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

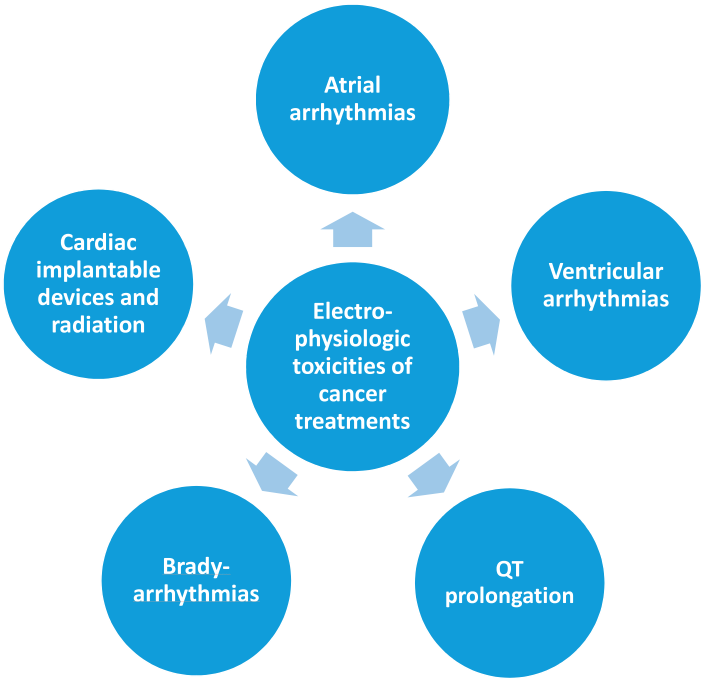

Figure 1.
Electrophysiologic toxicities of cancer treatments.

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.[7,8] 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 AF[11]; 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 Checkpoint inhibitors (pembrolizumab) Immunomodulatory agents (lenalidomide)	Atrial arrhythmias Atrial/ventricular arrhythmias, bradyarrhythmias Atrial arrhythmias	Inflammatory like from CRS Myocarditis/inflammatory 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] Nilotinib, sunitinib, vandetanib[40-42] Ibrutinib[43] ALK Inhibitors[44,45] (crizotinib)	Atrial arrhythmias QT prolongation Ventricular arrhythmias Bradyarrhythmias	PI3K pathway inhibition Impaired intracellular signaling leading to enhanced late sodium and decreased potassium currents Unknown 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.

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Dr. Fradley is a consultant for Novartis.

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

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin. 2018 Jan;68(1):7-30.

2. Buza V, Rajagopalan B, Curtis AB. Cancer Treatment-Induced Arrhythmias: Focus on Chemotherapy and Targeted Therapies. Circ Arrhythm Electrophysiol. 2017 Aug;10(8).

3. Mahmood SS, Fradley MG, Cohen JV, et al. Myocarditis in Patients Treated With Immune Checkpoint Inhibitors. J Am Coll Cardiol. 2018 Apr 24;71(16):1755-64.

4. January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol. 2019 Jul 9;74(1):104-32.

5. Tamargo J, Caballero R, Delpón E. Cancer chemotherapy and cardiac arrhythmias: a review. Drug Saf. 2015 Feb;38(2):129-52.

6. Feliz V, Saiyad S, Ramarao SM, Khan H, Leonelli F, Guglin M. Melphalan-induced supraventricular tachycardia: incidence and risk factors. Clin Cardiol. 2011 Jun;34(6):356-9.

7. Kilickap S, Barista I, Akgul E, Aytemir K, Aksoy S, Tekuzman G. Early and late arrhythmogenic effects of doxorubicin. South Med J. 2007 Mar;100(3):262-5.

8. Mazur M, Wang F, Hodge DO, et al. Burden of Cardiac Arrhythmias in Patients With Anthracycline-Related Cardiomyopathy. JACC Clin Electrophysiol. 2017 Feb;3(2):139-50.

9. Fradley MG, Viganego F, Kip K, et al. Rates and risk of arrhythmias in cancer survivors with chemotherapy-induced cardiomyopathy compared with patients with other cardiomyopathies. Open Heart. 2017 Dec 17;4(2):e000701.

10. Zellos L, Richards WG, Capalbo L, et al. A phase I study of extrapleural pneumonectomy and intracavitary intraoperative hyperthermic cisplatin with amifostine cytoprotection for malignant pleural mesothelioma. J Thorac Cardiovasc Surg. 2009 Feb;137(2):453-8.

11. Petrini I, Lencioni M, Ricasoli M, et al. Phase II trial of sorafenib in combination with 5-fluorouracil infusion in advanced hepatocellular carcinoma. Cancer Chemother Pharmacol. 2012 Mar;69(3):773-80.

12. Byrd JC, Brown JR, O'Brien S, et al.; RESONATE Investigators. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. N Engl J Med. 2014 Jul 17;371(3):213-23.

13. Fradley MG, Gliksman M, Emole J, et al. Rates and Risk of Atrial Arrhythmias in Patients Treated With Ibrutinib Compared With Cytotoxic Chemotherapy. Am J Cardiol. 2019 Aug 15;124(4):539-544.

14. Leong DP, Caron F, Hillis C, et al. The risk of atrial fibrillation with ibrutinib use: a systematic review and meta-analysis. Blood. 2016 Jul 7;128(1):138-40.

15. Wiczer TE, Levine LB, Brumbaugh J, et al. Cumulative incidence, risk factors, and management of atrial fibrillation in patients receiving ibrutinib. Blood Adv. 2017 Sep 8;1(20):1739-48.

16. Mato AR, Clasen S, Pickens P, et al. Left atrial abnormality (LAA) as a predictor of ibrutinib-associated atrial fibrillation in patients with chronic lymphocytic leukemia. Cancer Biol Ther. 2018 Jan 2;19(1):1-2.

17. McMullen JR, Boey EJ, Ooi JY, Seymour JF, Keating MJ, Tam CS. Ibrutinib increases the risk of atrial fibrillation, potentially through inhibition of cardiac PI3K-Akt signaling. Blood. 2014 Dec 11;124(25):3829-30.

18. Lee DH, Fradley MG. Cardiovascular Complications of Multiple Myeloma Treatment: Evaluation, Management, and Prevention. Curr Treat Options Cardiovasc Med. 2018 Mar 6;20(3):19.

19. Heinzerling L, Ott PA, Hodi FS, et al. Cardiotoxicity associated with CTLA4 and PD1 blocking immunotherapy. J Immunother Cancer. 2016 Aug 16;4:50.

20. Alvi RM, Mahmood S, Hassan MZO, et al. The cardiovascular effects of chimeric antigen receptor T-cells. J Am Coll Cardiol. 2019 Mar;73(9 Suppl 1):722.

21. January CT, Wann LS, Alpert JS, et al.; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol. 2014 Dec 2;64(21):e1-76.

22. D'Souza M, Carlson N, Fosbøl E, et al. CHA2DS2-VASc score and risk of thromboembolism and bleeding in patients with atrial fibrillation and recent cancer. Eur J Prev Cardiol. 2018 Apr;25(6):651-8.

23. Hu WS, Lin CL. Impact of atrial fibrillation on the development of ischemic stroke among cancer patients classified by CHA2DS2-VASc score-a nationwide cohort study. Oncotarget. 2018 Jan 10;9(7):7623-30.

24. Lip GY, Frison L, Halperin JL, Lane DA. Comparative validation of a novel risk score for predicting bleeding risk in anticoagulated patients with atrial fibrillation: the HAS-BLED (Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, Drugs/Alcohol Concomitantly) score. J Am Coll Cardiol. 2011 Jan 11;57(2):173-80.

25. Fradley M, Ellenberg K, Swanson J, et al. Patterns of anticoagulation use in cancer patients with atrial fibrillation and/or atrial flutter. J Am Coll Cardiol. 2019 Mar;73(9 Suppl 1):504.

26. Shah S, Norby FL, Datta YH, et al. Comparative effectiveness of direct oral anticoagulants and warfarin in patients with cancer and atrial fibrillation. Blood Adv. 2018 Feb 13;2(3):200-9.

27. Wang ML, Rule S, Martin P, et al. Targeting BTK with ibrutinib in relapsed or refractory mantle-cell lymphoma. N Engl J Med. 2013 Aug 8;369(6):507-16.

28. Ganatra S, Sharma A, Shah S, et al. Ibrutinib-Associated Atrial Fibrillation. JACC Clin Electrophysiol. 2018 Dec;4(12):1491-1500.

29. Fradley MG, Moslehi J. QT Prolongation and Oncology Drug Development. Card Electrophysiol Clin. 2015 Jun;7(2):341-55.

30. Naing A, Veasey-Rodrigues H, Hong DS, et al. Electrocardiograms (ECGs) in phase I anticancer drug development: the MD Anderson Cancer Center experience with 8518 ECGs. Ann Oncol. 2012 Nov;23(11):2960-3.

31. Lenihan DJ, Kowey PR. Overview and management of cardiac adverse events associated with tyrosine kinase inhibitors. Oncologist. 2013;18(8):900-8.

32. Roboz GJ, Ritchie EK, Carlin RF, et al. Prevalence, management, and clinical consequences of QT interval prolongation during treatment with arsenic trioxide. J Clin Oncol. 2014 Nov 20;32(33):3723-8.

33. US Food and Drug Administration [Internet]. Silver Spring, MD: US Food and Drug Administration, 2019. Warning: Differentiation syndrome and cardiac conduction abnormalities; 2019 [cited 2019 Jul 22]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/021248s015lbl.pdf.

34. National Comprehensive Cancer Network [Internet]. Plymouth Meeting, PA: National Comprehensive Cancer Network; 2019. Cancer-associated venous thromboembolic disease; 2018 Feb [cited 2019 Jul 22]. Available from: https://www.nccn.org/professionals/physician_gls/pdf/vte.pdf.

35. Infante JR, Cassier PA, Gerecitano JF, et al. A Phase I Study of the Cyclin-Dependent Kinase 4/6 Inhibitor Ribociclib (LEE011) in Patients with Advanced Solid Tumors and Lymphomas. Clin Cancer Res. 2016 Dec 1;22(23):5696-705.

36. Armanious MA, Mishra S, Fradley MG. Electrophysiologic Toxicity of Chemoradiation. Curr Oncol Rep. 2018 Apr 11;20(6):45.

37. Abdel-Rahman O. Toxicity patterns associated with chemotherapy/immune checkpoint inhibitor combinations: a meta-analysis. Immunotherapy. 2019 Apr;11(6):543-54.

38. Porta-Sánchez A, Gilbert C, Spears D, et al. Incidence, Diagnosis, and Management of QT Prolongation Induced by Cancer Therapies: A Systematic Review. J Am Heart Assoc. 2017 Dec 7;6(12).

39. Fradley MG, Pinilla-Ibarz J. Arrhythmic complications of tyrosine kinase inhibitors. Future Cardiol. 2015 Jul;11(4):395-9.

40. Kim TD, le Coutre P, Schwarz M, et al. Clinical cardiac safety profile of nilotinib. Haematologica. 2012 Jun;97(6):883-9.

41. Zang J, Wu S, Tang L, et al. Incidence and risk of QTc interval prolongation among cancer patients treated with vandetanib: a systematic review and meta-analysis. PLoS One. 2012;7(2):e30353.

42. Porta-Sánchez A, Gilbert C, Spears D, et al. Incidence, Diagnosis, and Management of QT Prolongation Induced by Cancer Therapies: A Systematic Review. J Am Heart Assoc. 2017 Dec 7;6(12).

43. Guha A, Derbala MH, Zhao Q, et al. Ventricular Arrhythmias Following Ibrutinib Initiation for Lymphoid Malignancies. J Am Coll Cardiol. 2018 Aug 7;72(6):697-8.

44. 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 Apr;5(4):617-22.

45. Zhang Z, Huang TQ, Nepliouev I, et al. Crizotinib Inhibits Hyperpolarization-activated Cyclic Nucleotide-Gated Channel 4 Activity. Cardiooncology. 2017;3.

46. McGuire WP, Rowinsky EK, Rosenshein NB, et al. Taxol: a unique antineoplastic agent with significant activity in advanced ovarian epithelial neoplasms. Ann Intern Med. 1989 Aug 15;111(4):273-9.

47. Arbuck SG, Strauss H, Rowinsky E, et al. A reassessment of cardiac toxicity associated with Taxol. J Natl Cancer Inst Monogr. 1993(15):117-30.

48. Johnson DB, Balko JM, Compton ML, et al. Fulminant Myocarditis with Combination Immune Checkpoint Blockade. N Engl J Med. 2016 Nov 3;375(18):1749-55.

49. Zaremba T, Jakobsen AR, Søgaard M, et al. Risk of device malfunction in cancer patients with implantable cardiac device undergoing radiotherapy: a population-based cohort study. Pacing Clin Electrophysiol. 2015 Mar;38(3):343-56.

50. Viganego F, Singh R, Fradley MG. Arrhythmias and Other Electrophysiology Issues in Cancer Patients Receiving Chemotherapy or Radiation. Curr Cardiol Rep. 2016 Jun;18(6):52.

51. Grant JD, Jensen GL, Tang C, et al. Radiotherapy-Induced Malfunction in Contemporary Cardiovascular Implantable Electronic Devices: Clinical Incidence and Predictors. JAMA Oncol. 2015 Aug;1(5):624-32.

52. Brambatti M, Mathew R, Strang B, et al. Management of patients with implantable cardioverter-defibrillators and pacemakers who require radiation therapy. Heart Rhythm. 2015 Oct;12(10):2148-54.