

Electrophysiologic Complications in Cancer Patients

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ABSTRACT: In recent years, dramatic advances in both cancer diagnosis and treatment have led to significantly increased survival rates. As such, cardiovascular toxicities due to oncologic treatments are more frequently identified. Although heart failure and cardiomyopathy have historically been the cardiotoxicities most associated with cancer therapeutics, it is now recognized that all components of the cardiovascular system can be affected. In this review, we discuss electrophysiologic complications of cancer treatments, including atrial and ventricular tachyarrhythmias as well as bradyarrhythmias, and recommend a multidisciplinary approach with both cardiologists and oncologists to provide safe and effective care to these patients.

INTRODUCTION

Dramatic advances in cancer diagnosis and treatment over the past decade have led to significantly increased survival rates.¹ As a result, there is increasing recognition of treatment-related complications, some of which may not become apparent until decades after therapy is completed. Cardiovascular toxicities can significantly affect morbidity and mortality independent of the malignancy. Previous research on treatment-related cardiotoxicity had focused on heart failure, cardiomyopathy, and coronary artery disease; however, cardiovascular diseases including myocarditis, hypertension, and arrhythmias are increasingly being observed.^{2,3} Atrial arrhythmias such as atrial fibrillation or atrial flutter occur relatively frequently, whereas ventricular arrhythmias are much less common despite the significant attention to the risks of QT prolongation with oncology therapeutics (Figure 1).² In this review, we discuss cancer treatments frequently associated with arrhythmias and provide methods to screen, detect, and manage these complications.

ATRIAL ARRHYTHMIAS

The overall prevalence of atrial fibrillation (AF) in the general population is around 1% to 2%,⁴ and its presence can lead to an increased risk of heart failure or stroke. It is also frequently observed in cancer patients, with an overall prevalence of 4% to 5%, and can be associated with either the cancer itself or with different therapeutic agents.⁵ For example, breast cancer, colorectal cancer, and hematologic malignancies are all associated with increased rates of atrial fibrillation.

Certain chemotherapeutic medications such as ibrutinib (a Bruton's tyrosine kinase inhibitor), melphalan (an alkylating agent), and anthracyclines (including doxorubicin) are known to cause AF at an incidence higher than 10%.² The pathophysiology of cancer-associated AF remains uncertain.

There is some data to suggest that this type of AF is related to the chronic inflammation inherent in malignancy, although specific cancer therapeutics can lead to arrhythmias via direct myocardial toxicity or through on- or off-target effects on intracellular signaling pathways.²

Alkylating Agents

Alkylating agents such as melphalan and cyclophosphamide are used for multiple solid and hematologic malignancies ranging

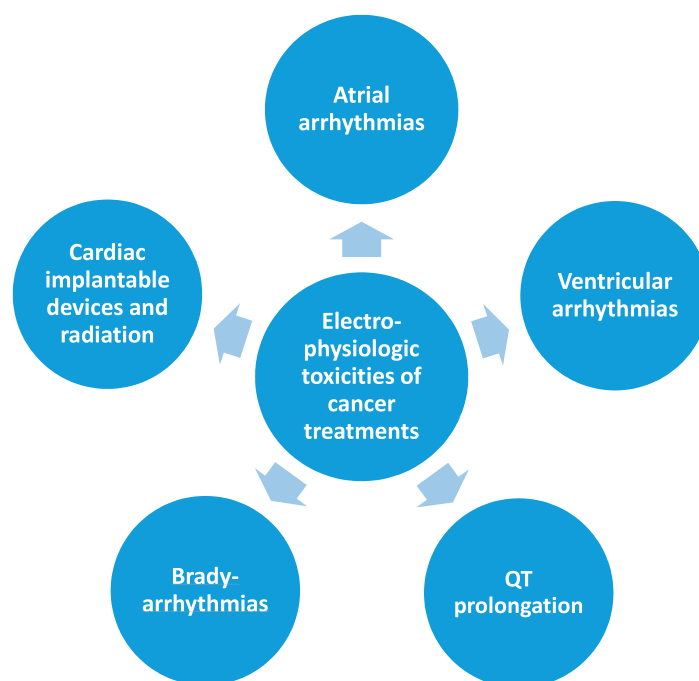


Figure 1.
Electrophysiologic toxicities of cancer treatments.

from leukemia, lymphoma, and multiple myeloma to breast and ovarian cancer.² Alkylating agents act by disrupting the structural formation of the DNA double helix. Melphalan is used prior to stem cell transplantation. In a retrospective study of more than 1,000 stem cell transplants performed at the Moffitt Cancer Center, roughly 5% developed AF. Looking at specific chemotherapy regimens, 11% of patients exposed to melphalan-based regimens developed supraventricular arrhythmias, including AF.⁶ The risk is heightened in the setting of cardiovascular risk factors or chronic kidney disease and in the elderly.

Anthracyclines

Anthracyclines such as doxorubicin, daunorubicin, and idarubicin are a commonly used class of chemotherapeutics that treat a variety of malignancies, including breast cancer, leukemia, lymphoma, and sarcoma. Although the cardiotoxicities most associated with anthracyclines are cardiomyopathy and heart failure, arrhythmias can also frequently occur, with rates up to 10.3%.⁷ Atrial arrhythmias are particularly common in the setting of anthracycline-induced cardiomyopathy (in one study, 56.6% of patients developed AF), but they can also occur in the absence of left ventricular dysfunction.^{7,9} The mechanism of arrhythmia in the setting of cardiomyopathy is thought to occur through structural changes to the myocardium, such as fibrosis, or through direct toxicity to cardiac myocytes, leading to ion channel dysfunction and free radical particle accumulation. Interestingly, the risk of atrial arrhythmia associated with anthracycline-induced cardiomyopathy is similar to other nonischemic etiologies (33%-44%).⁹

Platinum Agents

Platinum compounds such as cisplatin are used in various cancers, including head and neck squamous cell carcinomas and non-small cell lung cancers. Although the risk of AF is quite low with cisplatin administered systemically, rates can be as high as 66% when it is infused directly into the pericardium.¹⁰

Tyrosine Kinase Inhibitors

Therapeutics targeting abnormal cell signaling pathways, typically resulting from mutated or overactive protein kinases, have significantly improved the outcomes of various cancers. Multiple tyrosine kinase inhibitors, including sunitinib and sorafenib, are associated with AF¹¹; however, AF is especially common with the Bruton's tyrosine kinase inhibitor ibrutinib. In the RESONATE study, rates of AF were reported at 5%,¹² although multiple subsequent publications have indicated significantly higher rates ranging from 10% to 15%.¹³ A recent meta-analysis reported the incidence of AF with ibrutinib at 3.3 per 100 person-years.¹⁴ The median time to the development

of arrhythmias was 3 to 4 months in various studies, and 76% occurred within the first year of therapy. A history of atrial fibrillation, an intermediate or high Framingham Heart Study AF score, and enlarged left atrium (per electrocardiogram, or ECG) were associated with a higher risk of developing AF in the setting of ibrutinib use.^{15,16} The etiology of ibrutinib-associated AF has not been completely elucidated. One proposed mechanism is through inhibition of the cardiac PI3K-Akt signaling pathway.¹⁷

Immunotherapies

Immunotherapies include a spectrum of therapies such as immunomodulatory agents (thalidomide, lenalidomide), interleukin-2 immunotherapy, immune checkpoint inhibitors, and chimeric antigen receptor T-cell (CAR-T) therapy. Lenalidomide has been associated with the development of AF in 4% to 7% of patients, especially if used in conjunction with bortezomib or carfilzomib (therapy for multiple myeloma).¹⁸ Although cases of AF have been reported with immune checkpoint inhibitors such as pembrolizumab and nivolumab, they mainly occur in the setting of myocarditis, the most frequent cardiotoxicity observed with this class of therapeutics.^{3,19} The most recent development in immunotherapy is CAR-T therapy, in which T cells of patients are collected and genetically modified to attack cancer cells. Cytokine release syndrome associated with CAR-T therapy can be quite serious, with preliminary studies showing that these patients actually have higher cardiovascular morbidity and mortality, including arrhythmias.²⁰

PREVENTION OF ATRIAL FIBRILLATION-ASSOCIATED THROMBOEMBOLISM

The early diagnosis and risk stratification of AF in cancer patients is critically important. A detailed history that includes any previous cardiac risk factors, such as coronary heart disease, hypertension, or diabetes, is essential. For patients at higher risk, a baseline ECG prior to initiating cancer treatment may be beneficial. Once diagnosed, the benefits of anticoagulation to reduce thromboembolism must be balanced with the risk of possible increased bleeding. The CHA₂DS₂-VASc score, which is more sensitive than the original CHADS₂ score, is recommended to estimate stroke risk in the setting of AF and atrial flutter (AFL). Regardless of cancer status, anticoagulation is recommended for AF/AFL with a CHA₂DS₂-VASc \geq 2 in men and \geq 3 in women in the absence of significant contraindications.²¹ Nevertheless, the validity of these scoring systems in cancer patients has been questioned. For example, D'Souza et al. reported higher rates of thromboembolism in patients with cancer (versus those who were cancer free) and AF who had lower CHADS₂-VASc scores but lower rates of thromboembolism in those who had higher scores.²² In a different study, the CHADS₂ score was unable to predict thromboembolism in cancer patients with new-onset AF.²³

Moreover, the HAS-BLED score, which is used to estimate bleeding risk, is not accurate in cancer patients.²⁴ Nevertheless, in a study from the Moffitt Cancer Center evaluating cancer patients with AF and a strong indication for anticoagulation (ie, high CHA2DS2-VASc and low HAS-BLED scores), only 55.6% received an anticoagulant. Moreover, thrombocytopenia was present in only 18.9% of those patients who were not offered anticoagulation.²⁵ As such, further education and research is necessary to ensure that patients with AF and cancer receive optimal care to reduce the risk of thromboembolism.

In general, direct oral anticoagulants (DOACs) are preferred over warfarin for both the general population and cancer patients.^{21,26} Among the DOACs, rivaroxaban and edoxaban had similar bleeding risks while apixaban had lower bleeding risk when compared with warfarin in a MarketScan database analysis of cancer patients with AF.²⁶ Nevertheless, there is no prospective clinical trial investigating the safety and efficacy of DOACs in cancer patients with AF. Moreover, there is a significant risk of drug-drug interactions between anticoagulants and cancer therapeutics. For example, in a safety analysis of patients with mantle cell lymphoma who take ibrutinib, 2% of those concurrently treated with warfarin developed subdural hematomas.²⁷ As such, the concomitant use of warfarin and ibrutinib should be avoided. Additionally, DOACs interact with the cytochrome P450 system and/or p-glycoprotein, which can lead to adverse effects including increased bleeding.²⁸

VENTRICULAR ARRHYTHMIAS AND QT PROLONGATION

Ventricular arrhythmias occur less frequently than atrial arrhythmias; however, the potential complications of sudden cardiac arrest are far more serious. Most ventricular arrhythmias occur secondary to another cardiotoxicity, such as myocarditis or ischemia, but therapies such as ibrutinib may have direct proarrhythmic effects on the ventricular myocardium. In addition, multiple agents are known to prolong the QT interval, which can also increase the risk of developing torsade de pointes (TdP), a specific type of polymorphic ventricular tachycardia. In general, ventricular arrhythmias are not usually observed unless the QT interval is > 500 ms or there is a change of ≥ 60 ms.²⁹ Despite the significant attention paid to this potential cardiotoxicity, actual arrhythmic event rates remain extremely low, especially if reasonable risk mitigation strategies are implemented. For example, a study from MD Anderson Cancer Center evaluating ECGs from patients enrolled in phase 1 clinical trials reported a 20% incidence of QT interval prolongation, but episodes of TdP were exceedingly rare.³⁰ In general, approaches for monitoring and preventing QT prolongation in patients taking cancer therapeutics include avoiding concomitant use of other QT prolonging drugs, initiating aggressive electrolytic replacement, and performing routine ECG monitoring.³¹

Anthracyclines

Ventricular arrhythmias associated with anthracyclines occur primarily in the context of chemotherapy-induced cardiomyopathy. In a study by Mazur et al. of 23 patients with implantable cardioverter defibrillators for anthracycline-related cardiomyopathy, the incidence of nonsustained ventricular tachycardia (NSVT) and sustained VT/ventricular fibrillation (VF) was 73.9% and 30.4%, respectively.⁸ A study by Fradley et al. reported similar results, with an incidence of NSVT and combined VT/VF of 44.4% that was comparable to other types of nonischemic cardiomyopathy.⁹

Arsenic Trioxide

Arsenic trioxide led to dramatically improved survival rates (> 90%) for acute promyelocytic leukemia. Despite its oncologic benefits, arsenic trioxide commonly leads to QT prolongation. An analysis of more than 3,000 electrocardiograms from 113 patients treated with arsenic trioxide reported a Fridericia-corrected QT interval of > 500 ms in 26%.³² Although no clinically significant arrhythmias were observed, the US Food and Drug Administration (FDA) has issued a black box warning for arsenic-induced QT interval prolongation and TdP, with recommendations to discontinue therapy if the QT interval prolongs to > 500 ms and resume therapy once the QT interval is < 460 ms.^{32,33} Additionally, ECG screening and regular electrolyte optimization is recommended before and during therapy.³⁴

Cyclin-Dependent Kinase 4/6 Inhibitors

Ribociclib, a cyclin-dependent kinase (CDK) 4/6 inhibitor approved for the treatment of hormone receptor (HR)-positive and HER2-negative breast cancers, is associated with QT prolongation. One study showed prolongation in 9% of patients treated at the recommended initial dose, with up to 33% of patients demonstrating QT lengthening at doses > 600 mg/day.³⁵ The current recommendation is to obtain an ECG at baseline, at day 14 of the first cycle, at the beginning of the second cycle, and then as clinically indicated. Therapy should not be initiated if the QTcF is > 450 ms, and it should be held or stopped if the QTcF lengthens to > 480 ms.

Fluoropyrimidines

5-fluorouracil (5-FU) is a fluoropyrimidine antimetabolite primarily used with gastrointestinal malignancies. Associated ventricular arrhythmias occur mainly in the setting of coronary vasospasm; this leads to myocardial ischemia, which is the primary cardiotoxicity of 5-FU.³⁶ Although patients receiving 5-FU regimens demonstrate an increase in ventricular premature

complexes during the first 24 hours of treatment, a meta-analysis of 3,223 patients found the incidence of ventricular tachycardia to be only 0.16%.³⁷

Tyrosine Kinase Inhibitors

Multiple tyrosine kinase inhibitors are associated with QT prolongation, including dasatinib, nilotinib, sunitinib, and

vandetanib. Despite this, QT prolongation does not appear to be a class-related effect, and adverse clinical events are rare.^{38,39} For example, in phase I clinical trials of nilotinib, the mean QT prolongation was 5 to 15 ms, and in the Evaluating Nilotinib Efficacy and Safety in Clinical Trials-Newly Diagnosed Patients (ENESTnd) trial, there were no reported QT intervals > 500 ms and no episodes of TdP with nilotinib.⁴⁰ Nevertheless, nilotinib carries an FDA black box warning for QT prolongation.

| DRUG CLASS | EXAMPLE | ASSOCIATED ARRHYTHMIAS | POTENTIAL MECHANISM |
|--|---|---|---|
| Alkylating agents ⁶ | Melphalan | Atrial arrhythmias | Unknown |
| Anthracyclines ⁷⁻⁹ | Doxorubicin Epirubicin | Atrial arrhythmias Ventricular arrhythmia | Free radical/toxin accumulation, myocardial damage/cardiomyopathy Myocardial damage/cardiomyopathy, increased ventricular repolarization indices |
| Arsenic ^{32,33} | | QT prolongation | Potassium channel inhibition |
| Cyclin-dependent kinase 4/6 inhibitors ³⁵ | Ribociclib | QT prolongation | Unknown |
| Fluoropyrimidines ^{36,37} | 5-fluorouracil Capecitabine | Ventricular arrhythmias | Secondary to coronary vasospasm/ myocardial ischemia |
| Immunotherapies ^{19,20} | CAR-T therapy | Atrial arrhythmias | Inflammatory like from CRS |
| | Checkpoint inhibitors (pembrolizumab) | Atrial/ventricular arrhythmias, bradyarrhythmias | Myocarditis/inflammatory |
| | Immunomodulatory agents (lenalidomide) | Atrial arrhythmias | Unknown |
| Platinum agents ¹⁰ | Cisplatin | Atrial arrhythmias | Direct myocardial irritation |
| Taxanes ^{46,47} | Paclitaxel | Bradyarrhythmias | Effects on histamine receptor |
| Tyrosine kinase inhibitors | Ibrutinib, sorafenib, sunitinib ¹¹⁻¹⁷ | Atrial arrhythmias | PI3K pathway inhibition |
| | Nilotinib, sunitinib, vandetanib ⁴⁰⁻⁴² | QT prolongation | Impaired intracellular signaling leading to enhanced late sodium and decreased potassium currents |
| | Ibrutinib ⁴³ | Ventricular arrhythmias | Unknown |
| | ALK Inhibitors ^{44,45} (crizotinib) | Bradyarrhythmias | Decrease If (funny channel) currents in sinoatrial nodal cells |

Table 1.

Arrhythmias associated with different cancer therapeutics.^{6-17,19,20,32,33,35-37,40-47}

Vandetanib has a similar warning, although QT prolongation is more substantial with this agent.⁴¹ Despite these warnings, a review and meta-analysis by Porta-Sánchez et al. shows that while sunitinib, nicotinic, and vandetanib had a considerable effect on the QT interval, this was not predictive of an increased risk of TdP and other ventricular arrhythmias.⁴²

Ventricular arrhythmias may also occur in the absence of QT prolongation. Although the majority of these events will occur in the context of another cardiotoxicity (eg, anthracycline-induced cardiomyopathy or 5-FU-induced ischemia), certain agents, such as ibrutinib, may be directly arrhythmogenic. In a larger study evaluating ventricular arrhythmias in patients taking ibrutinib without underlying cardiovascular disease, the incidence was 669 per 100,000 person-years, which was significantly higher when compared with patients not taking ibrutinib (12.9 RR, $P < .001$; AER 11.9, $P < .001$).⁴³ The mechanism of ibrutinib-associated ventricular arrhythmias has not been elucidated. Table 1 highlights the types of arrhythmias associated with various anticancer agents.^{6-17,19,20,32,33,35-37,40-47}

BRADYARRHYTHMIAS AND CARDIOVASCULAR IMPLANTABLE ELECTRONIC DEVICES

Certain cancer therapeutics have been associated with bradyarrhythmias and atrioventricular blocks. While most of these episodes are asymptomatic, pacemaker placement may be necessary in rare instances. Anaplastic lymphoma kinase (ALK) inhibitors are agents primarily used in the treatment of non-small cell lung cancer and are commonly associated with sinus bradycardia. The incidence of crizotinib-induced bradycardia is as high as 42%; however, the majority of these patients were asymptomatic and dose adjustment was rarely necessary.^{44,45} Interestingly, bradycardia appears to be a marker for tumor response. Taxanes, particularly paclitaxel, are known to cause bradycardia, with rates as high as 29%; however, clinically significant events are rare.^{46,47} In contrast, conduction disorders including complete heart block that requires pacemaker placement can be the first manifestation of immune checkpoint inhibitor myocarditis.⁴⁸

The management of cardiovascular implantable electronic devices (CIEDs), including pacemakers and defibrillators, is becoming an increasingly important issue in cancer patients, especially those undergoing radiation therapy. For example, rates of radiation in patients with a CIED increased by 199% in Denmark between 2003 and 2012.⁴⁹ While a complete discussion about the issues surrounding CIEDs and radiation is beyond the scope of this review, there are a few important points worth highlighting. Defibrillators tend to be more sensitive to the effects of ionizing radiation compared to pacemakers, but complication rates are generally lower with current-generation

CIEDs.⁵⁰ The most common radiation-associated complications are relatively benign and include temporarily increased pacing rates, device resets, and safety mode reversions. Serious device failure is extremely uncommon. Although significant attention is often paid to cumulative absorbed radiation, device malfunction is more associated with the use of high energy beams (> 10 MV), which can produce neutrons that are known to damage device hardware and software.⁵¹ For example, a study from MD Anderson Cancer Center illustrated a 7% device malfunction in CIEDs among patients receiving high-energy radiation therapy > 10 MV.⁵¹ Nevertheless, there is significant variability in the published recommendations and best practices to mitigate the risk of CIED damage from radiation.⁵² Future consensus documents and guidelines will be necessary to ensure safe and effective radiation therapy for patients with CIEDs.

CONCLUSION

Cardiovascular toxicities from oncologic treatment are becoming increasingly common due to increased recognition and improved cancer survival rates. Although traditionally much of the focus of cardio-oncology has been on heart failure and cardiomyopathy, it is now recognized that cancer therapeutics can affect all aspects of the cardiovascular system, including arrhythmic and other electrophysiologic complications. Evaluation and management of tachy- and bradyarrhythmias in cancer patients can be nuanced and challenging. As such, a multidisciplinary approach that includes oncologists and cardio-oncologists is needed to reduce the risk of cardiotoxicity while ensuring that patients continue to receive necessary cancer treatments.

KEY POINTS

- Various cancer treatments are associated with the development of atrial and ventricular arrhythmias.
- Anticoagulation for atrial fibrillation presents multiple unique challenges in cancer patients.
- QT interval prolongation is common with cancer therapies but rarely leads to ventricular arrhythmias.
- Most bradyarrhythmias are asymptomatic and do not require intervention apart from checkpoint inhibitor-induced heart block.

Conflict of Interest Disclosure:

Dr. Fradley is a consultant for Novartis.

Keywords:

cardio-oncology, atrial arrhythmias, ventricular arrhythmias, bradyarrhythmias, cardiotoxicity

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