Anticancer Drug-Related Nonvalvular Atrial Fibrillation: Challenges in Management and Antithrombotic Strategies

Antonella Tufano, MD, PhD[1] Maurizio Galderisi, MD[2] Luca Esposito, MD[2] Valentina Trimarco, PhD[3] Daniela Sorriento, MD[2] Guy Gerusalem, MD, PhD[4] Marco Picardi, MD[1] Patrizio Lancellotti, MD[5,6] Fabrizio Pane, MD[1]

[1] Dipartimento di Medicina Clinica e Chirurgia, Università Federico II, Napoli, Italy
[2] Dipartimento di Scienze Biomediche Avanzate, Università Federico II, Napoli, Italy
[3] Dipartimento di Neuroscienze e Scienze Riproduttive ed Odontostomatologiche, Università Federico II, Napoli, Italy
[4] Department of Medical Oncology, CHU Sart Tilman Liège and Liège University, Liège, Belgium

Address for correspondence Antonella Tufano, MD, PhD, Department of Clinical Medicine and Surgery, Regional Reference Centre for Coagulation Disorders, Federico II University Hospital, Via S. Pansini, 5. 80131 Naples, Italy (e-mail: atufano@unina.it).

[5] University of Liège Hospital, GIGA Cardiovascular Sciences, Department of Cardiology, Heart Valve Clinic, CHU Sart Tilman, Liège, Belgium
[6] Gruppo Villa Maria Care and Research, Anthea, Hospital, Bari, Italy

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Abstract

Cancer patients may experience nonvalvular atrial fibrillation (AF) as a manifestation of cardiotoxicity. AF may be a direct effect of a neoplasm or, more often, appear as a postsurgical complication, especially after thoracic surgery. AF may also develop as a consequence of anticancer therapy (chemotherapy or radiotherapy), a condition probably underestimated. Cancer patients with AF require a multidisciplinary approach involving oncologists/hematologists, cardiologists, and coagulation experts. An echocardiogram should be performed to detect possible abnormalities of left ventricular systolic and diastolic function, as well as left atrial dilation and the existence of valvular heart disease, to determine pretest probability of sinus rhythm restoration, and identify the best treatment. The choice of antiarrhythmic treatment in cancer patients may be difficult because scanty information is available on the interactions between anticancer agents and antiarrhythmic drugs. A careful evaluation of the antithrombotic strategy with the best efficacy/safety ratio is always needed. The use of vitamin K antagonists (VKAs) may be problematic because of the unpredictable therapeutic response and high bleeding risk in patients with active cancer who are undergoing chemotherapy and who may experience thrombocytopenia and changes in renal or hepatic function. Low molecular weight heparins (in particular for short and intermediate periods) and non-VKA oral anticoagulants (NOACs) should be preferred. However, the possible pharmacological interactions of NOACs with both anticancer and antiarrhythmic drugs should be considered. Based on all these considerations, antiarrhythmic and anticoagulant therapy for AF should be tailored individually for each patient.

Keywords
- atrial fibrillation
- cancer
- drug interaction
- stroke
- anticoagulants

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Atrial fibrillation (AF), the most frequent sustained supraventricular arrhythmia, affects approximately 1.5 to 2% of the general population. Its rate increases with aging, involving up to 18% of the population over 85 years of age.[1] Patients experiencing AF represent a group at higher cardiovascular risk, as they have a fivefold increased risk of ischemic stroke, a threefold increased risk of heart failure, and a twofold mortality rate.[1] Predisposing factors for AF include arterial systemic hypertension, coronary artery disease, valvular heart disease, mitral regurgitation, heart failure, and primary cardiomyopathies, but also extracardiac disorders such as chronic obstructive pulmonary disease, sleep apnea syndrome, thyroid dysfunction, electrolyte imbalances, and chronic kidney disease.[1]

Cancer patients may experience a wide spectrum of arrhythmias, including nonvalvular AF.[2,3] Data on the prevalence of AF in this setting are limited. In a large epidemiological study ($n = 24{,}125$), 2.4% of patients were already affected by AF at the time of cancer diagnosis and 1.8% developed new-onset AF during cancer treatment.[4] In this study, cancer patients with AF had a twofold increased risk of thromboembolic events and a sixfold higher risk of heart failure, even after adjustment for common cardiovascular risk factors (hazard ratios: 1.98 and 6.3, respectively).[4]

Although AF may be a preexisting disease before cancer diagnosis (long-lasting persistent AF according to European Society of Cardiology [ESC] guidelines),[1] multiple causes can induce paroxysmal, persistent, or permanent AF in cancer patients.[5] AF may be due to a direct effect of a neoplasm (intracardiac localization or extracardiac compression), or, more often, appear as a postsurgical complication, especially during/after thoracic surgery (for lung, esophageal cancer) or abdominal surgery for colon cancer.[5] AF may also develop during or after anticancer treatments (chemotherapy and radiotherapy), a condition probably underestimated, since data on drug-induced AF mainly derive from individual reports, and comprehensive data on the real prevalence of new-onset AF induced by antineoplastic drugs are still scanty.[3,6,7]

AF adds a severe burden to cancer patients in terms of clinical management and prognosis.[4,8] The anticoagulation of cancer patients experiencing AF represents an additional problem because of the need to balance thromboembolic and bleeding risk. These two risks are both inherently increased in relation with the neoplasm itself and the effect of anticancer treatments. A 2016 ESC position paper on anticancer treatments and cardiovascular toxicity has recently underlined the difficult management of cancer patients experiencing AF.[3]

This narrative review was designed to deal with anticancer drug-related AF and the intrinsic mechanisms underlying AF and provide information and suggestions on antiarrhythmic and antithrombotic management.

Our search on PubMed was performed by matching "atrial fibrillation" with "anti-cancer drugs" or "anti-cancer therapy" in general but also with "chemotherapies," "chemotherapeutics," "inhibitors of tyrosin kinase," "cytokines," and "monocolonal antibodies" and also searching "interaction" of the specific anti-cancer drugs with "anti-arrhythmic drugs" and "vitamin K antagonist oral anticoagulants," "non-vitamin K antagonist oral anticoagulants, "oral anticoagulants," "direct oral anticoagulants," "DOACs," and "NOACs."

General Mechanisms of Anticancer Drug-Induced Atrial Fibrillation

Anticancer drugs may induce AF through multiple mechanisms (►**Fig. 1**). The most common underlying factors include release of proinflammatory cytokines, abnormalities in calcium homeostasis, and direct myocardial damage.[9] For instance, anthracyclines reduce the antioxidant effect of cardiomyocytes interfering with catalase activity and glutathione-peroxidase.[6,7] Also, the increase in vagal and adrenergic tones, often due to hypotension, myocardial ischemia, and abnormal

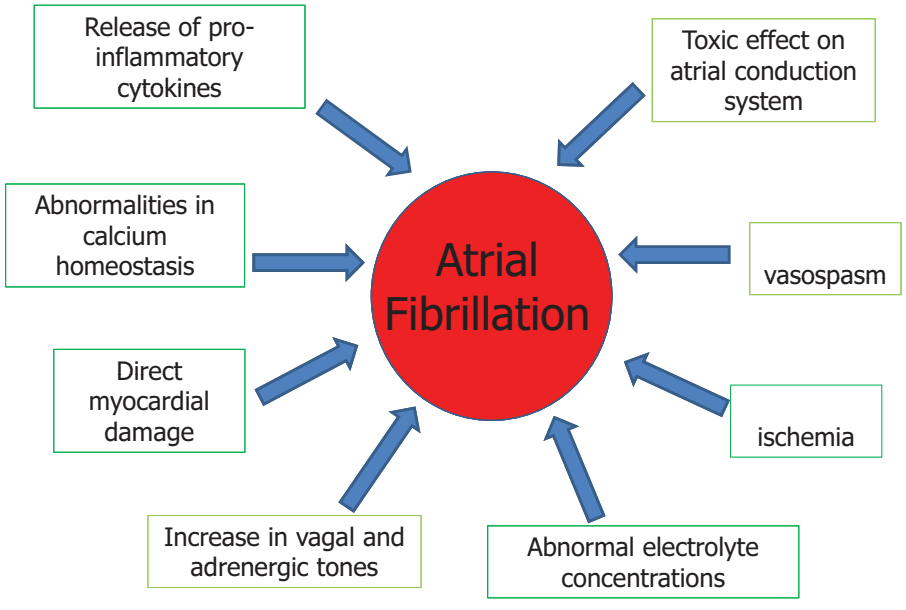

Fig. 1 Mechanisms underlying anticancer drugs induced atrial fibrillation.

electrolyte concentrations, may be involved, especially when using alkylating agents, anthracyclines, antimetabolites, docetaxel, 5-fluorouracil, gemcitabine, rituximab, paclitaxel, alemtuzumab, and etanercept.[9] Additional arrhythmogenic substrates include coronary vasospasm, through inhibition of endothelial nitric oxide synthesis and generation of reactive oxygen species mediating oxidative damage on the vessel wall, and a direct cardiotoxic effect on the atrial conduction system.[9] All these effects are combined with a systemic proinflammatory state, which is typical of malignancies.[10] AF associates with increased levels of C-reactive protein, suggesting a key role of an inflammatory state in AF development/maintenance. Inflammatory mediators exert detrimental effects on atrial structural substrates, modulating calcium homeostasis and connexins that trigger AF, activate fibrotic pathways, and contribute to atrial remodeling.[10]

Associations of Cancer Drugs with Atrial Fibrillation

►**Table 1** summarizes the list of the main anticancer drugs responsible for AF. The association of anthracyclines, cisplatin, melphalan, 5-fluorouracil, and capecitabine with AF is well known.[6] Anthracyclines (doxorubicin)[11,12] and alkylating agents,[13–19] in particular cisplatin (largely used in lung adenocarcinoma and mesothelioma), are the anticancer drugs mostly associated with AF onset. Of note, intrapericardial cisplatin administration after pericardiocentesis, administered to patients with lung adenocarcinoma and malignant cardiac tamponade, induced paroxysmal AF in 12% of patients.[20] Ifosfamide, melphalan, and cyclophosphamide, which are used in hematological malignancies, can also induce AF.[21–26] A retrospective study on 1,221 patients who, from 1998 to 2005, received bone marrow transplant and a melphalan-based regimen, demonstrated a higher rate of supraventricular arrhythmias, including AF, than any other chemotherapeutic regimen. Of the 438 patients who received melphalan, 48 (11%) developed AF or supraventricular tachycardia.[27] 5-fluorouracil and capecitabine, frequently used in gastrointestinal cancer, can also induce AF.[15,28] Bisphosphonates, used at high doses for the treatment of malignant hypercalcemia and bone metastases, were associated with 8% risk of developing AF or supraventricular tachycardia and 4% risk of stroke, even 6 years after therapy completion.[29]

Table 1 List of cancer drugs associated with the risk of AF

Antineoplastic drugs and AF				
Drug		**Neoplasia**	**AF incidence**	**Mechanism of action**
Chemotherapy drugs	5-FU[15,28,68]	Gastrointestinal, breast	0.93%	Hypotension Direct myocardial damage Heart failure Myocardial ischemia
	Cisplatin[13–19]	Lung, testicle, stomach, esophagus, bladder, ovary, head/neck	12–32%	Electrolyte alterations
	Doxorubicin[6,11,12] Mitoxantrone[42]	ALL, HL, NHL, breast, lung, ovary	1.3–10%	Direct myocardial damage (oxidative damage on the vessel wall) Heart failure Abnormalities in calcium homeostasis
	Gemcitabine[6,7]	Pancreas, lung, bladder	8.2%	Direct myocardial damage Release of proinflammatory cytokines
	Ifosfamide[21]	Sarcoma, bladder, breast, NHL	10%	Direct myocardial damage Heart failure
	Melfalan[22–26]	MM, ovary, breast, sarcoma	6.6–8.3% 1.7–22.5% (elderly)	Electrolyte alterations
	Paclitaxel[6]	Breast, ovary, sarcoma, lung	0.18%	Release of proinflammatory cytokines
Cytokines	Interleukin-2[34]	Melanoma	1.9–13.3%	Direct myocardial damage Hypotension
Tyrosine kinase inhibitors	Ibrutinib[30–32]	CLL, WM, MCL	6–9%	Direct myocardial damage (inhibition of p110a protein in cardiomyocytes)
	Sunitinib[34,36]	Kidney, GIST, pNET	Isolated reports	Heart failure
Mo Ab	Trastuzumab[43]	Breast	Isolated reports	Heart failure

Abbreviations: 5-FU, 5-fluorouracil; AF, atrial fibrillation; ALL, acute lymphocytic leukemia; CLL, chronic lymphocytic leukemia; GIST, gastrointestinal stromal tumor; HL, Hodgkin lymphoma; MCL, mantle cell lymphoma; MM, multiple myeloma; Mo Ab, monoclonal antibodies; NHL, non-Hodgkin lymphoma; pNET, primitive neuroectodermal tumors; WM, Waldenstrom's macroglobulinemia.

Ibrutinib, inhibitor of Bruton kinases, recently approved for treatment of chronic lymphatic leukemia, Waldenstrom's macroglobulinemia, and second-line therapy of mantle cells lymphoma, was responsible for newly onset AF in three different clinical trials, in particular in the first 6 months of treatment.[30–32] In a European phase II study of rituximab in 138 patients with newly diagnosed mantle cell lymphoma and previously treated mantle cell lymphoma, immunocytoma, and small B-cell lymphocytic lymphoma, one case of newly onset AF was reported.[33] In a phase II trial of outpatients with metastatic renal cell cancer taking subcutaneous interleukin-2 plus interferon-$\alpha - 2\beta$, two cases of AF developed during a 5-year follow-up.[34] In patients with metastatic renal cell carcinoma pretreated with sunitinib, one out of three patients experienced AF within the first 2 weeks of sorafenib therapy[35]; this occurred also when using a combination of sunitinib and lenalidomide.[36] Isolated reports described the occurrence of AF with azathioprine,[37–40] docetaxel,[41] mitoxantrone,[42] and trastuzumab.[43] Despite the lack of clear data, it is conceivable that radiotherapy could also induce AF through the development of heart failure.[44]

Management of Chemotherapy-Induced Atrial Fibrillation

Pharmacological and Electrical Cardioversion

Antiarrhythmic drugs should be tailored individually in cancer patients with AF (►**Table 2**). Rate control should be achieved mainly with β-blockers or nondihydropyridine calcium channel blockers or their combination. Digoxin can be used only in patients with overt heart failure, in whom verapamil and diltiazem are contraindicated.[3] Scant information is available on the interaction between anticancer agents and antiarrhythmic drugs. This becomes particularly relevant when choosing pharmacological cardioversion in AF patients. The concomitant administration of targeted therapies could increase plasma levels of both anticancer and antiarrhythmic drugs because of impaired hepatic metabolism of cytochrome P450 or inhibition of P-glycoprotein-mediated (P-gp) transport of the targeted drugs. In addition, targeted therapies can result in QT interval prolongation as a direct effect,[45,46] or due to concomitant conditions, mainly electrolyte disturbances (vomiting/diarrhea), or treatment with loop diuretics.[3] Accordingly, cancer patients experiencing AF shall be monitored by 12-lead ECG (electrocardiogram) when treated with QT-prolonging drugs or presenting with a history of QT prolongation, thyroid dysfunction, or electrolyte disorders.[3] Amiodarone, the only antiarrhythmic drug to have been extensively tested in this clinical setting,[3] also slows down heart rate and is safe in patients with concomitant heart failure and/or coronary artery disease.[1] Discontinuation of targeted therapies or an alternative regimen shall be considered in patients treated with amiodarone during or after AF if corrected QT interval is more than 500 ms.[3] Synchronized direct electrical cardioversion can be considered according to the ESC guidelines.[1] Pretreatment with amiodarone per os during the anticoagulation period can increase the efficacy of electrical cardioversion.[1] The maintenance or the restored sinus rhythm is important, especially for the difficulties in providing adequate antithrombotic therapy over time in neoplastic patients. Catheter ablation of AF, a procedure well established for restoring and maintaining sinus rhythm,[1] can be considered in cancer patients as a second choice after failure of pharmacological and electrical cardioversion of AF.[1]

Anticoagulant Drugs

The antithrombotic treatment of AF in patients undergoing anticancer therapies is complicated by the prothrombotic state of the cancer itself, which is due to expression/release of procoagulants by tumor cells, platelet activation, and endothelial dysfunction.[47] Further complicating factors include possible use of angiogenesis inhibitors and bleeding tendency of intracranial and hematological neoplasms.[48]

To date, no guidelines are available for antithrombotic treatment of cancer patients experiencing AF, and current clinical scores for prediction of thromboembolic events (mainly CHA_2DS_2-VASc) and bleeding (HAS-BLED) have not yet been validated in this context.[3] If the risk of stroke is likely to be underestimated, it is also true that cancer may generally predispose to bleeding. The recent ESC Position Paper on cancer treatment and cardiovascular toxicity clearly stated that the decision on antithrombotic therapy

Table 2 Main items of antiarrhythmic therapy for AF in cancer patients

1	Rate control by β-blockers or nondihydropyridine calcium channel blockers or their combination
2	Pharmacological cardioversion (preferably amiodarone, 5–7 mg/kg IV over 1 to 2 h followed by 50 mg/h IV to a maximum of 1 g over 24 h) taking into account: Drug interaction of targeted therapies with antiarrhythmic drugs QT interval prolongation of anticancer therapies
3.	Synchronized direct electrical cardioversion in hemodynamically unstable patients with AF longer than 48 h and when antiarrhythmic therapy fails to restore sinus rhythm after an effective 3-wk anticoagulation or after a transesophageal echocardiography ruling out the presence of left atrial/appendage thrombi
4.	Maintenance of the restored sinus rhythm, preferably by amiodarone per os for at least 4 wk after electrical cardioversion
5.	Catheter ablation of AF after failure of pharmacological and electrical cardioversion of AF

Abbreviations: AF, atrial fibrillation; IV, intravenously.

Table 3 Main items of anticoagulant therapy in AF in cancer patients

1	Anticoagulation preferred in patients with CHA_2DS_2-VASc $\geq$ 2 and platelet count $>$ 50,000/mm^3
2	Adoption of VKAs only in selected cases (e.g., patients with preexisting AF and stable INR) taking into account interaction with anticancer therapies
3.	Use of LMWH for short-to-intermediate time periods at least in metastatic cancer, mostly exposed to bleeding risk, or perioperatively (biopsies, cancer surgery) as a bridging therapy
4.	Adoption of NOACs with caution, taking into account interactions with anticancer therapies and antiarrhythmic drugs

Abbreviations: AF, atrial fibrillation; INR, International normalized ratio; LMWH, low molecular weight heparin; NOACs, non-VKA oral anticoagulants; VKAs, vitamin K antagonists.

for stroke prevention may be quite challenging and should not be based only on the risk assessment scores used for the general population.[3] However, anticoagulation should be considered in patients with CHA_2DS_2-VASc $\geq$ 2 and a platelet count of $>$50,000/mm^3[31] and guaranteed for at least 4 weeks after successful electrical cardioversion (►**Table 3**).[1]

There is a controversy as to which anticoagulant is the best. The use of vitamin K antagonists (VKAs) in cancer patients with AF is very problematic, mainly because of the difficulty to maintain a stable international normalized ratio (INR) resulting from multiple factors including inhomogeneous dietary intake due to vomiting/nausea, low body weight, and interaction with undergoing anticancer drugs.[49] VKAs metabolism, which is modulated by multiple cytochrome P-450 isozymes, can be influenced by concomitant therapies. Interactions with anticancer therapy itself include abnormalities in synthesis and catabolism of clotting factors, alteration of VKAs absorption, and reduced production of vitamin K by gut flora.[49] The anticoagulant response to VKAs and the bleeding risk are, therefore, unpredictable in this context as well as in relation to possible changes in renal and hepatic function occurring during the clinical course of these patients. The benefit–risk ratio of VKAs has been investigated in cancer patients suffering from venous thromboembolism (VTE).[50] In a recent retrospective, nonrandomized study following 2,168 consecutive patients with nonvalvular AF and newly diagnosed malignancy for an average of 4 years, no significant difference was observed in the composite end-point of major adverse cardiac events (ischemic stroke, myocardial infarction, pulmonary embolism) or major bleeding in patients treated with VKAs when compared with those who were not anticoagulated; however, only 12% of patients on VKA therapy achieved a target INR of 2 to 3, and difficulty in maintaining therapeutic anticoagulation likely contributed to the observed lack of benefit.[51] In a large population of war veterans taking warfarin for AF or VTE, warfarin control worsened significantly over a period of 6 months following newly diagnosed cancer compared with cancer-free patients.[52]

In relation with its likely lower risk of interaction with anticancer drugs, the use of low molecular weight heparin (LMWH) is recommended in cancer patients experiencing VTE (at least for 3 months after the acute event),[50,52,53] but no information is available for AF patients. A short-to-intermediate use of LMWH could be promoted in metastatic cancer, particularly if at high bleeding risk,[3] or perioperatively.[54] In some studies, LMWH showed an antiangiogenic role, which could be theoretically beneficial even to blunt cancer progression.[55,56] Non-VKA antagonist oral anticoagulants (NOACs) could present advantages in cancer patients with AF because of their short half-life, less food interaction than VKAs, and no need for laboratory monitoring. However, their use is still not standardized in these patients. The main phase III AF clinical trials comparing dabigatran, rivaroxaban, apixaban, and edoxaban to warfarin excluded patients with active cancer.[1] Encouraging data on NOACs efficacy and safety have been provided by a meta-analysis on cancer patients with VTE[57] but not with AF. Indeed, in a Danish nationwide population-based cohort study, the absolute risks of thromboembolic or bleeding complications were nearly the same in AF patients with and without cancer who filled a prescription for VKAs or NOACs.[58] Although these findings generate enthusiasm over the use of NOACs, caution shall be warranted. First of all, NOACs cannot be preferred in patients with gastrointestinal malignancies, who are highly predisposed to major bleeding, since this risk can be increased further by the use of specific anticancer drugs.[44] Second, but more important, possible pharmacological interactions between NOACs and anticancer therapies shall be taken into account. Medications interfering with the P-gp and/or the cytochrome system, especially CYP3A4 mitochondrial enzyme, may alter NOACs plasma concentration and induce abnormalities in their anticoagulant effect.[59] An important interaction for all NOACs consists of resecretion mediated by the P-gp transporter (after gut absorption), which can also be involved in renal clearance; as a result, the competitive inhibition of this pathway will induce increased plasma levels. Dabigatran and, to a lesser extent, the other three NOACs (rivaroxaban, apixaban, edoxaban) are substrates of P-gp and therefore influenced by inducers and inhibitors of this transporter. Obviously, inducers will reduce NOACs exposure, thus increasing the thrombotic risk, whereas inhibitors will increase the bleeding risk.[60] Of interest, several antiarrhythmic drugs used in AF (verapamil, dronedarone, amiodarone, and quinidine) are P-gp inhibitors or competitors, a finding that highlights a possible reciprocal interference with NOACs. CYP3A4 participates in hepatic oxidative metabolism of both rivaroxaban and apixaban, whereas dabigatran and, for most part, edoxaban metabolism do not involve CYP3A4.[61] Several anticancer drugs interact with the activity of CYP3A4, P-gp transporter, or both (►**Table 4**).[49] These interactions involve tyrosine kinase inhibitors such as crizotinib, ibrutinib, and nilotinib (but not gefitinib and erlotinib), which interfere with P-gp, possibly

Table 4 Cancer drugs interacting with CYP3A4 or P-glycoprotein

	CYP3A4		P-glycoprotein	
Inducer	**Vinca alkaloids** Paclitaxel (++) **Tyrosine kinase inhibitors** Vemurafenib (+) **Hormonal agents** Enzalutamide (+++) **Immune-modulating agents** Dexamethasone (+++) Prednisone (++)		**Vinca alkaloids** Vinblastine **Anthracyclines** Doxorubicin **Immune-modulating agents** Dexamethasone	
Inhibitor	**Vinca alkaloids** Vinblastine (+) Vincristine (+) Vinorelbine (+) Docetaxel (+) **Topoisomerase inhibitors** Etoposide (+) **Anthracyclines** Doxorubicin (+) Idarubicin (+) **Alkylating agents** Cyclophosphamide (+) Ifosfamide (+) Lomustine (+) **Tyrosine kinase inhibitors** Imatinib (++) Dasatinib (+) Nilotinib (+) Lapatinib (+) Crizotinib (++)	**Hormonal agents** Tamoxifen (+) Anastrozole (+) Bicalutamide (++) Abiraterone (++) **Immune-modulating agents** Cyclosporine (++) Sirolimus (+) Temsirolimus (+) Tacrolimus (+)	**Tyrosine kinase inhibitors** Imatinib Nilotinib Lapatinib Sunitinib Crizotinib Vandetanib **Hormonal agents** Tamoxifen Enzalutamide Abiraterone **Immune-modulating agents** Cyclosporine Tacrolimus Dexamethasone	
Substrate	**Vinca alkaloids** Vinblastine (+++) Vincristine (+++) Vinorelbine (+++) Docetaxel (+++) Paclitaxel (+++) **Topoisomerase inhibitors** Irinotecan (+++) Etoposide (+++) **Anthracyclines** Doxorubicin (+++) **Alkylating agents** Cyclophosphamide (+) Ifosfamide (+++) Busulfan (+++) **Tyrosine kinase inhibitors** Imatinib (+++) Dasatinib (+++) Nilotinib (+++) Erlotinib (+++) Gefitinib (+++) Lapatinib (+++)	Sunitinib (+++) Sorafenib (+) Crizotinib (+++) Vemurafenib (+) Vandetanib (+++) **Monoclonal antibodies** Brentuximab (+++) **Hormonal agents** Tamoxifen (+++) Letrozole (+) Fulvestrant (+) Flutamide (+++) Enzalutamide (+++) Abiraterone (+++) **Immune-modulating agents** Cyclosporine (+++) Sirolimus (+++) Everolimus (+++) Temsirolimus (+++) Tacrolimus (+++) Dexamethasone (+++) Prednisone (+)	**Vinca alkaloids** Vinblastine Vincristine Docetaxel Paclitaxel **Antimetabolites** Methotrexate **Topoisomerase inhibitors** Irinotecan Etoposide **Anthracyclines** Doxorubicin Daunorubicin Idarubicin **Alkylating agents** Bendamustine **Intercalating agents** Mitomycin C	**Tyrosine kinase inhibitors** Imatinib Nilotinib Lapatinib Crizotinib Vemurafenib **Immune-modulating agents** Cyclosporine Sirolimus Everolimus Temsirolimus Tacrolimus Dexamethasone

Note: Values in bold indicate CYP3A4 and P-glycoprotein interactions, respectively.

modifying anticoagulant concentrations. This is particularly important for ibrutinib, which, in addition to the already mentioned risk of AF, also induces a platelet function defect, which, through drug interactions (it undergoes a CYP3A4-mediated metabolism), may increase the bleeding risk of antithrombotic treatment.[30–32] Although NOACs confer a lower bleeding risk than VKAs in patients suffering from AF during ibrutinib therapy, the CYP3A4 inhibitors increase susceptibility to this drug.[62] Accordingly, anticoagulation with either rivaroxaban or apixaban is not advisable; a better option is dabigatran or edoxaban under these circumstances. Also, antimicrotubule inhibitors, such as taxanes and vinca alkaloids, and mammalian target of rapamycin inhibitors (except for everolimus) showed significant interactions with NOACs.[49] Accordingly, NOACs undergo significant fluctuations in plasma concentrations and require dose adjustment due to interaction of antineoplastic agents with CYP3A4 or P-gp. Monoclonal antibodies, and platinum-derived and

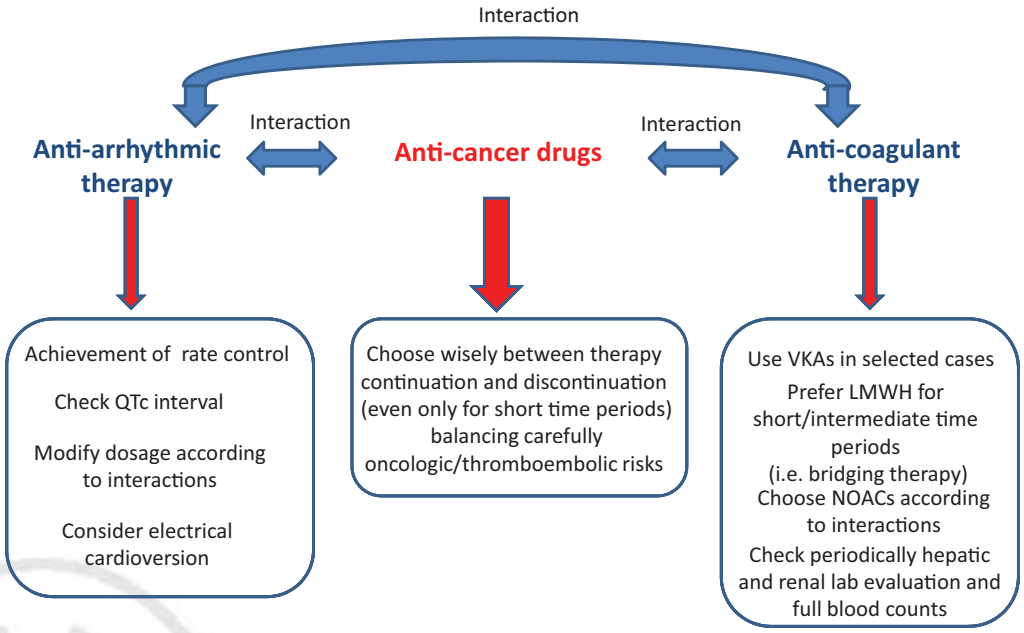

Fig. 2 A proposed algorithm for the oncological and cardiac management of new-onset atrial fibrillation in cancer patients. LMWH, low molecular weight heparin; NOACs, nonvitamin K antagonist oral anticoagulants; QTc, corrected QT; VKAs, vitamin K antagonists.

intercalating agents were not reported as exerting any kind of interaction, and no definite influence was observed on anthracyclines, alkylating agents, topoisomerase inhibitors, or hormonal agents.[49]

Practical Implications

Cancer patients with AF require a multidisciplinary approach to face the different problems associated with the onset of this arrhythmia (►**Fig. 2**). A main aspect is the preliminary identification of patients more prone to AF, such as those with preexisting (paroxysmal, persistent, or permanent) AF and/or affected by arterial hypertension, diabetes, or coronary artery disease. The cooperation of oncologists/hematologists and cardiologists is mandatory at this stage to choose the most appropriate anticancer therapy, balancing cardiovascular risk with prognostic factors of each malignancy. Patients at a high risk of AF should be managed choosing anticancer drugs that are less aggressive (e.g., pegylated liposomal doxorubicin)[63] and poorly associated with AF.

When the onset of AF occurs during oncological therapy, the decision regarding whether to continue, adapt the dosage, or withdraw anticancer drugs is of paramount importance. This can be a dramatic choice, which could be attenuated by a brief interruption of treatment, again weighing oncological and cardiac risks. In any case, the first attempt shall aim to achieve optimal heart rate control and normal sinus rhythm with antiarrhythmic drugs, mainly with the most documented amiodarone. An echocardiogram should be performed before commencing antiarrhythmic therapy for detecting possible reduction of left ventricular ejection fraction, and, whenever available, of the novel global longitudinal strain, which is altered at earlier stage as a result of cardiotoxicity.[64] The evidence of diastolic dysfunction and coexisting valve heart disease (in particular mitral regurgitation and aortic stenosis), as well pulmonary hypertension, should be searched.[64] This imaging evaluation is fundamental to determine pretest probability of sinus rhythm restoration and to establish optimal cardiac treatment choice. The assay of brain natriuretic peptide (BNP) or N-terminal-proBNP can be useful when suspecting heart failure to be responsible for AF onset.

A careful evaluation of the antithrombotic strategy with better efficacy/safety ratio is always needed. Since VKAs interact with several oncological treatments, in patients with active cancer undergoing chemotherapy, coagulation experts traditionally prefer LMWH (in general as a short- to intermediate-term strategy), especially in patients with high bleeding risk or in the case of metastatic disease. The choice of NOACs during/after anticancer therapy is supported by efficacy and safety evidenced in subgroup analyses and meta-analyses of VTE studies.[50]

When choosing the anticoagulant strategy, patient preferences should be considered and a careful follow-up needs to be adopted.[3] A complete clinical examination for bleeding symptoms/signs and a regular laboratory evaluation of renal and hepatic function, as well as periodical full blood counts, including platelets, should be performed. At the present time, of the four available NOACs, one could prefer dabigatran in patients for whom long-term anticoagulation is envisaged, mainly because of the availability of a specific antidote, idarucizumab, which can stop bleeding rapidly.[65] However, the choice of any NOAC should always be guided by the renal and hepatic function, and the interactions with anticancer and antiarrhythmic drugs, both of which can increase thromboembolic or bleeding risk. An anticoagulant with fast onset could allow for early electrical cardioversion, for example, 4 hours after a single dose of a NOAC, an approach which has recently been validated for rivaroxaban[66] and is also now available using edoxaban with the same strategy.[67]

Conclusion

AF is frequently observed in patients being treated for cancer and can lead to increased morbidity and mortality in this population. Management of AF in cancer patients can be challenging given the possible drug–drug interactions between anticancer therapies and both antiarrhythmic drugs and anticoagulants. These medications should be tailored to individual patients. A constant consultation of oncologists/hematologists with cardiologists and coagulation experts in a multidisciplinary approach is warranted when deciding whether to continue or withdraw anticancer therapy, somewhat facilitated by the existence of multiple therapeutic options.

Conflict of Interest
The authors declare no conflict of interest.

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