Arrhythmia Challenges in Cardio-Oncology

High-Risk Therapies, Management, and Anticoagulation

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KEY WORDS

• Cardiotoxicity • Arrhythmia • Atrial fibrillation • Ventricular arrhythmia • Bradyarrhythmia • Anticoagulation • Antiarrhythmics

KEY POINTS

- Cancer therapy-induced atrial fibrillation is a common co-morbidity and a rate control strategy with beta-blockers is the preferred management.
- Cancer patients with atrial fibrillation are both at increased risk of thromboembolic events and bleeding which complicates the use of anticoagulation, therefore, contributing to underutilization.
- Direct oral anticoagulants are the preferred agent in cancer patients.
- Ventricular arrhythmias are rare but life-threatening arrhythmias induced by cancer therapies and select patients may benefit from implantable cardiac defibrillators.
- Bradyarrhythmias from cancer therapies are typically benign and self-limiting but important to recognize as select patients may benefit from permanent pacing.

INTRODUCTION

Cardiovascular disease (CVD) and cancer are the leading cause of mortality in the United States. In 2021, there were 695,547 and 605,213 deaths due to heart disease and cancer, respectively.[1] With novel oncologic and cardiac therapies, survival has improved leading to increased life-expectancy albeit with chronic illness burden. Arrhythmia management in patients with cancer, whether active or in remission, can be quite challenging. In this review, we will discuss high-risk oncological therapies, prevention, and management of Atrial fibrillation (AF), Ventricular Arrhythmias (VA), and Bradyarrhythmias.

ATRIAL FIBRILLATION

Atrial Fibrillation in Cancer

Atrial fibrillation (AF) is the most common cardiac arrhythmia encountered among cancer patients. Patients at highest risk are those suffering from esophageal and lung cancers, as well as hematologic malignancies, such as multiple myeloma (MM), leukemia, and non-Hodgkin's lymphoma.[2] Breast cancer survivors who are less than 40 years of age appear to have a 2-fold higher risk of AF compared to patients without cancer.[3] While cancer is an inherent nidus for AF, cancer therapy-related cardiovascular toxicity (CTR-CVT) is the leading cause of AF in cancer

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populations and has been shown to be a risk factor for AF in breast cancer populations.[4] The sequela of cancer including electrolyte derangements, malnutrition, hypoxia, and aging contribute to the development of AF.[5] AF is often a chronic disease associated with an increased risk of thromboembolism, CVD, renal disease, and death.[6] Given the rising cancer incidence and improving cancer survivorship, there is a growing need for clinicians to screen and manage AF.[7]

Atrial Fibrillation: High-Risk Therapies

The association of anthracyclines and atrial arrhythmias is well established. AF induced by doxorubicin was first described in a cohort of 256 patients in 1978, and occurred in 2.2% of the treated individuals.[8] More recent studies have reported an incidence of new AF in 2.9% to 5% of patients, and an even higher incidence in a study by Onoue and colleagues, which reported 40% of the patients with post-anthracycline heart failure developed AF.[9,10]

Cisplatin is among the most commonly used chemotherapies with CTR-CVT secondary to generation of reactive oxygen species and mitochondrial dysfunction.[11] Evidence for cisplatin-induced AF is associated with intrapericardial and intracavitary administration with an incidence up to 32%.[12]

5-fluorouracil (5-FU) and other antimetabolites have the potential to cause CTR-CVT, including AF. Studies have associated 5-FU with AF, especially when administered in combination with cisplatin.[13] Capecitabine, a 5-FU pro-drug, has an AF incidence of 0.5% to 1.1%.[14,15] Fludarabine, when used alongside Busulfan and total body irradiation in hematopoietic stem cell transplantation, induced AF and atrial flutter (AFL) in approximately 8.3% of the patients.[16]

Androgen deprivation therapy (ADT) is an oral therapy for metastatic prostate cancer with an AF incidence of 11.1% over 3 years.[17] Abiraterone has the most significant risk of atrial tachyarrhythmias.[18] While prostate cancer patients typically have non-modifiable risk factors for AF (age and sex), abiraterone further increases the risk.[5]

Burton's tyrosine kinase (BTK) inhibitors are most often used to treat chronic lymphocytic leukemia and are perhaps the most pro-arrhythmogenic cancer therapies.[19] Ibrutinib, a first generation BTK inhibitor, likely has the highest risk of AF with a 15-fold increase in risk and a 2 year incidence of 38%.[20] Several meta-analyses have confirmed ibrutinib's high-risk association: across 16 studies, the incidence was 5.8 over 100 person-years and across 8 RCTs, the pooled relative risk of developing AF was 4.69 (95% confidence interval [CI], 2.17–7.64).[21,22] Left atrial enlargement identified on electrocardiograms and pre-existing heart failure were noted to increase the risk of developing ibrutinib-associated atrial fibrillation.[23]

Newer generation BTK inhibitors such as acalabrutinib, zanubrutinib, and pirtobrutinib exhibit higher BTK selectivity with lower risk of off-target effects.[24] Acalabrutinib has a lower reported rate of AF and AFL with a cumulative incidence of 5% to7%.[25,26] Zanubrutinib has an AF incidence of 1.9% to 4%.[27,28] Pirtobrutinib appears to have the lowest AF incidence with 1% to 3.8%, thought to be due to its noncovalent mechanism of inhibition.[29–31]

Other tyrosine kinase inhibitors (TKI) such as sorafenib, ponatinib, and CDK4/6 inhibitors have demonstrated risk of AF. Sorafenib when combined with 5-FU was observed to have an incidence of 5.1%.[32] Ponatinib has an advertised risk for AF of 4% per the manufacturer label; however, a randomized open-label study only accounted for 1.5% incidence.[33,34] CDK4/6 inhibitors were reported to have a 4.9% incidence of AF in a cohort of 1376 patients.[35]

Immune checkpoint inhibitors (ICI) are known to cause myocarditis; however, their inductive risk of AF is relatively understudied. In a 30-patient case series evaluating ICI cardiotoxicity, 9 patients (30%) had new diagnosis of atrial fibrillation.[36] Additionally, in 35 patients with ICI-associated myocarditis, 9 patients (25.7%) developed AF or AFL.[37] While risk is demonstrated in myocarditis, studies are needed to fully elucidate the risk of AF with ICI.

Chimeric antigen receptor-T cell (CAR-T) agents are novel therapies administered for refractory and relapsed MM and lymphoma. The incidence of AF in CAR-T has been reported at a range of 2% to 8%.[38,39] Among the highest are idecabtagene vicleucel with an incidence of 10.3% and axicabtagene ciloleucel with an incidence of 2.4%.[40–42] Cytokine release syndrome, an adverse event from CAR-T, has been associated with tachyarrhythmias, but its association with AF remains under studied.[40]

Cancer patients with history of radiotherapy exposure are more likely to develop AF and is associated with poor long-term outcomes.[43,44] Risk factors for radiation-associated AF include targeting the pulmonary veins or sinoatrial node.[45,46]

Numerous cancer-related therapies demonstrate evidence of inducing AF. Those with the highest risk appear to be BTK inhibitors, CAR-T, ADT, alkylating agents, and ICIs.

Management of Atrial Fibrillation in Cancer

Cardioversion

The acute management of symptomatic AF with hemodynamic instability should be direct current cardioversion (DCCV).[47] Post DCCV, patients are at increased risk of thrombus formation due to myocardial stunning and require anticoagulation (AC) for at least 4 weeks following cardioversion.[5] Pharmacologic cardioversion can be considered in cancer patients.[5] For cancer patients who are hemodynamically stable, cardioversion following transesophageal echocardiogram can be considered.[5] Cardioversion commits patients to uninterrupted AC which can be challenging in cancer patients who often have pancytopenia, tissue friability, and overall increased bleeding risk. Additionally, the long-term efficacy of cardioversion of AF in cancer populations remains in question.[48]

Rate control

Rate control with beta blockers (BB) is the preferred strategy and supported by the American Heart Association (AHA) and the European Society of Cardiology (ESC).[47,49] Beta blockers are preferred over non-dihydropyridine calcium channel blockers (NDCCB), as they pose a number of drug interactions due to inhibition of cytochrome p450 (CYP) 3A4 (**Table 1**).[22,47,49,50] NDCCB can be added to beta-blockers if additional rate control is required.[22] Medication reconciliation should be addressed for patients on NDCCB as close monitoring and possibly dose reduction is required depending on drug metabolism (see **Table 1**).[22]

Adverse drug interactions between chemotherapies and rate control agents can pose a challenge for AF management. CYP2D6 is inhibited by imatinib and abiraterone which can increase concentrations of metoprolol and carvedilol.[51] Digoxin can be considered in rare cases, but special attention needs to be given to medications with P-glycoprotein inhibition such as ibrutinib.[22] Ibrutinib-associated AF is a common yet challenging clinical scenario. Within the authors' institution, a rate control strategy with BB is preferred in these patients, given lower risk for drug interaction and prior demonstrated safety. Complications from the negative chronotropy and inotropy of rate control agents in cancer patients can be exacerbated by concomitant hypotension, dehydration, vasoplegia, and electrolyte derangements from malignancy and cancer therapy.

Rhythm control

Rhythm control is instituted in cases of symptomatic AF with inability to tolerate rate control or maintain sinus rhythm.[49] Studies have suggested early rhythm control can lower adverse events of AF; however, this strategy remains understudied. Class IC antiarrhythmics like flecainide and propafenone have no evidence in cancer patients. Class III antiarrhythmics have very limited evidence. A retrospective study of 81 cancer patients found ibutilide safe and effective for acute cardioversion of AF and AFL without serious adverse events.[52] Within the authors' center, rhythm control, by use of antiarrhythmic drugs, electrical cardioversion, or ablation is considered for ibrutinib-associated AF if the patient fails to have adequate symptom relief despite rate control, and if transitioning to another cancer therapy is not an option.

Ablation

Ablation can be considered for symptomatic persistent AF, albeit with considerations specific to cardio-oncology.[48] Prior to ESC and AHA cardio-oncology expert consensus, the role of AF ablation in cancer patients was not well studied.[47,49] One retrospective study compared patients with recent cancer (within 5 years) to those without cancer and found no significant difference in 1-year rate of efficacy or repeat ablation.[53] In fact, patients with a history of cancer were less likely to require antiarrhythmics following ablation.[53] Finally, a meta-analysis of ablation in cancer survivors found no significant difference in efficacy between cancer and non-cancer patients, but reported an increased risk of bleeding in cancer survivors.[54]

Anticoagulation for Atrial Fibrillation in Cancer

Risk of thromboembolism

Patients with active cancer are prone to thromboembolism (TE) due to a convalescence of inflammation, therapy adverse effects, malignancy pathophysiology, and surgery.[55] CHA_2DS_2-VASc stratifies risk of TE in AF patients which offers limited application in cancer patients, given malignancy and cancer therapy are not included as risk factors.[5] Furthermore, cancer onset and stage heavily influence risk of TE especially within the first year of cancer diagnosis.[56]

Despite these considerations, AHA expert consortium recommends a similar CHA_2DS_2-VASc risk profile to the general population: AC is recommended for scores $\geq$2 in men and $\geq$3 in women.[49] ESC recommends considering AC in those with CHA_2DS_2-VASc scores of 1 or 2 in the context of their cancer phenotype and cancer therapy.[47] Unfortunately, a recent study found CHA_2DS_2-VASc was not predictive of embolic risk in cancer patients but a score of 0 identified low-risk patients.[57] AC is under-prescribed in cancer patients with utilization rates of 44% to 57% for patients at risk of

Table 1
Drug interactions between common arrhythmogenic chemotherapies compared with antiarrhythmics

	Metoprolol	Carvedilol	Landiolol	Verapamil	Diltiazem	Digoxin	Flecainide	Propafenone	Amiodarone	Sotalol	Dofetilide	Ibutilide
Melphalan						X↓ (Abs↓)						
Fluorouracil						X↓ (Abs↓)	QTc↑	QTc↑	QTc↑	QTc↑	QTc↑	QTc↑
Capecitabine						X↓ (Abs↓)	QTc↑	QTc↑	QTc↑	QTc↑	QTc↑	QTc↑
Gemcitabine						X↓ (Abs↓)						
Doxorubicin (conventional)		Y↑ (PGP↓)		Y↑ (PGP↓)	Y↑ (3A4↓)	X↓ (Abs↓)		Y↑ (PGP↓)	Y↑ (PGP↓)			
Doxorubicin (liposomal)		Y↑ (PGP↓)		Y↑ (PGP↓)	Y↑ (3A4↓)	X↓ (Abs↓)		Y↑ (PGP↓)	Y↑ (PGP↓)			
Abiraterone	X↑ (2D6↓)	X↑ (2D6↓)					X↑ (2D6↓)	X↑ (2D6↓)				
Enzalutamide				X↑ (3A4↓)	X↑ (3A4↓)	X↑ (PGP↓)		X↑(3A4↓)	X↑(3A4↓)			
Aldesleukin	HoTN	HoTN	HoTN	HoTN	HoTN				HoTN	HoTN	X↑ (CYP-S)	
Lenalidomide						X↑ (PGP-C)						
Ibrutinib				Y↑ (3A4↓)	Y↑ (3A4↓)	X↑ (PGP-C)						
Acalabrutinib				Y↑ (3A4↓)	Y↑ (3A4↓)							
Zanubrutinib				Y↑ (3A4↓)	Y↑ (3A4↓)	X↑ (PGP↓)						
Pirtobrutinib				Y↑ (3A4↓)	Y↑ (3A4↓)	X↑ (PGP↓)					X↑ (3A4↓)	
Sorafenib							QTc↑	QTc↑	QTc↑	QTc↑	QTc↑	QTc↑
Ponatinib				Y↑ (3A4↓)	Y↑ (3A4↓)							
Pazopanib		Y↑ (PGP↓)		Y↑ (PGP↓)	Y↑ (PGP↓)		QTc↑	Y↑(PGP↓), QTc↑	Y↑(PGP↓), QTc↑	QTc↑	QTc↑	QTc↑
Sunitinib				Y↑ (3A4↓)	Y↑ (3A4↓)		QTc↑	QTc↑	QTc↑	QTc↑	QTc↑	QTc↑
Imatinib				Y↑ (3A4↓)	Y↑ (3A4↓)			X↑(3A4↓)	X↑(3A4↓)		X↑ (3A4↓)	
Nilotinib				XY↑ (3A4↓)	XY↑ (3A4↓)		QTc↑	QTc↑	QTc↑	QTc↑	QTc↑	QTc↑
Dasatinib				Y↑ (3A4↓)	Y↑ (3A4↓)		QTc↑	QTc↑	QTc↑	QTc↑	QTc↑	QTc↑
Crizotinib	Brady	Brady	Brady	Y↑ (3A4↓)	Y↑ (3A4↓)	Brady	Brady, QTc↑	Brady, QTc↑	QTc↑ (3A4↓)	QTc↑ (3A4↓)	QTc↑ (3A4↓)	QTc↑ (3A4↓)
Alectinib	Brady	Brady	Brady	Brady	Brady	Brady	Brady	Brady	Brady	Brady		
Brigatinib	HTN, Brady	HTN, Brady	Brady	Y↑ (3A4↓)	Y↑ (3A4↓)	Brady	Brady	Brady	Brady	Brady		
Lorlatinib				X↓ (3A4↑)	X↓ (3A4↑)	X↑ (PGP↓)		X↓ (3A4↑)	X↓ (3A4↑)			
Ceritinib	Brady	Brady	Brady	Brady	Brady	Brady	Brady	Brady, QTc↑	Brady, QTc↑	Brady, QTc↑	QTc↑	QTc↑
Bortezomib	HoTN	HoTN	HoTN	Y↑ (3A4↓)	Y↑ (3A4↓)				HoTN			
Arsenic Trioxide	HoTN	HoTN	HoTN	HoTN	HoTN		QTc↑	QTc↑	QTc↑	QTc↑	QTc↑	QTc↑
Thalidomide	Brady	Brady	Brady	Brady	Brady	Brady	Brady	Brady	Brady	Brady		
Docetaxel				Y↑ (3A4↓)	Y↑ (3A4↓)	X↓ (Abs↓)						
Cabazitaxel				Y↑ (3A4↓)	Y↑ (3A4↓)	X↓ (Abs↓)						
Paclitaxel (conventional)	HoTN	HoTN	HoTN	Y↑ (3A4↓)	Y↑ (3A4↓)	X↓ (Abs↓)			HoTN	HoTN		
Paclitaxel (protein bound)				Y↑ (3A4↓)	Y↑ (3A4↓)	X↓ (Abs↓)						
Cyclophosphamide						X↓ (Abs↓)			X Tox↑			

Interaction Risk	
Effect	Avoid
Effect	High Risk
Effect	Moderate Risk
Effect	Low Risk

Mechanism	
(2D6↓)	CYP2D6 Inhibition
(3A4↓)	CYP3A4 Inhibition
(3A4↑)	CYP3A4 Inducer
(CYP-S)	Cytochrome substrate interaction
(PGP↓)	P-glycoprotein Inhibition
(PGP-C)	P-glycoprotein competition
(Abs↓)	Decreased drug absorption

Effects	
HTN	Hypertension
HoTN	Hypotension
Brady	Bradycardia
QTc↑	QTc prolongation
X↑	Column Variable Drug Increases
X↓	Column Variable Drug Decreases
Y↑	Row Variable Drug Variable Increases

If no mechanism is listed, then literature is not available to describe the mechanism. CYP: Cytochrome P450. High-risk therapies should consider alternatives, moderate risk should be monitored, and low-risk therapies should be monitored in select patient populations.

Data from Interaction risk based on Lexicomp, Accessed March 14, 2024.

TE.[58,59] However, cancer patients with AF prescribed AC had better clinical outcomes and reduced risk of all-cause mortality.[58]

Risk of bleeding

Anticoagulation in the oncology population often confers risk of bleeding given complications of cancer therapy, bleeding diathesis, and malnutrition. Initiation of anticoagulation poses a significant challenge to oncologists and cardiologists alike. A meta-analysis by Balomenakis and colleagues suggested cancer patients with AF were at significantly higher risk of bleeding and all-cause mortality.[60] Conversely, AF patients with cancer have higher risks of all-cause mortality, major bleeding, and intracranial hemorrhage (ICH), but are not at higher risk of ischemic events.[55,61] While hemorrhagic risk stratification tools are limited, ORBIT performed the best in predicting any risk of bleeding in AF in cancer pateints.[62] Bleeding risk tools do not take account thrombocytopenia and intracerebral metastasis which in part could explain the underutilization of AC for AF in cancer patients.[63] When recommending anticoagulation to patients on ibrutinib, patients' medical history, including prior bleeding and TE history, as well as associated risk factors should be considered.

Oral anticoagulation

Warfarin, a vitamin K antagonist (VKA), was the first oral anticoagulant utilized for TE prevention in AF patients. Direct oral anticoagulants (DOACs) and VKAs have similar efficacy in preventing TE in cancer patients.[61,64,65] However, a study of cancer patients found VKAs, but not DOACs, to be independently predictive of bleeding.[57] Furthermore, when compared to DOACs, VKAs are associated with higher mortality in cancer patients due to higher risk of bleeding and ICH.[66–68] In these populations, apixaban and rivaroxaban have superior safety and efficacy profiles with apixaban having the lowest rate of bleeding.[67] Finally, DOACs are primarily metabolized by CYP3A4,

so it is imperative to consider drug interactions with chemotherapeutics (**Table 2**).[50,69] DOACs offer a safer adverse effect profile compared to VKAs and are the preferred AC for AF in cancer patients.

Left atrial appendage occlusion

For patients with high TE risk and contraindications to long-term AC, left-atrial appendage occlusion (LAAO) can be considered.[5,48] However, patients need to tolerate AC for at least 45 days post-LAAO and dual-antiplatelet therapy for 6 months.[70] In a small cohort of 55 patients following LAAO, there was no significant difference in ischemic stroke events or bleeding between patients with and without cancer.[71] However, 2 studies reported patients with active cancer who received LAAO had higher odds of peri-procedural complications including TE, pericardial effusion requiring drainage, and major bleeding.[72,73]

VENTRICULAR ARRHYTHMIAS

Introduction

Ventricular arrhythmias (VA) can often be life threatening leading to hemodynamic collapse. Cancer patients have an increased risk of ventricular tachycardia (VT) and ventricular fibrillation (VF). A study reported 32% of cancer patients with implantable cardiac defibrillators (ICD) experience VT/VF within first 2 years of cancer diagnosis while patients with metastatic disease were at a significantly higher risk of VA at 41%.[74] Cancer therapy or drug-induced QTc prolongation increases risk of VA and is an important modifiable risk factor for prevention. Pharmacovigilance studies have raised concern for multiple agents, but those with robust evidence of VA include anthracyclines, arsenic trioxide, 5-FU, TKI, ICI, and CAR-T.

High-Risk Therapies

Anthracyclines are used for numerous cancers and are associated with QTc prolongation. Anthracyclines have a reported VA incidence of 6%, but VA often manifests years after exposure.[75,76] One study found VA in anthracycline-associated cardiomyopathy (AACM) has a similar prevalence of VA in ischemic cardiomyopathy (ICM).[77] This suggests anthracycline's arrhythmogenicity is secondary to drug-induced cardiomyopathy, but more studies are needed to establish this association.

5-FU has multiple case reports of inducing VA by inciting premature ventricular contractions.[78–81] In 1992, De Forni and colleagues reported 5-FU had a VA incidence of 1.1%.[82] Capecitabine was initially reported to have a slighter higher VA incidence of 2.1%, but a more recent and robust prospective study reported a VA incidence of 7.3%.[83,84] 5-FU and capecitabine's arrhythmogenicity is likely due to drug-induced coronary artery vasospasm which could subsequently lead to transient ischemia and VA.[85]

Table 2
Drug interactions between arrhythmogenic chemotherapy and anticoagulation

	Warfarin	Enoxaparin	Rivaroxaban	Dabigatran	Apixaban	Edoxaban
Fluorouracil	X↑ (2C9↓)					
Capecitabine	X↑ (2C9↓)					
Gemcitabine	X↑ (2C9↓)					
Enzalutamide	X↓ (2C9↑)		X↑(3A4↓)	X↑ (PGP↓)	X↑(3A4↓)	X↑ (PGP↓)
Aldesleukin	X↑ (CYP-S)					
Ibrutinib	Hem	Hem	Hem	Hem	Hem	Hem
Acalabrutinib	Hem	Hem	Hem	Hem	Hem	Hem
Zanubrutinib	Hem	Hem	Hem	Hem	Hem	Hem
Pirtobrutinib	Hem	Hem	Hem	X↑ (PGP↓)	Hem	X↑ (PGP↓)
Sorafenib	INR↑					
Imatinib	X↑		X↑(3A4↓)		X↑(3A4↓)	
Nilotinib			X↑(3A4↓)		X↑(3A4↓)	
Dasatinib	Hem	Hem	Hem	Hem	Hem	Hem
Crizotinib	X↑		X↑(3A4↓)		X↑(3A4↓)	
Alectinib	X↑					
Lorlatinib	X↓ (2C9↑)		X↓ (PGP↑)	X↓ (PGP↑)	X↓ (PGP↑, 3A4↑)	X↓ (PGP↑)
Ceritinib	X↑ (2C9↓)		X↑(3A4↓)		X↑(3A4↓)	
Paclitaxel (conventional)	INR↑					
Paclitaxel (protein bound)	INR↑					
Cyclophosphamide	X↓					

Interaction Risk	
Effect	Avoid
Effect	High Risk
Effect	Moderate Risk
Effect	Low Risk

Mechanism	
(2C9↓)	CYP2C9 Inhibition
(2C9↑)	CYP2C9 Inducer
(3A4↓)	CYP3A4 Inhibition
(3A4↑)	CYP3A4 Inducer
(CYP-S)	Cytochrome substrate interaction
(PGP↓)	P-glycoprotein Inhibition
(PGP↑)	P-glycoprotein Inducer

Effects	
Hem	Hemorrhage, mechanism unknown
X↑	Column Variable Drug Increases
X↓	Column Variable Drug Decreases
Y↑	Row Variable Drug Variable Increases
Y↓	Row Variable Drug Decreases

If no mechanism is listed, then literature is not available to describe the mechanism. CYP: Cytochrome P450, INR: International Normalized Ratio. High-risk therapies should consider alternatives, moderate risk should be monitored, and low-risk therapies should be monitored in select patient populations

Data from Interaction risk based on Lexicomp, Accessed March 14, 2024.

Arsenic trioxide has been speculated to have the highest risk of QTc prolongation.[86] However, only a few reports of VA associated with arsenic trioxide exist.[87–89] Tyrosine kinase inhibitors (TKIs) are known to be among the most arrhythmogenic anti-cancer therapies. Ibrutinib in particular has an incidence of VA from 596 to 788 events per 100,000 person-years.[90,91] Acalabrutinib has a slightly lower rate with 394 events per 100,000 person-years.[92] A recent study of pazopanib, sunitinib, imatinib, nilotinib, and dasatinib found QTc prolongation in 28.8% of the patients with 14 cases of life-threatening VA.[93]

ICI-induced VA is speculated to be due to drug-induced myocarditis. Power and colleagues reviewed 147 patients with ICI myocarditis and reported 15% of the patients experienced 1 or more VA.[94] The most common was VT or VF, and 7.5% of the patients experienced life-threatening VA with complete heart block. Additionally, QRS duration is increased in ICI myocarditis and is associated with adverse cardiovascular outcomes.[95]

Finally, CAR-T therapies have a variable risk of VA depending on the agent. A study found among 1475 hospitalized patients treated with CAR-T, 4.7% experienced VT.[96] However, a study focused on axicabtagene ciloleucel reported VA in only 0.7% of the patients.[40] Overall, the rate of VA in CAR-T varies and could be over reported in hospitalized patients. Evidence for VA from CTR-CVT is difficulty to elucidate due to the multifocal nature and acuity of the disease.

Management of Ventricular Arrhythmias

QTc monitoring

In cancer populations, Fridericia correction is preferred for QTc calculation while Bazett correction is not recommended.[97,98] All patients should receive a baseline ECG prior to cancer therapy initiation. An absolute safe QTc interval to start chemotherapy is less than 450 ms in men and less than 460 ms in women.[99] However, a limit of QTc less than 480 ms can considered with periodic monitoring.[47] If initial QTc greater than 480 ms then it is recommended to consider alternative treatment and if initial QTc greater than 500 ms then it is recommended to choose an alternative treatment.[47]

All patients with safe initial QTc intervals should be periodically monitored for electrocardiogram (ECG) changes.[100] Patients who are prescribed high-risk therapies should have QTc monitoring before and after all dose adjustments.[101] Therapy can be continued with periodic monitoring as long as the patient is asymptomatic, the QTc is less than 480, the change in QTc remains less than 60 ms, and there have been no VA events.[47,102] If the QTc increases to 480 to 500 ms, the authors recommend continuing treatment with weekly ECG after second evaluation for modifiable risk factors, reducing QTc prolonging medications, and correcting electrolyte abnormalities.[47]

Cardioversion and medical management of ventricular arrhythmias

Prior to initiating cancer therapy, baseline ECG should be obtained to assess for QRS and QT prolongation which can be associated with an increased risk of VA.[103] For patients with asymptomatic non-sustained VA, the best approach is to assess, monitor, and replete electrolytes with specific attention to magnesium, potassium, phosphorus, and calcium.[49,104] For those with symptomatic non-sustained VT, cancer therapy should be dose reduced or discontinued after multidisciplinary discussions.[105]

Patients with recurrent symptoms or life-threatening VA require emergent resuscitation, DCCV, along with discontinuation of their cancer therapy. For patients who are hemodynamically stable, a conservative approach can be taken with IV antiarrhythmics including amiodarone, lidocaine, or procainamide.[104]

For prevention of VA, beta-blockers are first-line therapy due to their safer adverse effect and drug interaction profile. Evidence suggests beta-blockers can suppress VA in patients with structurally normal heart, which is common in CTR-CVT.[104] Ablation can be considered for patients with recurrent VA when antiarrhythmics are ineffective or intolerable.[104]

Role of devices in cancer therapy-induced ventricular arrhythmias

Given improvement in prognosis and patient life-expectancy in cancer, ICDs could be a viable option when life expectancy is greater than 1 year.[47] In a study of patients with ICDs, Mazur and colleagues found similar survival rates amongst patients with AACM and ICM.[77] A study consisting of 149 cancer patients with ICDs implanted for secondary prevention found two-thirds of patients were alive at 3 years.[106]

Multicenter Automatic Defibrillator Implantation Trial-Chemotherapy-Induced Cardiomyopathy (MADIT-CHIC) is a trial which investigated cardiac resynchronization therapy (CRT) implantation for CTR-CVT. The trial reported that patients with CTR-CVT with ejection fraction (EF) $\leq$ 35% and QRS greater than 120 ms and on optimized guideline direct medical therapy had a significant benefit in left ventricular (LV) ejection fraction, LV end-systolic volume, and LV end-diastolic volume with CRT.[107]

It is vital to consider anatomic challenges in cancer patients who have undergone prior axillary lymph node dissections or concurrent central venous access.[108] It is also important to consider future needs for radiation therapy to areas where ICDs are typically implanted. In select cases, subcutaneous ICDs can be utilized when vascular access is difficult. Subcutaneous ICDs were noninferior to transvenous ICDs and associated with fewer infectious complications.[109] Subcutaneous ICD implantation could be a more desirable option for cancer patients given cancer's associated risk of TE and infection.

BRADYARRHYTHMIA AND BLOCKS

Introduction

Beyond tachyarrhythmias, cancer therapy-induced bradyarrhythmias and conduction disease (CD) also impact cancer therapy. The most induced bradyarrhythmia reported is sinus bradycardia (SB). Long-term ECG monitoring is often employed to detect bradyarrhythmias. Management is often conservative, but some patients may benefit from permanent pacemakers.

High-Risk Therapies

Ibrutinib has some evidence for bradyarrhythmia. A study reported that 50 out of 2000 patients on ibrutinib developed CD in form of atrioventricular block and bundle branch blocks, with a respective incidence of 1.6% and 0.7%.[110]

Thalidomide is used to treat myeloma with an incidence of symptomatic SB up to 19%.[111] These patients sometimes required pacemaker implantation, but typically recovered after thalidomide discontinuation.[111,112] Overall, there are numerous agents which can elicit bradycardia but the total burden of disease remains understudied.

ALK inhibitors are associated with bradyarrhythmias. These agents include the first generation crizotinib as well as the newer generation agents like alectinib, brigatinib, and lorlatinib.[113] Rate of sinus bradycardia for crizotinib was reported to be 11% to 15%.[114,115] Alectinib was originally reported to have a rate of sinus bradycardia of 6.6%.[114] However, 2 more recent studies demonstrated significantly higher incidence rates of 42% to 51%.[116,117] Brigatinib was associated with a similar rate of 8.8%, while ceritinib appeared to have the lowest rate of 2.3% to 3%.[114,118,119] Providers may need to consider ceritinib as the ALK inhibitor of choice in patients with low baseline heart rates.

Reports of taxane-associated sinus bradycardia have not been investigated in the modern era. In the early 1990s, asymptomatic sinus bradycardia was reported in 10.4% to 30% of patients; hence, patients did not require intervention.[120–122]

Total body radiation and chest radiation have been associated with bradycardia and conduction disease, demonstrated by 2 case series of 9 total patients.[123,124] Improvement in radiation targeting has made radiation-induced conduction disease rare. However, a recent study from 2022 showed a trend of breast cancer patients treated with radiotherapy more often required future pacemaker placement compared to those without radiation exposure (P=.09).[125]

Management of Cancer Therapy-Induced Bradyarrhythmias and Blocks

Prior to initiating cancer therapy, clinicians must perform baseline ECG and medication reconciliation to minimize risk of drug-induced bradyarrhythmias. Initial evaluation and management of bradycardia secondary to CTR-CVT is largely similar to general populations and cardiology should be involved early in care.[126]

For patients treated with ICIs who develop heart block, steroids may be indicated to address inflammation causing CD. Heart blocks can be the first manifestation of ICI myocarditis and a high index of suspicion should be given to patients who develop blocks on ICIs.[37] In a study amongst 42 patients with ICI myocarditis, 36% developed complete heart block.[127] Attention must be paid to PR intervals in patients on ICI therapy. If PR interval prolongs over 300 milliseconds, patients must be closely monitored, hospitalized, and initiated on IV steroids if there is concern for myocarditis.[47]

Management of symptomatic high-degree blocks or conduction delays centers around multidisciplinary discussion regarding discontinuation or dose reduction of cancer therapy alongside telemetry monitoring.[47] Furthermore, permanent pacemakers (PPM) can be considered in patients with Class I indication and life expectancy greater than 1 year.[108] Device implantation necessitates a multidisciplinary discussion to consider patient prognosis, anatomy, and burden of disease.[47] PPMs have been shown to provide benefit even in populations aged greater than 80 years, so discussion regarding cancer prognosis plays a vital role in shared decision-making.[128] Significant device (PPM or ICD)-related complications during radiotherapy are exceedingly rare, and should not exclude patients who would otherwise benefit.[129] Finally, if patients experience symptomatic bradycardia and no alternative chemotherapies are available, it is reasonable to consider PPM placement in context of a meaningful prognosis.[47] However, it is

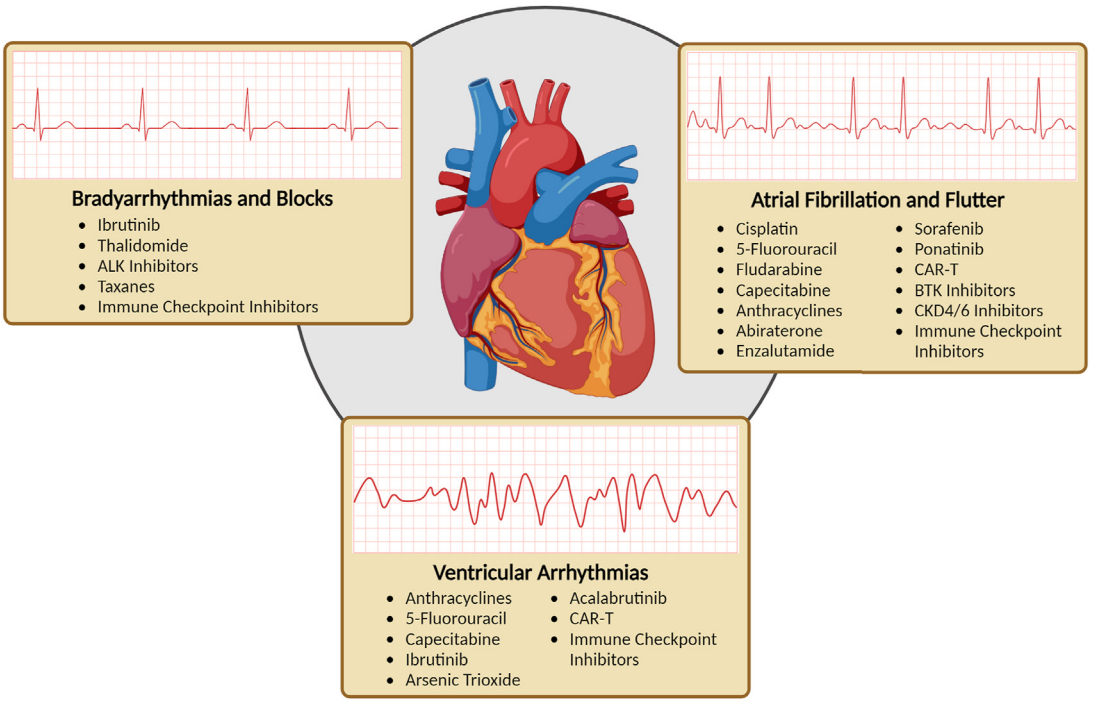

Fig. 1. High-risk arrhythmogenic anti-cancer therapies. (Created with BioRender.com.)

important for clinicians to be able to recognize as early as first-degree atrioventricular (AV) block in patients treated with ICIs, given the risk of transformation into fulminant myocarditis.

SUMMARY

In this review, we have discussed various arrhythmias induced by cancer therapies and their respective challenges and caveats to management (Fig. 1). Due to disease milieu, CTR-CVT, and therapy complications such as pancytopenia, these patients are at higher risk of both TE and bleeding with limited tools for risk stratification. Incidence and severity of arrhythmia depends on patient risk factors, comorbidities, baseline cardiac function, cancer staging, and cancer agents.

Currently, no studies exist evaluating the efficacy and safety of rhythm control agents in arrythmias induced by cancer therapies. This issue could be addressed with cohort studies of high-risk treatments such as ibrutinib. Furthermore, given the complexity of anticoagulation in cancer patients, studies on AC strategies could elucidate the safest option. Given the limited utility of CHA_2DS_2-VASc in cancer patients, the authors emphasize the need for a thromboembolic risk stratification score for oncology population should be developed. Finally, there are scarce studies on cancer survivors or while in remission and the long-term impact of arrythmias.

Anthracyclines, TKIs, and BTKi are among the cancer therapies most likely to cause arrhythmias. Clinicians must closely monitor patients on immunotherapy who develop arrhythmias with consideration of ICI-induced myocarditis. Device therapy should be considered in patients with life expectancy over a year and warrants a multidisciplinary discussion between patients and their providers.

CLINICS CARE POINTS

- Atrial fibrillation thought to be induced by cancer therapy should be treated with a rate control strategy. Beta-blockers are preferred when patients are hemodynamically stable.
- The choice for anticoagulation in atrial fibrillation must be tailored to individual patient scenarios. CHA_2DS_2-VASc and bleeding risk tools have limited evidence for use in cancer patient populations. Direct oral anticoagulants are preferred but warfarin can still be used.
- There is limited evidence for ventricular arrhythmias induced by cancer therapy. However, it is important to pay close attention to QTc and QRS intervals after starting cancer therapy.

- Device therapies including permanent pacemakers and implantable cardiac defibrillators can be utilized in cancer patients, but their use should be tailored to individual patient scenarios and prognosis.

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