10-1-2022

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Abstract: Cancer therapy has made major progress in the past several decades, but treatments are often accompanied by significant side effects. Arrhythmias are a widespread complication of some antineoplastic drugs, with atrial fibrillation (AF) being the most often encountered drug-associated arrhythmia. Preexisting AF risk factors are commonly present in cancer patients who develop drug-associated AF, and active cancer itself may cause or promote AF. Although anticancer drugs may induce AF in cancer patients without AF risk factors, it appears that most drug-associated AF develop when cancer drugs add or aggravate precancer-existing and/or cancer-related pro-AF factors/alterations, additively or synergistically producing AF. Abnormalities in intracellular calcium activity seem to be involved in the generation of anticancer drug–induced AF. In cancer survivors with cancer therapy–induced cardiomyopathy, AF often occurs, with most of the arrhythmias likely to develop secondary to the cardiomyopathy. AF may lead to modification or even cessation of cancer therapy. The management of AF in patients with cancer is currently conducted largely based on pragmatic assumptions. This review briefly discusses AF caused by anticancer drugs and the underlying mechanisms.

Key Words: atrial fibrillation, cardio-oncology, arrhythmias, cancer therapy

(*J Cardiovasc Pharmacol*™ 2022;80:540–546)

INTRODUCTION

The treatment of patients with cancer has significantly improved in recent decades, largely due to the appearance of novel anticancer therapies and early diagnosis of cancer. However, these successful therapies are often accompanied with significant side effects. Cancer therapy–associated cardiovascular (CV) side effects, include cardiomyopathies, arrhythmias, myocarditis, hypotension, and cytokine release syndrome.[1–3] The growing number of patients with serious cancer therapy–related CV complications and a better recognition of these complications led to the appearance a novel subfield in medicine in 2000–2010, called cardio-oncology.[4] Cardio-oncology can be defined as investigation, diagnosis, prevention, monitoring, and treatment of CV diseases caused or aggravated by anticancer therapy.

The occurrence of atrial fibrillation (AF) in patients with cancer is significantly greater than that in those without cancer when adjusted to the other confounding factors.[5–9] A greater incidence of AF is reported for patients with active cancer and in patients with non–life-threatening cancer that do not require active therapy.[6,10] The risk of AF is highest during the first 3 months after cancer diagnosis.[5–7] In a Danish nationwide study, an increase in AF occurrence in cancer patients was observed for all major types of cancer, with lung cancer patients having the highest incidence.[6] Greater AF occurrence in cancer versus noncancer patients can be due to cancer therapy, cancer itself, and preexisting CV comorbidities.[1,2,11]

It has been increasingly reported in the past 2 decades that arrhythmias are a widespread complication of some antineoplastic drugs, with AF being the most often encountered proarrhythmia.[1,3,11–14] Data on anticancer drug-associated AF is scarce, largely coming from small, nonrandomized, and uncontrolled studies, with little or no information on AF occurrence before cancer treatment. The absence or insufficient amount of information on AF occurrence in cancer patients before treatment is a critical problem when estimating drug-induced AF incidence. Not only may cancer patients have a precancer AF history (reported in up to 13% of the patients[9,15]) but also active cancer itself appears capable of AF induction.[1,2,11] Many of the drug-related AF cases in cancer patients are associated with the use of multiple anticancer agents (applied simultaneously or consequently) and with the use of the drugs following surgery,[16–19] adding to the uncertainties of AF incidence and causality. Pharmacodynamic drug-to-drug interactions may play some role in AF generation in patients with cancer, but this issue has been poorly investigated.[20] Postoperative AF frequently occurs following oncological surgeries (particularly thoracic surgeries).[5,21] Such AF, however, is usually transient, appearing and disappearing within days after the surgery.[21]

AF in cancer patients may increase morbidity and mortality and also result in modifying or even halting cancer medication.[1,2,14] The management of patients with cancer and AF is poorly defined. It is assumed that AF in these patients should be generally managed similarly to that in noncancer patients.[1,2] The prime aim of the review is to discuss the

Received for publication September 30, 2021; accepted November 11, 2021.
From the *Lankenau Institute for Medical Research, Wynnewood, PA; and †Sidney Kimmel College of Medicine, Thomas Jefferson University, Philadelphia, PA.
W.W. Smith Charitable Trust.
The author reports no conflicts of interest.
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occurrence and mechanisms of AF associated with anticancer drugs.

AF ASSOCIATED WITH CHEMOTHERAPY

Chemotherapy is a mainstay treatment for many types of cancer, such as breast cancer, leukemias, lymphomas, and multiple myeloma. Although chemotherapeutic agents predominantly destroy rapidly dividing cancerous cells, they can damage noncancerous tissues as well, including the heart. The fact that chemotherapy can cause AF in cancer patients during treatment was widely recognized in the first decade of the 21st century.[11,12,22–24] AF is reported to occur in up to 10% of patients during treatment with anthracyclines.[3,11,12,25] The use of cisplatin was associated with AF in 12%–32% of cancer patients,[3,12,23] with the highest AF incidence reported following intrapericardial infusion of cisplatin.[23] Melphalan is reported to be associated with AF in 7%–22% of the patients with cancer.[12,22,24,26] Melphalan is applied as a preconditioning treatment before bone marrow transplantation in patients with multiple myeloma.[1] Bone marrow transplantation alone does not appear to cause AF.[11] In multiple studies, AF was recorded in 0%–1.3% of cancer patients during treatment with 5-fluorouracil (5-FU).[27] Use of capecitabine for treating breast cancer was associated with AF in 1.1% of patients (5 of 452).[28]

Anthracyclines may cause or contribute to new-onset AF months after the end of the therapy. In a prospective observational study involving 249 non-Hodgkin's lymphoma patients treated with anthracyclines, cumulatively, 15 patients (6%) developed new-onset AF during a mean follow-up of 34 months (ECG recordings were obtained monthly).[29] The first AF case was detected 7 months after the start of anthracycline treatment.[29]

Among the chemotherapy agents, it is anthracyclines that most often cause cardiomyopathy. Anthracycline-induced cardiomyopathy usually develops years after anthracycline therapy, and such cardiomyopathy is likely to be a critical causal factor of AF in cancer survivors. It was reported that cancer survivors with anthracyclines-mediated and nonanthracyclines-mediated cardiomyopathy had a high prevalence of AF (56.5% and 53.1%, respectively).[30]

AF ASSOCIATED WITH TYROSINE KINASE INHIBITORS (TKIs)

B-cell receptor activity is vital for the proliferation of malignant B cells, and Bruton's tyrosine kinase (BTK) is an essential enzyme in the B-cell receptor signaling pathway. The introduction of ibrutinib, a BTK inhibitor, in 2013 revolutionized the management of patients with B-cell-related cancer types, such as chronic lymphocytic leukemia and mantle cell lymphoma,[31] but AF has been observed in 6%–38% of patients treated with ibrutinib.[2,3,32,33] The relative risk of developing AF following ibrutinib administration is reported at 3.9–15.0.[33–36] Ibrutinib has been the most prominent anticancer agent inducing AF.[2,32,33,37]

The second-in-class BTK inhibitor acalabrutinib was clinically approved for the treatment of refractory or relapsed mantle cell lymphoma in 2017, with a warning risk for the development of AF or atrial flutter (https://www.calquence.com). AF was observed in 7% of patients (10/134) with relapsed/refractory lymphocytic leukemia treated with acalabrutinib for a median of 41 months.[38] It appears that acalabrutinib induces AF but is less likely to do so than ibrutinib. In a randomized controlled trial comparing zanubrutinib (a novel BTK inhibitor) with ibrutinib, AF was observed in 2% and 15% of cancer patients (2/100 and 15/98), respectively.[36]

Approximately 95% of patients with chronic myeloid leukemia (CML) have a chromosomal abnormality (Philadelphia chromosome), resulting in the chimeric fused oncogene BCR-ABL. BCR-ABL tyrosine kinase is critically involved in the generation of CML, and inhibition of this kinase causes a curative effect. Among the prominent BCR-ABL TKIs, ponatinib appears to be associated with AF induction. In a randomized open-label study, AF was recorded in 1.5% (3/155) of CML patients given ponatinib.[39] The Food and Drug Administration package insert indicates that the incidence of atrial tachyarrhythmias with ponatinib is 5%, with most cases being AF.

Angiogenesis is essential for the growth and spread of cancerous tissue, and vascular endothelial growth factor (VEGF) is critical for angiogenesis. Inhibition of VEGF pathway with TKI blockers is effective in the treatment of colorectal cancer, metastatic renal cell carcinoma, and the like. In one study, when sorafenib was combined with 5-FU, AF was observed in 5.1% of patients (2/39) with advanced hepatocellular carcinoma.[16] Limited available data indicate that, when used alone, VEGF pathway inhibitors do not or rarely induce AF.

AF ASSOCIATED WITH PROTEASOME INHIBITORS

Proteasome inhibitors (carfilzomib and bortezomib) stimulate the activation of programmed cell death in cancer cells (via preventing the degradation of proapoptotic factors). In a retrospective study, atrial arrhythmias (AF and atrial tachycardia) were recorded in 7% of multiple myeloma patients treated with carfilzomib (9/130).[40] In a case-controlled study, AF/atrial flutter incidence was greater with proteasome inhibitors versus controls (14% [3/21] vs. 3% [2/75] patients, respectively).[41]

AF ASSOCIATED WITH HER2-TARGETED DRUGS

Overexpression of the human epidermal growth factor receptor 2 [HER2] is significantly involved in the development and progression of tumors in 15%–30% of patients with breast cancer. Some patients with gastric and colon cancer also have HER2 abnormalities. Inhibition of HER2 with trastuzumab (the first clinically approved HER2-targeted monoclonal antibody) considerably improved the outcomes of breast cancer patients with HER2 overexpression. The use of trastuzumab, often adjuvant to anthracyclines, has rarely been associated with AF (in a meta-analysis of 15 studies; only 37 of 8124 patients [0.46%] treated with trastuzumab were recorded with AF).[42] Of note, trastuzumab is often

avoided in cancer patients with significant cardiac diseases (trastuzumab may cause or augment cardiomyopathy, particularly in adjuvant treatment to anthracyclines). When trastuzumab was applied in patients with nonlimited cardiac comorbidity (adjuvant to anthracycline- and taxane-based regimens), AF was recorded in 19% of patients (7/37).[17]

AF ASSOCIATED WITH IMMUNOTHERAPY

The prime purpose of immunotherapy in cancer patients is to enhance or revive the ability of the immune system to recognize and destroy cancerous tissues. Developed cancer tumor is capable of escaping native immunity. The first immunotherapy used for anticancer treatment explored the property of interleukin-2 (IL-2) to promote the expansion of T cells (1980–1990).[43] The treatment of metastatic melanoma and renal cancer with IL-2 (aldesleukin) translated to sustainable antitumor outcomes,[43] but it was associated with AF in 4.3%–8% of treated patients,[44,45] among other side effects. Lenalidomide, a multifactorial immunomodulatory agent, is approved to treat multiple myeloma and myelodysplastic syndrome (in combination with dexamethasone). In 2 randomized and double-blinded studies, AF incidence was 2.6% versus 0.6% (9/346 vs. 2/342) in patients treated with lenalidomide plus dexamethasone versus placebo plus dexamethasone, respectively.[19]

Currently, the most prominent type of anticancer immunotherapy is immune checkpoint inhibitors (ICIs), which are used to treat melanoma, breast cancer, colon cancer, and the like. ICIs are monoclonal antibodies, and they target 3 checkpoints: cytotoxic T-lymphocyte–associated antigen-4 (CTLA-4), and programmed death receptor 1 (PD-1) and its ligand (PD-L1). These checkpoints are critical for self-tolerance, reducing the probability of autoimmune reactions. In the case of cancer, the checkpoints usually function properly, allowing the activation of cytotoxic T cells to result in the destruction of cancerous tissue. However, the cancer environment may modify the checkpoints in a way that reduces the activation of cytotoxic T cells, resulting in more efficient survival, growth, and spread of malignant tumors. ICIs increase the probability of proper activation of the cytotoxic T cells targeting cancer, at the expense of certain side effects. CV complications of ICI treatments are reported to occur in 1%–5% patients and include myocarditis, pericarditis, vasculitis, and arrhythmias.[46] Among patients who experience ICI-related CV cardiotoxicity, the incidence of AF was reported to be 30% in one study (9/30 patients).[47] Analyzing and comparing CV adverse case events in patients who received ICIs (n = 31,321) with those who received all other drugs (n = 16,346,451) in VigiBase, the World Health Organization's (WHO) global database of individual case safety reports, Salem et al found that atrial arrhythmias were encountered significantly more often with ICI application (in 0.71% vs. 0.42% patients, respectively).[48] Considering that ICI-induced cardiotoxicity occurs in 1%–5% patients,[46] the occurrence of ICI-associated AF seems relatively low.

Another type of immunotherapy is adoptive cell transfer (ACT), which uses genetically modified T cells derived from the patients. Chimeric antigen receptor T cell (CAR-T) therapy, a subtype of ACT, significantly improved the treatment of hematological B-cell-related cancer, targeting B-cell-specific CD19 that is overexpressed in B-cell malignancies. Frequent adverse effects of CAR-T therapy are cytokine release syndrome, hypertension, and neurotoxicity. In one study, new-onset AF was recorded in 7.5% of hematological cancer patients treated with CAR-T (11/145).[49] In another study, 3% of patients with hematological cancer patients (5/137) who received CAR-T developed de novo atrial arrhythmias (3 AF or atrial flutter and 2 atrial tachycardia).[15] AF was detected in 14% of patients (6/43) with advanced stage metastatic melanoma treated with ACT with tumor-infiltrating lymphocytes (TIL).[50] An AF history was recorded only in 1 of 6 patients who developed AF.[50]

THE OTHER ANTICANCER DRUGS AND AF

Only a portion of anticancer drugs have been associated with the induction of AF (Table 1). Analyzing the reporting frequency of individual cases of AF associated with anticancer drugs in the WHO case safety report database, Alexandre et al[37] identified that 19 of 176 anticancer drugs were significantly associated with AF.

There are many anticancer agents, used alone or in combination, that have been associated with AF in case reports and small or uncontrolled studies (such as cyclophosphamide, sunitinib, paclitaxel, imatinib, nilotinib, lapatinib, pembrolizumab, and sorafenib + 5-FU),[16] making the estimation of AF induction by these agents uncertain. The application of gemcitabine (an antimetabolite) and vemurafenib (a BRAF kinase inhibitor) may be associated with AF induction (as indicated in some reviews[1,3,13]), but the supporting published evidence does not seem to be apparent. The use of gemcitabine in elderly patients with lung cancer was associated with AF in combination with vinorelbine (an alkaloid) but not when applied alone (in 4/49 and 0/49 patients, respectively).[51] In a study testing the safety of vemurafenib in 3226 patients with melanoma having the BRAF V600E mutation, AF was not reported among the side effects.[52]

It is important to recognize that many cancer treatment studies exclude patients with significant CV diseases, avoiding potential side effects and thereby reducing the potential for AF induction by cancer drugs. CV diseases are common in patients with cancer, and some "no AF" anticancer agents may potentially cause AF if used in cancer patients with significant CV diseases.

MECHANISMS OF CANCER THERAPY–INDUCED AF

Cancer therapy induces AF by altering AF-sensitive atrial electrophysiological parameters, directly, indirectly, or both. For a better understanding of cancer therapy–induced AF, it is worth briefly reviewing the mechanisms underlying AF and prime electrophysiological factors related to AF.[53] AF can be generated by abnormalities in impulse formation (ie, focal activity) and electrical conduction (ie, reentry). AF is initiated by focal sources, and the arrhythmia can be maintained by reentrant and focal activities.[53,54] Until recently, it

TABLE 1. Anticancer Agents Associated With AF in Patients With Cancer

Anticancer Agents		Atrial Fibrillation		Cancer Use	Refs
		Active Cancer	Cancer Survivors		
Chemotherapy: anthracyclines	Doxorubicin	++	++*	Breast, sarcoma, lung, bladder, gastric, prostate, leukemia, lymphoma	1,12
Chemotherapy: alkylating agents	Melphalan	++	NA	Multiple myeloma, ovarian, neuroblastoma, SCT	1,12
Chemotherapy: platinum-based agents	Cisplatin	++	NA	Lung, bladder, testicular, breast, esophageal, heard and neck	1,12
Tyrosine kinase inhibitors	Ibrutinib	+++	+†	CCL, SLL, MCL, WM, cGVHD	33–35
	Acalabrutinib	+	NA	CCL, SLL	38,‡
	Ponatinib	+	NA	CML, Ph^+ ALL	39
Proteasome inhibitors	Carfilzomib	+	NA	Multiple myeloma	40,41
	Bortezomib	+	NA	Multiple myeloma	41
Antimetabolites	5-fluorouracil	+	NA	Colon, pancreatic, breast, HNC	27
	Capecitabine	+	NA	Breast, colon, gastric, pancreatic	28
HER2 blockers	Trastuzumab§	+	NA	Breast	17
ICI therapy	Ipilimumab, Nivolumab, pembrolizumab	+	NA	Melanoma, lung, kidney, bladder, HNC, lymphoma	1
ACT therapy	Tisagenlecleucel, Axicabtagene ciloleucel	+	NA	B-cell acute lymphoblastic leukemia, large B-cell lymphoma	1
	ACT-TIL	+	NA	Melanoma	50
Immuno-modulatory agents	Lenalidomide	+	NA	Myelodysplastic syndrome, multiple myeloma, MCL	1,19,37
	Aldesleukin (IL-2)	+	NA	Melanoma, renal cell carcinoma	44,45

*Secondary to cancer therapy–induced cardiomyopathy.
†Ibrutinib treatment is typically indefinite and may cause AF months or years after the end of active cancer symptoms.
§Seems to occur largely in patients with preexisting cardiac abnormalities.
‡https://www.calquence.com.
ACT-TIL, adoptive cell transfer with tumor infiltrated lymphocytes; CML, chronic myeloid leukemia; CCL, chronic lymphocytic leukemia; cGVHD, chronic graft versus host disease; HNC, head and neck cancer; ICI, immune checkpoint inhibitor; MCL, mantle cell lymphoma; NA, not available; SCT, stem cell transplant; SLL, Small lymphocytic lymphoma; WM, Waldenstrom's macroglobulinemia; Ph+, ALL—Philadelphia chromosome-positive acute lymphoblastic leukemia.

was strongly believed that AF was primarily maintained by a reentrant mechanism. However, with the improvement of mapping technologies, increasingly more researchers either record reentry only sporadically and short-lived or not record it at all (for review[55]). Moreover, most of those who consistently record reentries during AF use the phase-mapping approach for reentry detection that, as recently reported, has a low specificity for identifying reentry.[56] It seems the role of reentry in the maintenance of AF is overestimated and focal source(s) may play the leading role.[55]

Rapid focal sources are usually associated with intracellular calcium (Ca_i^{2+}) abnormalities.[53] Pharmacological agents causing an augmentation of Ca_i^{2+} (such as isoproterenol) are known to acutely induce or promote AF.[57] Among the anticancer agents inducing AF, only doxorubicin and ibrutinib have been tested for their effect on Ca_i^{2+}, and both have been found to produce abnormalities in cardiac Ca_i^{2+} (as discussed later).[58,59] Reentrant activities are caused by disturbances in electrical propagation of excitation.[53,54] It has not been determined if anticancer drugs inducing AF inhibit the sodium channel (thereby producing conduction abnormalities). Yet even if they do, it does not seem to be relevant to AF caused by drugs because sodium channel blockers typically prevent or terminate AF and do not or very rarely cause AF de novo.[55,60] Theoretically, conduction abnormalities secondary to the induction or aggravation of atrial structural remodeling by anticancer drugs may cause or promote AF (assuming that such conduction abnormities are more arrhythmogenic than those caused by sodium channel inhibition). Still, if it is the case, drug-induced significant atrial structural remodeling is expected to develop weeks or months after the start of treatment, and, thus, it may be relevant to AF occurring at that time but not to AF occurring within several days of treatment. Also note that although there is a strong association between atrial structural remodeling and AF vulnerability, it is unclear if atrial structural remodeling plays a causative or mediating role in AF generation.[61] Shortening of atrial effective refractory period (ERP) is a sensitive marker of atrial vulnerability to AF,[54,55] and pharmacological agents shortening atrial ERP readily promote AF (such as adenosine, acetylcholine, etc).[55,60] It is unknown if anticancer drugs associated with AF abbreviate atrial ERP.

Ibrutinib is the most prominent anticancer drug inducing AF.[33,35,37] There are several experimental studies that specifically investigated the underlying mechanisms. In neonatal rat myocytes, phosphoinositide 3-kinase (PI3K) signaling is reduced by acute application of ibrutinib, and this effect has been proposed to contribute to the pro-AF effect of

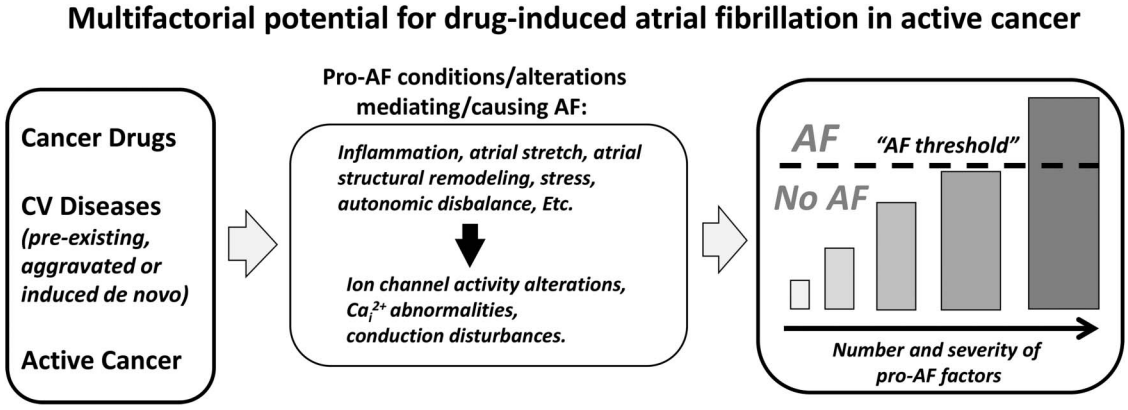

FIGURE 1. The more pro-AF factors and the greater their severity, the higher potential for initiation and perpetuation of drug-associated AF. Patients with active cancer who develop drug-associated AF commonly have overlapping conditions promoting AF: anticancer drugs, cancer itself, and cardiovascular (CV) diseases (preexisting, aggravated, or induced de novo). These conditions (separately or in a combination) may translate (directly or indirectly) to pro-AF electrophysiological alterations in the atrium, causing AF. Most drug-associated AF in patients with active cancer appear to develop when cancer drugs add or aggravate preexisting and/or cancer-related pro-AF factors, additively and synergistically reaching "AF threshold.".

ibrutinib.[62] PI3K regulates several ion channels (including the sodium, potassium, and calcium channels)[63] that, theoretically, may account for pro-AF effect of ibrutinib. However, inhibition of PI3K is linked to the prolongation of cardiac repolarization[63] that is typically anti-AF not pro-AF,[55] and the use of PI3K inhibitors has not been associated with AF,[64] questioning the validity of the "PI3K hypothesis". Of note, ibrutinib-mediated AF commonly appears in several months after the start of the therapy, suggesting that the pro-AF effect of ibrutinib in cancer patients is due to chronic rather than acute effect of the drug. It was shown recently that a 4-week treatment of mice with ibrutinib resulted to a high AF inducibility, left atrial enlargement, cardiac fibrosis, and myocardial inflammation. All were accompanied with the inhibition of the C-terminal of Src kinase. Moreover, cardiac-specific knockout of this kinase in mice led to AF, left atrial enlargement, fibrosis, and inflammation.[65] These data suggest that pro-AF effect of ibrutinib is mediated by the inhibition of the C-terminal of Src kinase. In another study, AF induced by 4-week treatment of ibrutinib in mice was associated with atrial structural remodeling and abnormalities in Ca_i^{2+}.[58]

The mechanisms of AF induced by the other anticancer drugs have been not or much less investigated. Anthracyclines can induce AF during the treatment,[12,22–24] which may be related to a direct induction of abnormalities in atrial Ca_i^{2+} (acute doxorubicin impairs Ca_i^{2+} in cardiac myocytes[59]). Cancer survivors having anthracycline-induced cardiomyopathy often develop AF. This arrhythmia is likely to be commonly mediated by the cardiomyopathy.[1–3] It seems that immunotherapy agents that cause AF do so secondary to pro-AF complications. New-onset AF in patients treated with CAR-T and ICI therapies is strongly associated with adverse effects (such as cytokine release syndrome[15,49] and myocarditis[48]).

Cancer may contribute to drug-induced AF or even cause AF itself.[11,21] Active cancer is associated with a number of pro-AF factors, such as systemic inflammation, electrolyte and endocrine abnormalities, and stress.[11,21] Among these factors, inflammation is believed to be the most prominent pro-AF factor.[21] Inflammation may induce or promote AF by altering electrophysiological parameters of the atria directly (via dysregulation of Ca_i^{2+} handling or via alteration of ion channel function) and/or indirectly (via atrial structural remodeling causing conduction disturbances).[66]

Cancer patients who develop drug-associated AF commonly have some preexisting AF risk factors (CV diseases, AF history, etc).[11,13] Cancer agents themself may induce or aggravate pro-AF complications (such as hypertension).[1,3,11] Although anticancer drugs may cause AF in cancer patients without AF risk factors,[11,13] it seems that most of the drug-associated AF occurring in the course of treatment develops when cancer drugs add or exacerbate precancer-existing and/or cancer-related pro-AF factors/alterations, reaching an "AF threshold" (Fig. 1). The risk factors for AF associated with cancer drugs can be CV abnormalities (hypertension, cardiomyopathy, etc), advanced age, history of AF, stress, dosages of drugs, concomitant or prior application of other medications or therapies, and the like. These diseases and conditions may translate (directly or indirectly via mediators, such as inflammation and atrial stretch) to pro-AF electrophysiological alterations in the atrium (such as abnormalities in atrial Ca_i^{2+}), leading to AF generation (Fig. 1). Notably, the greatest incidence of AF in patients with cancer takes place during the first several months after cancer diagnosis,[5,7] that is, when the intensity of anticancer therapy and potency of pro-AF cancer-associated alterations (such as inflammation, stress, etc) are at a maximum. Thus, mechanisms of AF generation by anticancer agents are poorly investigated. Alterations in atrial Ca_i^{2+} seem to be involved in drug-induced AF. The participation of conduction disturbances in the generation of cancer drug-induced AF is uncertain. If drug-induced AF is caused by conduction abnormalities, they are likely secondary to atrial structural

remodeling and not to direct inhibition of the sodium channel, with the related AF occurring weeks or months and not days after the start of treatment. It is important to study the effect of anticancer agents on atrial ERP and Ca_i^{2+}, which appear to be the most relevant parameters for the estimation of drug-induced AF.

MANAGEMENT OF PATIENTS WITH CANCER AND AF

It is known that AF increases morbidity and mortality in cancer and noncancer patients (largely due to the induction of thromboembolism and heart failure),[29,67] but the adverse impact of AF and management of AF in cancer patients are much less understood than in noncancer population.[1–3] Among the particular concerns are that both AF and cancer increase the risk of thromboembolism; cancer itself increases the risk of bleeding, and some anticancer medications may increase the risk of thromboembolism or bleeding (such as ibrutinib, ponatinib, and lenalidomide).[2,3] It is well recognized that there is a major challenge in the risk stratification for thromboembolism and bleeding in patients with cancer and AF.[1,2] Note, although cancer promotes arterial thromboembolism less prominently than venous thromboembolism, the risk of the former is about double in the first 6 months after cancer diagnosis.[68]

If cancer may alter the choice of rate and rhythm control, anticoagulation strategy, cardioversion and ablation of AF, and appendage occlusion are poorly understood.[1] There is little or no solid data-based guidelines for the management of AF in patients with cancer. It is pragmatically assumed that the management of AF should generally be similar for cancer and noncancer patients, with some important adjustments for cancer patients.[1,2] The most recent recommendations for the management of patients with cancer and AF are detailed in the American Heart Association statement (2021).[1]

ACKNOWLEDGMENTS

The author is grateful to Larry Hanover for editorial assistance.

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