldenström's macroglobulinemia. Ibrutinib use is strongly associated with the development of AF, which seems to be a primary CTIA. In a recent meta-analysis, the relative risk of AF was found to be 3.86 (confidence interval 95%, 1.97–7.54).[60] The incidence of AF in clinical trials has ranged from 5% to 7%, with a median time to onset 3.0 to 3.8 months after initiation of ibrutinib and 76% of cases occurring within the first year of therapy. The risk of AF appears early, continues to accrue with ongoing therapy, and can persist for ≤2 weeks after discontinuation of ibrutinib. The clinical consequences and optimal management of AF in these patients is unclear. In a retrospective analysis of 56 ibrutinib-induced AF cases, AF was persistent in 63% of patients, despite treatment. Development of AF led to permanent discontinuation of ibrutinib in 46% of cases. Ibrutinib also increased the bleeding risk in these patients, with 14% of nonthrombocytopenic patients with AF experiencing major bleeding during treatment, which would complicate the use of anticoagulants.[61]

Table 4. Arrhythmic Profile of Different Tyrosine Kinase Inhibitors[51–53]

Medication	Common Arrhythmias, %	Rare Arrhythmias	Mean QTc Change, ms	QTc >500 ms, %	TdP, %
Afatinib	NA	NA	1.6	NA	NA
Alectinib	SB (5.1–20)	NA	5.3	0.45	NA
Axitinib	NA	NA	6.1	0.66	NA
Bosutinib	NA	AF, CAVB, SB, PAC	2.6	0.2	NA
Cabozantinib	NA	SCD, ST	10–15	NA	NA
Ceritinib	SB (3)	PAC	NA	0.33	NA
Cobimetinib	AF* (3)	NA	1.2	1.2*	NA
Crizotinib	SB (5–69)	NA	9.7–13.3	1.3	NA
Dasatinib	SVT (13)	PVC, VT	3–6	0.96	NA
Ibrutinib	AF (4.8–16)	PVC, VT	<10	NA	NA
Imatinib	NA	AF, SCD	NA	NA	NA
Lapatinib	NA	AF, SCD, SVT	5.8–13.5	6.2	NA
Lenvatinib	NA	SCD	–5.7	1.5	NA
Nilotinib	NA	AF, AVB, SCD	5–15	0.68–1.2	NA
Osimertinib	NA	NA	14–16.2	0.2	NA
Pazopanib	NA	SB	4.4	1.04–1.97	0.21–0.34
Ponatinib	AF (7)	CAVB, SB, SVT	–3.6	NA	NA
Regorafenib	NA	AF	–4	NA	NA
Ruxolitinib	NA	SB, SVT, VT	3.28	NA	NA
Sorafenib	AF (5.1)†	SB, SVT	4.2–9	NA	NA
Sunitinib	NA	AF, SB	9.6–15.4	0.52	<0.1
Trametinib	NA	NA	NA	4‡	NA
Vandetanib	NA	SCD, VT	14–35	7–14	0.09–0.16
Vemurafenib	AF (1.5)	SB, ST, PAC, PVC, VT	12.8–15.1	1.5–2.9	Rare

5-FU indicates 5-fluorouracil; AF, atrial fibrillation; AVB, atrioventricular block; CAVB, complete atrioventricular block; NA, not available; PAC, premature atrial complexes; SB, sinus bradycardia; SCD, sudden cardiac death; ST, sinus tachycardia; SVT, supraventricular arrhythmia; TdP, torsades de pointes.

*If +vemurafenib.

†If combined with 5-FU.

‡If combined with dabrafenib.

Nilotinib is a BCR-ABL tyrosine kinase inhibitor used in the management of refractory Philadelphia chromosome–positive chronic myeloid leukemia. Nilotinib use is associated with ECG changes, including conduction disturbances, ST-T–wave changes, and QTc prolongation, in ≤20% of patients. The incidence of QTc prolongation >30 or >60 ms has been reported in 26% and 0.4% to 2.1% of patients, respectively.[62,63] QTc prolongation of >500 ms is observed in <1% of patients. SCD was reported in 0.6% of patients. For these reasons, nilotinib carries a black box warning for QTc prolongation and SCD.[63]

Ponatinib is another breakpoint cluster region-Abelson tyrosine kinase inhibitor used in the treatment of resistant Philadelphia chromosome–positive chronic myeloid leukemia or acute lymphoblastic leukemia. Its use has been associated with significant tachyarrhythmias and bradyarrhythmias that may be primary or secondary to cardiomyopathy or arterial thrombosis. In a phase-2 trial, supraventricular arrhythmias, especially AF, were commonly seen. Three out of 449 patients also required pacemaker implantation because of symptomatic bradyarrhythmias. Ponatinib does not have a significant effect on the QT interval.[64]

Vascular Endothelial Growth Factor Signaling Pathway Inhibitors

Sunitinib is a vascular endothelial growth factor inhibitor that is used in the treatment of advanced renal cell carcinoma, gastrointestinal stromal tumors, and pancreatic neuroendocrine tumors. Studies have shown dose-dependent QTc prolongation (average of 9.6 ms change at therapeutic doses),[65] with <0.1% incidence of torsades de pointes. Heart failure has been associated with sunitinib and can cause secondary arrhythmias.

Sorafenib is a small molecule tyrosine kinase inhibitor used in the treatment of unresectable hepatocellular carcinoma and advanced renal cell carcinoma. Mild QTc prolongation is commonly seen with sorafenib, ranging from 4.2 to 9.0

ms, with no cases of QTc >500 ms or a change from baseline ≥60 ms reported.[66] The most common CTIA associated with sorafenib is AF, with the incidence reaching 5.1% if sorafenib is used in combination with 5-FU.[67]

Vandetanib is a tyrosine kinase inhibitor used in the treatment of refractory medullary thyroid carcinoma. It is well known to cause QTc prolongation, and this is one of most common reasons for its discontinuation or dose reduction.[68] The effect is dose-dependent, with a mean change in QTc of 14 to 35 ms. Some trials showed ≤36% of patients developing a >60 ms increase in QTc interval, with a 7% to 14% incidence of QTc>500 ms. Torsades de pointes is less commonly seen (0.09%–0.16%). This agent carries a black box warning for an increased risk of QTc prolongation, torsades de pointes, and SCD.[69]

Vemurafenib is a BRAF kinase inhibitor used in the treatment of malignant melanoma. QTc prolongation is also relatively common with vemurafenib treatment.[70] It occurs in 5% of patients and is among the most common adverse events leading to drug discontinuation. In clinical trials, a QTc interval increase >60 ms from baseline occurred in 5%, with 1.5% to 2.9% of the patients developing QTc interval prolongation >500 ms.[71] Arrhythmias are much less common, with AF/AFL having the highest incidence at 1.5%.[72]

Human Epidermal Growth Factor Receptor 2/neu Inhibitors

Trastuzumab is a human epidermal growth factor receptor 2/neu inhibitor used in the treatment of certain breast and gastric cancers. The most common cardiotoxicity of trastuzumab is cardiomyopathy, which is reversible in most instances with discontinuation of the drug. Rare cases of malignant ventricular arrhythmias, usually secondary to left ventricular systolic dysfunction, have been reported.[73] Other human epidermal growth factor receptor 2/neu receptor inhibitors, such as pertuzumab and lapatinib, are also associated with left ventricular systolic dysfunction but are rarely associated with CTIA. Lapatinib can significantly prolong QTc >500 ms in 6.2% of patients, but there have been no reported cases of torsades de pointes.

Immune Check Point Inhibitors

Pembrolizumab is a programmed death receptor-1 inhibitor recently approved for the treatment of non–small cell lung carcinoma, malignant melanoma, and squamous cell carcinoma of the head and neck. Because it is a relatively new drug, the exact incidence of CTIA with this drug is not entirely known. Autoimmune myocarditis is the most common cardiotoxicity associated with pembrolizumab. Rare cases of sinus tachycardia with ventricular bigeminy, AF, and SCD[74] have been reported with its use, and they are likely secondary CTIA from autoimmune myocarditis.

Ipilimumab is a cytotoxic T-lymphocyte antigen 4 inhibitor that was recently approved for use in metastatic melanoma. The drug has been associated with immune-mediated myocarditis and pericarditis. Given the limited experience with ipilimumab, there are only limited case reports of AF and malignant ventricular arrhythmias associated with this drug.[74]

Nivolumab is a programmed death receptor-1 inhibitor approved for the treatment of metastatic non–small cell lung carcinoma, metastatic melanoma, advanced renal cell carcinoma, and Hodgkin's lymphoma. AV block and rare cases of ventricular arrhythmias has been reported during nivolumab treatment, possibly as a consequence of myocarditis.[75]

Other Monoclonal Antibodies

Cetuximab is an epidermal growth factor receptor inhibitor used in the treatment of metastatic colon cancer, non–small cell lung carcinoma, and head and neck cancer. Although cetuximab use did not result in a clinically meaningful prolongation of the QTc interval in a multicenter trial with 51 patients, there has been some concern for an increased incidence of SCD with its use. In one study, cardiopulmonary arrest/SCD occurred in 2% of patients treated with RT and cetuximab as compared with none in the group treated with RT alone.[76] In another study, fatal cardiac disorders or SCD were reported in 3% of 219 patients treated with cetuximab and platinum-based therapy with 5-FU as compared with 2% of 215 patients treated with chemotherapy alone. For this reason, the medication carries a black box warning about an increased risk of cardiopulmonary arrest/sudden death.[76] Hypomagnesemia secondary to cetuximab possibly contributes to some of these cases, with at least one case of ventricular fibrillation occurring in a patient with documented severe hypomagnesemia.[77]

Necitumumab is a monoclonal IgG1 antibody to the epidermal growth factor receptor and is used in the treatment of metastatic squamous non–small cell lung carcinoma. Its effect on the QTc interval is minimal. However, in clinical trials, cases of cardiopulmonary arrest or SCD occurred in 3% of patients in the group treated with necitumumab and gemcitabine/cisplatin versus 0.6% treated with gemcitabine/cisplatin combination alone, again possibly because of hypomagnesemia. Therefore, necitumumab also carries a black box warning for hypomagnesemia and an increased risk of cardiopulmonary arrest/sudden death.[78]

Other Agents

Interleukin-2

Interleukin-2 (IL-2) is available as a recombinant protein, aldesleukin, which is used in the treatment of metastatic renal cell carcinoma and metastatic melanoma. Its use is associated with severe cardiotoxicity, including CTIA. The vast majority are SVT/AF, with an incidence ranging from 9.7% to 17%. AF alone can be found in 4.3% to 8.0% of patients.[79] Ventricular arrhythmias can also occur, sometimes requiring termination of therapy. However, the frequency of life-threatening VT is low (0.4%–1.1%).[80] Various vasopressors that are used for IL-2-induced hypotension have been speculated to be the underlying mechanism for the CTIA.

Arsenic Trioxide

Arsenic trioxide is used in the treatment of acute promyelocytic leukemia. Cardiac toxicity reported in arsenic trioxide poisoning includes various ECG abnormalities, such as ST-T–wave changes, first-degree AV block, sinus tachycardia, and QTc interval prolongation.[81]

Some degree of QTc prolongation with arsenic trioxide is observed in most if not all patients. In one study, QTc intervals ≥500 ms developed in 26.3% of patients. In an analysis of 3011 ECGs from 113 patients treated with arsenic trioxide, 90% of the patients had QTc >470 ms and 65% had QTc >500 ms using Bazett's formula.[82] QTc prolongation has been associated with the development of torsades de pointes; the incidence was as high as 16% in one study.[83]

Other ventricular arrhythmias are common with the use of arsenic trioxide, including PVCs and nonsustained VT.[84] Cases of SCD have also been reported. Transient AV block, sometimes requiring temporary pacing to continue arsenic trioxide treatment, has also been described.

Amsacrine

Amsacrine has a mode of action similar to anthracyclines. It can also cause ECG changes similar to anthracyclines, including ST segment elevation, T-wave inversion or flattening, prominent U waves, and significant prolongation of the QTc interval. Its use has been associated with the development of SVT, AF/AFL, multiple PVCs, asymptomatic VT, and fatal ventricular fibrillation. Some cases of ventricular fibrillation have occurred in the setting of documented electrolyte abnormalities that can develop right after amsacrine administration.[85] The importance of maintaining electrolyte balance must be emphasized because amsacrine is relatively safe to use even in patients with left ventricular systolic dysfunction, provided the potassium level is strictly monitored.[86]

Radiation Therapy

RT is often used in combination with chemotherapy for the treatment of many cancers. RT can induce multiple long-term sequelae, including coronary artery disease because of accelerated coronary atherosclerosis, cardiomyopathy, valvular disease, or pericarditis because of associated fibrosis. These sequelae can result in secondary CTIA. RT has been associated with various nonspecific ECG changes, including QTc interval prolongation, although the most common manifestations are nonspecific T-wave changes and decreased QRS amplitude.[87] RT can also affect the conduction system of the heart, with a wide spectrum of manifestations from incomplete right bundle branch block to complete AV block.[88] It can also cause malfunction of permanent pacemakers, implantable cardioverter defibrillators, and cardiac resynchronization therapy devices in ≤7% of patients, although permanent or severe damage is rare.[89] This is specifically seen in neutron-producing RT.

Conclusions

Recent advances in cancer treatment, including many targeted therapies, have resulted in improved prognosis for patients with malignancies, albeit with a significant burden because of adverse effects from cardiac arrhythmias. It is, thus, important for cardiologists and electrophysiologists to know the association of individual chemotherapeutic agents with specific arrhythmias to identify drug-mediated arrhythmias early and treat them effectively. Many new combination treatments for various cancers continue to emerge, which make arrhythmia risk assessment and management even more complex. Further studies are required to identify the mechanisms leading to CTIA with various cancer therapies and, thereby, help prevent and treat such arrhythmias. Future cancer drug discovery pathways should incorporate ways to study the cardiac electrophysiological properties of these agents to help prevent significant cardiac morbidity and mortality in these patients.

Disclosures

None.

References

1. Livingston RB, Carter SK. Daunomycin (NSC-82151). In: *Chemotherapy Fact Sheet*. Bethesda, MD: Program Analysis Branch. Chemotherapy, National Cancer Institute; 1970:12–13.
2. Guglin M, Aljayeh M, Saiyad S, Ali R, Curtis AB. Introducing a new entity: chemotherapy-induced arrhythmia. *Europace*. 2009;11:1579–1586. doi: 10.1093/europace/eup300.
3. Marieb EN, Hoehn K. *Human anatomy & physiology*. 9th ed. Glenview, IL: Pearson Education, Inc; 2013.
4. US Department of Health and Human Services. *Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0*. Bethesda, MD: National Cancer Institute. 2009;09-5410.
5. Ostenfeld EB, Erichsen R, Pedersen L, Farkas DK, Weiss NS, Sørensen HT. Atrial fibrillation as a marker of occult cancer. *PLoS One*. 2014;9:e102861. doi: 10.1371/journal.pone.0102861.
6. Zhang S, Liang F, Tannock I. Use and misuse of common terminology criteria for adverse events in cancer clinical trials. *BMC Cancer*. 2016;16:392. doi: 10.1186/s12885-016-2408-9.
7. Bagnes C, Panchuk PN, Recondo G. Antineoplastic chemotherapy induced QTc prolongation. *Curr Drug Saf*. 2010;5:93–96.
8. Doxorubicin. FDA package insert. Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/062921s022lbl.pdf. Accessed May 2, 2017.
9. Dindogru A, Barcos M, Henderson ES, Wallace HJ Jr. Electrocardiographic changes following adriamycin treatment. *Med Pediatr Oncol*. 1978;5:65–71.
10. Horacek JM, Jakl M, Horackova J, Pudil R, Jebavy L, Maly J. Assessment of anthracycline-induced cardiotoxicity with electrocardiography. *Exp Oncol*. 2009;31:115–117.
11. Iwata N, Karasawa M, Omine M, Maekawa T, Suzuki T, Kawai Y. Aclarubicin-associated QTc prolongation and ventricular fibrillation. *Cancer Treat Rep*. 1984;68:527–529.
12. Galetta F, Franzoni F, Cervetti G, Cecconi N, Carpi A, Petrini M, Santoro G. Effect of epirubicin-based chemotherapy and dexrazoxane supplementation on QT dispersion in non-Hodgkin lymphoma patients. *Biomed Pharmacother*. 2005;59:541–544. doi: 10.1016/j.biopha.2004.12.003.
13. Kilickap S, Barista I, Akgul E, Aytemir K, Aksoy S, Tekuzman G. Early and late arrhythmogenic effects of doxorubicin. *South Med J*. 2007;100:262–265. doi: 10.1097/01.smj.0000257382.89910.fe.
14. Steinberg JS, Cohen AJ, Wasserman AG, Cohen P, Ross AM. Acute arrhythmogenicity of doxorubicin administration. *Cancer*. 1987;60:1213–1218.
15. Mazur M, Wang F, Hodge DO, Siontis BL, Beinborn DS, Villarraga HR, Lerman A, Friedman PA, Herrmann J. Burden of cardiac arrhythmias in patients with anthracycline-related cardiomyopathy. *JACC Clin Electrophysiol*. 2017;3:139–150. doi: 10.1016/j.jacep.2016.08.009.
16. Wortman JE, Lucas VS Jr, Schuster E, Thiele D, Logue GL. Sudden death during doxorubicin administration. *Cancer*. 1979;44:1588–1591.
17. Kishi S, Yoshida A, Yamauchi T, Tsutani H, Lee JD, Nakamura T, Naiki H, Ueda T. Torsade de pointes associated with hypokalemia after anthracycline treatment in a patient with acute lymphocytic leukemia. *Int J Hematol*. 2000;71:172–179.
18. Kupari M, Volin L, Suokas A, Timonen T, Hekali P, Ruutu T. Cardiac involvement in bone marrow transplantation: electrocardiographic changes, arrhythmias, heart failure and autopsy findings. *Bone Marrow Transplant*. 1990;5:91–98.
19. Ramireddy K, Kane KM, Adhar GC. Acquired episodic complete heart block after high-dose chemotherapy with cyclophosphamide and thiotepa. *Am Heart J*. 1994;127:701–704.
20. Olivieri A, Corvatta L, Montanari M, Brunori M, Offidani M, Ferretti GF, Centanni M, Leoni P. Paroxysmal atrial fibrillation after

high-dose melphalan in five patients autotransplanted with blood progenitor cells. *Bone Marrow Transplant*. 1998;21:1049–1053. doi: 10.1038/sj.bmt.1701217.
21. Mileshkin LR, Seymour JF, Wolf MM, Gates P, Januszewicz EH, Joyce P, Prince HM. Cardiovascular toxicity is increased, but manageable, during high-dose chemotherapy and autologous peripheral blood stem cell transplantation for patients aged 60 years and older. *Leuk Lymphoma*. 2005;46:1575–1579. doi: 10.1080/10428190500235884.
22. Feliz V, Saiyad S, Ramarao SM, Khan H, Leonelli F, Guglin M. Melphalan-induced supraventricular tachycardia: incidence and risk factors. *Clin Cardiol*. 2011;34:356–359. doi: 10.1002/clc.20904.
23. Ulrickson M, Aldridge J, Kim HT, Hochberg EP, Hammerman P, Dube C, Attar E, Ballen KK, Dey BR, McAfee SL, Spitzer TR, Chen YB. 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;15:1447–1454. doi: 10.1016/j.bbmt.2009.07.014.
24. Kosmas C, Kallistratos MS, Kopterides P, Syrios J, Skopelitis H, Mylonakis N, Karabelis A, Tsavaris N. Cardiotoxicity of fluoropyrimidines in different schedules of administration: a prospective study. *J Cancer Res Clin Oncol*. 2008;134:75–82. doi: 10.1007/s00432-007-0250-9.
25. Polk A, Vaage-Nilsen M, Vistisen K, Nielsen DL. Cardiotoxicity in cancer patients treated with 5-fluorouracil or capecitabine: a systematic review of incidence, manifestations and predisposing factors. *Cancer Treat Rev*. 2013;39:974–984. doi: 10.1016/j.ctrv.2013.03.005.
26. Oztop I, Gencer M, Okan T, Yaren A, Altekin E, Turker S, Yilmaz U. Evaluation of cardiotoxicity of a combined bolus plus infusional 5-fluorouracil/folinic acid treatment by echocardiography, plasma troponin I level, QT interval and dispersion in patients with gastrointestinal system cancers. *Jpn J Clin Oncol*. 2004;34:262–268.
27. Yilmaz U, Oztop I, Ciloglu A, Okan T, Tekin U, Yaren A, Somali I, Alacacioglu A, Kirimli O. 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. doi: 10.1111/j.1742-1241.2007.01323.x.
28. 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;62:430–434.
29. Gridelli C, Cigolari S, Gallo C, Manzione L, Ianniello GP, Frontini L, Ferraù F, Robbiati SF, Adamo V, Gasparini G, Novello S, Perrone F; MILES Investigators. 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;31:277–284.
30. Faderl S, Ravandi F, Huang X, Garcia-Manero G, Ferrajoli A, Estrov Z, Borthakur G, Verstovsek S, Thomas DA, Kwari M, Kantarjian HM. A randomized study of clofarabine versus clofarabine plus low-dose cytarabine as front-line therapy for patients aged 60 years and older with acute myeloid leukemia and high-risk myelodysplastic syndrome. *Blood*. 2008;112:1638–1645. doi: 10.1182/blood-2007-11-124602.
31. Buchholz S, Dammann E, Stadler M, Krauter J, Beutel G, Trummer A, Eder M, Ganser A. Cytoreductive treatment with clofarabine/ara-C combined with reduced-intensity conditioning and allogeneic stem cell transplantation in patients with high-risk, relapsed, or refractory acute myeloid leukemia and advanced myelodysplastic syndrome. *Eur J Haematol*. 2012;88:52–60. doi: 10.1111/j.1600-0609.2011.01703.x.
32. Agura E, Cooper B, Holmes H, Vance E, Berryman RB, Maisel C, Li S, Saracino G, Tadic-Ovcina M, Fay J. Report of a phase II study of clofarabine and cytarabine in de novo and relapsed and refractory AML patients and in selected elderly patients at high risk for anthracycline toxicity. *Oncologist*. 2011;16:197–206. doi: 10.1634/theoncologist.2010-0220.
33. Van Ingen G, Visser R, Peltenburg H, Van Der Ark AM, Voortman M. Sudden unexpected death due to Taxus poisoning. A report of five cases, with review of the literature. *Forensic Sci Int*. 1992;56:81–87.
34. Kamineni P, Prakasa K, Hasan SP, Akula R, Dawkins F. Cardiotoxicities of paclitaxel in African Americans. *J Natl Med Assoc*. 2003;95:977–981.
35. McGuire WP, Rowinsky EK, Rosenshein NB, Grumbine FC, Ettinger DS, Armstrong DK, Donehower RC. Taxol: a unique antineoplastic agent with significant activity in advanced ovarian epithelial neoplasms. *Ann Intern Med*. 1989;111:273–279.
36. Arbuck SG, Strauss H, Rowinsky E, Christian M, Suffness M, Adams J, Oakes M, McGuire W, Reed E, Gibbs H. Greenfield RA, Montello M. A reassessment of cardiac toxicity associated with Taxol. *J Natl Cancer Inst*. 1992;15:117–130.
37. Olsen EA, Kim YH, Kuzel TM, Pacheco TR, Foss FM, Parker S, Frankel SR, Chen C, Ricker JL, Arduino JM, Duvic M. Phase IIb multicenter trial of vorinostat in patients with persistent, progressive, or treatment refractory cutaneous T-cell lymphoma. *J Clin Oncol*. 2007;25:3109–3115. doi: 10.1200/JCO.2006.10.2434.
38. Rathkopf DE, Picus J, Hussain A, Ellard S, Chi KN, Nydam T, Allen-Freda E, Mishra KK, Porro MG, Scher HI, Wilding G. A phase 2 study of intravenous panobinostat in patients with castration-resistant prostate cancer. *Cancer Chemother Pharmacol*. 2013;72:537–544. doi: 10.1007/s00280-013-2224-8.
39. Cabell C, Bates S, Piekarz R, Whittaker S, Kim YH, Currie M, Godfrey CJ, Schoonmaker C, Nichols J, Nix D, Burris HA. Systematic assessment of potential cardiac effects of the novel histone deacetylase (HDAC) inhibitor romidepsin. *Blood*. 2009;114:3709.
40. Noonan AM, Eisch RA, Liewehr DJ, Sissung TM, Venzon DJ, Flagg TP, Haigney MC, Steinberg SM, Figg WD, Piekarz RL, Bates SE. Electrocardiographic studies of romidepsin demonstrate its safety and identify a potential role for K(ATP) channel. *Clin Cancer Res*. 2013;19:3095–3104. doi: 10.1158/1078-0432.CCR-13-0109.
41. Shah MH, Binkley P, Chan K, Xiao J, Arbogast D, Collamore M, Farra Y, Young D, Grever M. Cardiotoxicity of histone deacetylase inhibitor depsipeptide in patients with metastatic neuroendocrine tumors. *Clin Cancer Res*. 2006;12:3997–4003. doi: 10.1158/1078-0432.CCR-05-2689.
42. Rajkumar SV, Gertz MA, Lacy MQ, Dispenzieri A, Fonseca R, Geyer SM, Iturria N, Kumar S, Lust JA, Kyle RA, Greipp PR, Witzig TE. Thalidomide as initial therapy for early-stage myeloma. *Leukemia*. 2003;17:775–779. doi: 10.1038/sj.leu.2402866.
43. Fahdi IE, Gaddam V, Saucedo JF, Kishan CV, Vyas K, Deneke MG, Razek H, Thorn B, Bissett JK, Anaissie EJ, Anaisse E, Barlogie B, Mehta JL. Bradycardia during therapy for multiple myeloma with thalidomide. *Am J Cardiol*. 2004;93:1052–1055. doi: 10.1016/j.amjcard.2003.12.061.
44. Rajkumar SV, Rosiñol L, Hussein M, Catalano J, Jedrzejczak W, Lucy L, Olesnyckyj M, Yu Z, Knight R, Zeldis JB, Bladé J. 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;26:2171–2177. doi: 10.1200/JCO.2007.14.1853.
45. Lenalidomide. FDA package insert. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021880s049lbl.pdf. Accessed May 2, 2017.
46. Yavaş Ö, Aytemir K, Çelik I. The prevalence of silent arrhythmia in patients receiving cisplatin-based chemotherapy. *Turkish J Cancer*. 2008;38:12–15.
47. Thix CA, Königsrainer I, Kind R, Wied P, Schroeder TH. Ventricular tachycardia during hyperthermic intraperitoneal chemotherapy. *Anaesthesia*. 2009;64:1134–1136. doi: 10.1111/j.1365-2044.2009.05993.x.
48. Zellos L, Richards WG, Capalbo L, Jaklitsch MT, Chirieac LR, Johnson BE, Bueno R, Sugarbaker DJ. A phase I study of extrapleural pneumonectomy and intracavitary intraoperative hyperthermic cisplatin with amifostine cytoprotection for malignant pleural mesothelioma. *J Thorac Cardiovasc Surg*. 2009;137:453–458. doi: 10.1016/j.jtcvs.2008.07.055.
49. Diwadkar S, Patel AA, Fradley MG. Bortezomib-induced complete heart block and myocardial scar: the potential role of cardiac biomarkers in monitoring cardiotoxicity. *Case Rep Cardiol*. 2016;2016:3456287. doi: 10.1155/2016/3456287.
50. Siegel D, Martin T, Nooka A, Harvey RD, Vij R, Niesvizky R, Badros AZ, Jagannath S, McCulloch L, Rajangam K, Lonial S. Integrated safety profile of single-agent carfilzomib: experience from 526 patients enrolled in 4 phase II clinical studies. *Haematologica*. 2013;98:1753–1761. doi: 10.3324/haematol.2013.089334.
51. Zamorano JL, Lancellotti P, Rodriguez Muñoz D, Aboyans V, Asteggiano R, Galderisi M, Habib G, Lenihan DJ, Lip GY, Lyon AR, Lopez Fernandez T, Mohty D, Piepoli MF, Tamargo J, Torbicki A, Suter TM; Authors/Task Force Members; ESC Committee for Practice Guidelines (CPG):. 2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC). *Eur Heart J*. 2016;37:2768–2801. doi: 10.1093/eurheartj/ehw211.
52. Shah RR, Morganroth J, Shah DR. Cardiovascular safety of tyrosine kinase inhibitors: with a special focus on cardiac repolarisation (QT interval). *Drug Saf*. 2013;36:295–316. doi: 10.1007/s40264-013-0047-5.

53. Strevel EL, Ing DJ, Siu LL. Molecularly targeted oncology therapeutics and prolongation of the QT interval. *J Clin Oncol*. 2007;25:3362–3371. doi: 10.1200/JCO.2006.09.6925.
54. Morcos PN, Bogman K, Hubeaux S, Sturm-Pellanda C, Ruf T, Bordogna W, Golding S, Zeaiter A, Abt M, Balas B. Effect of alectinib on cardiac electrophysiology: results from intensive electrocardiogram monitoring from the pivotal phase II NP28761 and NP28673 studies. *Cancer Chemother Pharmacol*. 2017;79:559–568. doi: 10.1007/s00280-017-3253-5.
55. Khozin S, Blumenthal GM, Zhang L, Tang S, Brower M, Fox E, Helms W, Leong R, Song P, Pan Y, Liu Q, Zhao P, Zhao H, Lu D, Tang Z, Al Hakim A, Boyd K, Keegan P, Justice R, Pazdur R. FDA approval: ceritinib for the treatment of metastatic anaplastic lymphoma kinase-positive non-small cell lung cancer. *Clin Cancer Res*. 2015;21:2436–2439. doi: 10.1158/1078-0432.CCR-14-3157.
56. Ceritinib. FDA package insert. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/205755s003s004lbl.pdf. Accessed May 2, 2017.
57. 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;5:617–622. doi: 10.1002/cam4.622.
58. 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;11:2043–2048. doi: 10.2217/fon.15.47.
59. Steinberg M. Dasatinib: a tyrosine kinase inhibitor for the treatment of chronic myelogenous leukemia and philadelphia chromosome-positive acute lymphoblastic leukemia. *Clin Ther*. 2007;29:2289–2308. doi: 10.1016/j.clinthera.2007.11.005.
60. Leong DP, Caron F, Hillis C, Duan A, Healey JS, Fraser G, Siegal D. The risk of atrial fibrillation with ibrutinib use: a systematic review and meta-analysis. *Blood*. 2016;128:138–140. doi: 10.1182/blood-2016-05-712828.
61. Lipsky AH, Farooqui MZ, Tian X, Martyr S, Cullinane AM, Nghiem K, Sun C, Valdez J, Niemann CU, Herman SE, Saba N, Soto S, Marti G, Uzel G, Holland SM, Lozier JN, Wiestner A. Incidence and risk factors of bleeding-related adverse events in patients with chronic lymphocytic leukemia treated with ibrutinib. *Haematologica*. 2015;100:1571–1578. doi: 10.3324/haematol.2015.126672.
62. Larson RA, Hochhaus A, Saglio G, Rosti G, Lopez JL, Stenke L, Nakamae H, Goldberg SL, Wang MC, Gallagher NJ, Hoenekopp A, Ortmann CE, Hughes TP, Kantarjian HM. 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.
63. Nilotinib. FDA package insert. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/022068s024lbl.pdf. Accessed May 2, 2017.
64. Ponatinib. FDA package insert. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/203469s022lbl.pdf. Accessed May 2, 2017.
65. Bello CL, Mulay M, Huang X, Patyna S, Dinolfo M, Levine S, Van Vugt A, Toh M, Baum C, Rosen L. Electrocardiographic characterization of the QTc interval in patients with advanced solid tumors: pharmacokinetic- pharmacodynamic evaluation of sunitinib. *Clin Cancer Res*. 2009;15:7045–7052. doi: 10.1158/1078-0432.CCR-09-1521.
66. Tolcher AW, Appleman LJ, Shapiro GI, Mita AC, Cihon F, Mazzu A, Sundaresan PR. A phase I open-label study evaluating the cardiovascular safety of sorafenib in patients with advanced cancer. *Cancer Chemother Pharmacol*. 2011;67:751–764. doi: 10.1007/s00280-010-1372-3.
67. Petrini I, Lencioni M, Ricasoli M, Iannopollo M, Orlandini C, Oliveri F, Bartolozzi C, Ricci S. Phase II trial of sorafenib in combination with 5-fluorouracil infusion in advanced hepatocellular carcinoma. *Cancer Chemother Pharmacol*. 2012;69:773–780. doi: 10.1007/s00280-011-1753-2.
68. Leboulleux S, Bastholt L, Krause T, de la Fouchardiere C, Tennvall J, Awada A, Gómez JM, Bonichon F, Leenhardt L, Soufflet C, Licour M, Schlumberger MJ. Vandetanib in locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 2 trial. *Lancet Oncol*. 2012;13:897–905. doi: 10.1016/S1470-2045(12)70335-2.
69. Thornton K, Kim G, Maher VE, Chattopadhyay S, Tang S, Moon YJ, Song P, Marathe A, Balakrishnan S, Zhu H, Garnett C, Liu Q, Booth B, Gehrke B, Dorsam R, Verbois L, Ghosh D, Wilson W, Duan J, Sarker H, Miksinski SP, Skarupa L, Ibrahim A, Justice R, Murgo A, Pazdur R. Vandetanib for the treatment of symptomatic or progressive medullary thyroid cancer in patients with unresectable locally advanced or metastatic disease: U.S. Food and Drug Administration drug approval summary. *Clin Cancer Res*. 2012;18:3722–3730. doi: 10.1158/1078-0432.CCR-12-0411.
70. Larkin J, Ascierto PA, Dréno B, Atkinson V, Liszkay G, Maio M, Mandalà M, Demidov L, Stroyakovskiy D, Thomas L, de la Cruz-Merino L, Dutriaux C, Garbe C, Sovak MA, Chang I, Choong N, Hack SP, McArthur GA, Ribas A. Combined vemurafenib and cobimetinib in BRAF-mutated melanoma. *N Engl J Med*. 2014;371:1867–1876. doi: 10.1056/NEJMoa1408868.
71. Flaherty L, Hamid O, Linette G, Schuchter L, Hallmeyer S, Gonzalez R, Cowey CL, Pavlick A, Kudrik F, Curti B, Lawson D, Chapman PB, Margolin K, Ribas A, McDermott D, Flaherty K, Cranmer L, Hodi FS, Day BM, Linke R, Hainsworth J. 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. doi: 10.1097/PPO.0000000000000024.
72. Larkin J, Del Vecchio M, Ascierto PA, Krajsova I, Schachter J, Neyns B, Espinosa E, Garbe C, Sileni VC, Gogas H, Miller WH Jr, Mandalà M, Hospers GA, Arance A, Queirolo P, Hauschild A, Brown MP, Mitchell L, Veronese L, Blank CU. Vemurafenib in patients with BRAF(V600) mutated metastatic melanoma: an open-label, multicentre, safety study. *Lancet Oncol*. 2014;15:436–444. doi: 10.1016/S1470-2045(14)70051-8.
73. Piotrowski G, Gawor R, Słomka R, Banasiak M, Strzelecki P, Gawor Z, Potemski P. 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;70:756–757.
74. Heinzerling L, Ott PA, Hodi FS, Husain AN, Tajmir-Riahi A, Tawbi H, Pauschinger M, Gajewski TF, Lipson EJ, Luke JJ. Cardiotoxicity associated with CTLA4 and PD1 blocking immunotherapy. *J Immunother Cancer*. 2016;4:50. doi: 10.1186/s40425-016-0152-y.
75. Behling J, Kaes J, Münzel T, Grabbe S, Loquai C. 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;27:155–158. doi: 10.1097/CMR.0000000000000314.
76. Cetuximab. FDA package insert. Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/125084s262lbl.pdf. Acessed May 2, 2017.
77. Kordelas L, Bauer S, Schuler M, Beelen DW, Gauler TC. Successful resuscitation of a patient with ventricular fibrillation due to hypomagnesemia under cetuximab therapy. *Tumor Diagnostik & Therapie*. 2014;35:25–27.
78. Necitumumab. FDA package insert. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/125547s000lbl.pdf. Accessed May 2, 2017.
79. Margolin KA, Rayner AA, Hawkins MJ, Atkins MB, Dutcher JP, Fisher RI, Weiss GR, Doroshow JH, Jaffe HS, Roper M. Interleukin-2 and lymphokine-activated killer cell therapy of solid tumors: analysis of toxicity and management guidelines. *J Clin Oncol*. 1989;7:486–498. doi: 10.1200/JCO.1989.7.4.486.
80. Atkins MB, Lotze MT, Dutcher JP, Fisher RI, Weiss G, Margolin K, Abrams J, Sznol M, Parkinson D, Hawkins M, Paradise C, Kunkel L, Rosenberg SA. High-dose recombinant interleukin 2 therapy for patients with metastatic melanoma: analysis of 270 patients treated between 1985 and 1993. *J Clin Oncol*. 1999;17:2105–2116. doi: 10.1200/JCO.1999.17.7.2105.
81. Soignet SL, Frankel SR, Douer D, Tallman MS, Kantarjian H, Calleja E, Stone RM, Kalaycio M, Scheinberg DA, Steinherz P, Sievers EL, Coutré S, Dahlberg S, Ellison R, Warrell RP Jr. United States multicenter study of arsenic trioxide in relapsed acute promyelocytic leukemia. *J Clin Oncol*. 2001;19:3852–3860. doi: 10.1200/JCO.2001.19.18.3852.
82. Roboz GJ, Ritchie EK, Carlin RF, Samuel M, Gale L, Provenzano-Gober JL, Curcio TJ, Feldman EJ, Kligfield PD. Prevalence, management, and clinical consequences of QT interval prolongation during treatment with arsenic trioxide. *J Clin Oncol*. 2014;32:3723–3728. doi: 10.1200/JCO.2013.51.2913.
83. Unnikrishnan D, Dutcher JP, Varshneya N, Lucariello R, Api M, Garl S, Wiernik PH, Chiaramida S. Torsades de pointes in 3 patients with leukemia treated with arsenic trioxide. *Blood*. 2001;97:1514–1516.
84. Shigeno K, Naito K, Sahara N, Kobayashi M, Nakamura S, Fujisawa S, Shinjo K, Takeshita A, Ohno R, Ohnishi K. Arsenic trioxide therapy in relapsed or refractory Japanese patients with acute promyelocytic leukemia: updated outcomes of the phase II study and postremission therapies. *Int J Hematol*. 2005;82:224–229. doi: 10.1532/IJH97.05044.

85. Weiss RB, Grillo-López AJ, Marsoni S, Posada JG Jr, Hess F, Ross BJ. Amsacrine-associated cardiotoxicity: an analysis of 82 cases. *J Clin Oncol*. 1986;4:918–928. doi: 10.1200/JCO.1986.4.6.918.
86. Arlin ZA, Feldman EJ, Mittelman A, Ahmed T, Puccio C, Chun HG, Cook P, Baskind P, Marboe C, Mehta R. Amsacrine is safe and effective therapy for patients with myocardial dysfunction and acute leukemia. *Cancer*. 1991;68:1198–1200.
87. Gomez DR, Yusuf SW, Munsell MF, Welsh JW, Liao Z, Lin SH, Pan HY, Chang JY, Komaki R, Cox JD, McAleer MF, Grosshans DR. Prospective exploratory analysis of cardiac biomarkers and electrocardiogram abnormalities in patients receiving thoracic radiation therapy with high-dose heart exposure. *J Thorac Oncol*. 2014;9:1554–1560. doi: 10.1097/JTO.0000000000000306.
88. Adams MJ, Lipshultz SE, Schwartz C, Fajardo LF, Coen V, Constine LS. Radiation-associated cardiovascular disease: manifestations and management. *Semin Radiat Oncol*. 2003;13:346–356. doi: 10.1016/S1053-4296(03)00026-2.
89. Grant JD, Jensen GL, Tang C, Pollard JM, Kry SF, Krishnan S, Dougherty AH, Gomez DR, Rozner MA. Radiotherapy-induced malfunction in contemporary cardiovascular implantable electronic devices: clinical incidence and predictors. *JAMA Oncol*. 2015;1:624–632. doi: 10.1001/jamaoncol.2015.1787.

KEY WORDS: antineoplastic agents ■ arrhythmias ■ cardiac ■ cardiotoxicity ■ neoplasm

Cancer Treatment–Induced Arrhythmias: Focus on Chemotherapy and Targeted Therapies

Vitaly Buza, Bharath Rajagopalan and Anne B. Curtis

Circ Arrhythm Electrophysiol. 2017;10:
doi: 10.1161/CIRCEP.117.005443
Circulation: Arrhythmia and Electrophysiology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 1941-3149. Online ISSN: 1941-3084