

## Atrial fibrillation in older adults with cancer

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**ABSTRACT** Cancer and atrial fibrillation (AF) are common co-morbid conditions in older adults. Both cancer and cancer treatment increase the risk of developing new AF which increases morbidity and mortality. Heart rate and rhythm control along with anticoagulation therapy remain the mainstay of treatment of AF in older adults with both cancer and AF. Adjustments to the treatment may be necessary because of drug interactions with concurrent chemotherapy. Cancer and old age increase the risk of both, thromboembolism and bleeding. The risk of these complications is further enhanced by concomitant cancer therapy, frailty, poor nutrition status and, coexisting geriatric syndromes. Therefore, careful attention needs to be given to the risks and benefits of using anticoagulant medications. This review focuses on the management of AF in older patients with cancer, including at the end-of-life care.

The association of cancer with atrial fibrillation (AF) is well known.<sup>[1–5]</sup> Patients with cancer have a two-fold risk of developing AF when compared to the general population even after adjusting for cardiovascular risk<sup>[3,6,7]</sup> Cancer-specific net survival has increased considerably over the past few decades due to significant advancements in cancer treatment, resulting in a growing population of older adults with concomitant cancer and coexisting complex geriatric comorbidities.<sup>[6]</sup> Cancer treatment, including chemotherapy, immunotherapy, radiation therapy and surgery, has been associated with cardiovascular complications, including coronary artery disease (CAD), cardiac arrhythmia and cardiomyopathy, among others. AF is one of the most common arrhythmias associated with both cancer and its treatment.<sup>[7–9]</sup> AF prevalence increases with age, as does the complication rate of its various therapies. Regardless of the etiology, the presence of AF in the setting of cancer raises concerns about low haemostatic reserve and increased morbidity.<sup>[10]</sup>

Currently, there are no specific guidelines for the management of AF in older adults with cancer. This paper reviews the incidence, pathogenesis, assessment of thromboembolic and bleeding risk, and the management of AF in older patients with cancer.

## METHODS

We searched the English literature in PubMed using the Mesh terms “Neoplasm”, “Chemotherapy”, “Atrial fibrillation”, “Anticoagulation”, “Cardio-oncology” alone and in various combinations. We identified articles published in and after the year 2000 by examining the abstract and selected 112 articles including systematic reviews, observational studies, and randomized clinical trials pertaining to our objectives. We reviewed 85 of these selected articles in detail. We also selected additional articles through citations mentioned in these articles.

## INCIDENCE AND PATHOGENESIS OF ATRIAL FIBRILLATION IN PATIENTS WITH CANCER

The prevalence of AF has been reported to be nearly 4 times higher in patients with cancer: 17.4 per 1000 person years (PY) compared with 3.7 per 1000 PY in the general population. This study also noted that AF was increasingly common in older adults with cancer.<sup>[4]</sup> The incidence of AF in patients with cancer varies by the type, stage and treatment of cancer. Although all major cancers are associated with an increased incidence of AF, observational

studies have demonstrated that patients with solid tumours, including prostate, colon and breast cancer have a high propensity for AF, with prostate cancer patients having a particularly high incidence of AF.<sup>[2-4]</sup> The underlying mechanisms are unknown, though a high median age at the time of diagnosis for these cancers may explain the higher incidence of AF.<sup>[11]</sup> An increased probability of being diagnosed with cancer within the first three months of a new AF diagnosis has also been described. This may become a future indicator for systemic occult cancer screening, especially for older adults.<sup>[5]</sup>

A variety of mechanisms, in addition to age, have been proposed to explain the high correlation between cancer and AF. Cancer-induced inflammation and oxidative stress are thought to be significant contributing factors<sup>[10]</sup>. A variety of pro-inflammatory cytokines such as C-reactive protein (CRP), interleukins (IL) in particular IL-2, IL-6 and IL-8, macrophage migration inhibitory factor (MIF) and tumour necrosis factor-alpha are elevated in cancer patients with AF.<sup>[8]</sup> Hypercoagulability in the setting of cancer may lead to AF caused by pulmonary micro-emboli. Elevated inflammatory markers can cause autonomic dysfunction, electrolyte abnormalities, myocardial structural changes and electrical remodelling.<sup>[8]</sup> Associated changes in calcium homeostasis and connexins can cause heterogeneous atrial conduction abnormalities including AF.<sup>[10]</sup>

Several cancer treatments including HER-2/Neu receptor blockers, alkylating agents, anthracycline agents, and anti-microtubular agents are associated with the development of new-onset AF.<sup>[9]</sup> Tyrosine kinase inhibitors (TKI) and certain immunomodulators such as interleukin-2 (IL-2) and antimetabolites, such as 5-Fluorouracil and gemcitabine, are also associated with new-onset AF.<sup>[9]</sup> (Table 1). Stem cell transplantation has also been linked to the development of atrial arrhythmia including AF especially in patients with concurrent diastolic dysfunction.<sup>[12]</sup> Chemotherapeutic agents can also cause myocyte deterioration, mitochondrial damage, ion channel dysfunction and atrial fibrosis causing structural and electrical changes in the myocardium and a resulting propensity for AF.<sup>[8]</sup> Cancer and cancer treatment associated complications, such as infection, anaemia, hypoxia, pleuritis, pericarditis and cardi-

omyopathy are all potential triggers for AF.<sup>[13]</sup> Neoplastic involvement of the heart, pericardium, mediastinum or lung can be another potential substrate for AF.<sup>[8,14]</sup> In addition, high adrenergic states following cancer surgery may precipitate or exacerbate AF.<sup>[10]</sup>

## MANAGEMENT OF ATRIAL FIBRILLATION IN THE SETTING OF CANCER

Clinicians caring for older adults with cancer should identify those patients who are most susceptible to cardiac arrhythmias by conducting a comprehensive baseline cardiovascular (CV) evaluation which includes obtaining personal and family cardiac history and performing a CV risk assessment. Optimizing the treatment of existing CV disease and minimizing CV risk factors are important when attempting to prevent cancer and cancer treatment related cardiotoxicity.<sup>[15]</sup>

Though treatment strategies for AF in older adults with cancer are similar to those used for the general population, there are special circumstances where treatment adjustments should be considered. These treatment strategies have been categorized into rate control, rhythm control and anticoagulation (Table 1).

### Rate Control

Beta-blockers (BB) and calcium channel blockers (CCB) are used for rate control in cancer patients with AF, similar to their use in the general population.<sup>[16]</sup> Beta-blockade has modest antiarrhythmic properties in AF induced by adrenergic stimulation from catecholamines. Digoxin was used more commonly in the past for rate control and may still be used if patients do not respond to BB and/or CCB. However, digoxin has the potential for significant interaction with other drugs; thus, it is not considered first-line therapy.<sup>[16,17]</sup>

### Rhythm Control

The decision to convert AF to sinus rhythm (rhythm control) is patient specific. There is less of an emphasis on rhythm control for older adults who are particularly susceptible to the side effects of antiarrhythmic medications. However, for patients who are significantly symptomatic from AF or whose AF is difficult to rate control, rhythm con-



**Table 1** Summary of atrial fibrillation management in patients with cancer.

Stroke risk assessment CHA <sub>2</sub> DS <sub>2</sub> VASc score (35) CHADS <sub>2</sub> Score	Does not take into account the prothrombotic state induced by malignancy or cancer drugs. CHADS <sub>2</sub> and CHA <sub>2</sub> DS <sub>2</sub> VASc scores are most commonly used for risk assessment.
Bleeding risk assessment HAS-BLED score	Does not include cancer as an additional variable; thus, may underestimate the risk.
Vitamin K Antagonist	Requires frequent monitoring of the INR. Increased INR variability due to malignancy. Cancer patients have higher incidence of sub-therapeutic INRs. Drug interactions with other medications. Increased incidence of thromboembolic events.
DOACs: Apixaban Dabigatran Rivaroxaban	Data available from observational studies, no robust randomized clinical trials to support evidence. Apixaban and dabigatran are non-inferior to warfarin in reducing the risk of ischemic stroke. Apixaban has shown to have lowest rates of bleeding complications. Derangements in hepatic and renal function requires closer monitoring and dose adjustments. Drug interactions can still occur.
Rate control	Beta blocker and calcium channel blockers.
Rhythm control Pharmacologic cardioversion: Amiodarone, Flecainide and Ibutilide	Amiodarone has a large volume of distribution leading to drug interactions. It increases risk of skin and mucosal damage with radiation in addition to incidence of cancer with amiodarone. Use of Flecainide may be limited by chemotherapy induced structural heart disease. Use of Ibutilide may be limited by use of concurrent QT prolonging medications.
Catheter ablation	Not well studied in cancer patients.
Maze procedure	Can be considered in patients undergoing thoracic surgery.

control may be indicated. Rhythm control involves electrical or pharmacologic restoration and maintenance of sinus rhythm (Table 2).

### Cardioversion

Both electrical and pharmacotherapeutic methods can be used to convert AF to sinus rhythm. Emergency electrical cardioversion is the first line therapy for unstable patients (altered mental status, hypotension, chest pain or hypoxia attributed to arrhythmia). For stable patients, cardioversion can be performed either electrically or pharmacologically. Flecainide and Ibutilide are anti-arrhythmic drugs commonly used for pharmacologic cardioversion.<sup>[17,18]</sup> However, many older adults, including those with cancer, have underlying structural heart disease,

which precludes the use of flecainide, because of its increased pro-arrhythmic effects in these patients (Table 2).<sup>[19]</sup>

### Maintenance of Sinus Rhythm

Maintenance of sinus rhythm can be difficult in AF patients with cancer who have underlying structural heart disease and long-standing AF.<sup>[20]</sup> Amiodarone, dofetilide and sotalol are the agents most commonly used for maintenance of sinus rhythm.<sup>[21]</sup>

In general, where possible, amiodarone should be avoided in older adults. The AGS Beers criteria for older adults regarding the use of amiodarone states, “avoid as first-line therapy for atrial fibrillation unless patient has heart failure or substantial left ventricular hypertrophy”. It is effective for maintaining

**Table 2** Chemotherapy drugs associated with atrial fibrillation.

Drug Classification	Drugs
Targeted therapies	Ibrutinib
Tyrosine kinase inhibitors	Cetuximab, crizotinib, sunitinib, sorafenib
Anthracycline agents	Adiramyacin A, doxorubicin
Alkylating agents	Cisplatin, melphalan, cyclophosphamide, ifosfamide
HER-2/neu receptor blockers	Trastuzumab
Antimetabolites	5-fluorouracil, gemcitabine
Antimicrotubule agents	Paclitaxel, docetaxel
Histone deacetylase inhibitors	Depsipeptide, belinostat
Proteasome inhibitors	Bortezomib



sinus rhythm but has greater toxicities than other antiarrhythmics used in atrial fibrillation".<sup>[22]</sup> Amiodarone may be particularly problematic for older adults receiving certain cancer treatments. There is a strong temporal relationship between taxane therapy such as paclitaxel and docetaxel that is used for the treatment of a variety of cancers including breast, non-small cell lung and ovarian cancer, and the development of severe skin and mucosal toxicity due to a reduction in taxane clearance in patients taking amiodarone.<sup>[23]</sup> Amiodarone has also been shown to increase negative radiation effects on skin and mucosa.<sup>[24]</sup>

Dofetilide a class III antiarrhythmic agent with efficacy comparable to amiodarone may be a better choice to maintain sinus rhythm in older adults who have a normal QTc interval. It is worth noting, however, that several cancer treatments can contribute to a prolonged QTc and associated life-threatening arrhythmia. Kinase inhibitors such as dasatinib and ruxolitinib that are used to treat chronic myeloid leukaemia and myelofibrosis can result in a prolonged QTc interval. Arsenic trioxide used to treat promyelocytic leukaemia can also cause a prolonged QTc interval. The use of some anti-emetics medications such as ondansetron which are commonly used to prevent and treat nausea in cancer patients can also contribute to a prolonged QTc.<sup>[13]</sup> Sotalol may also be used but it is less effective for

rhythm control than either amiodarone or dofetilide.<sup>[21]</sup> (Table 3)

Catheter ablation is a well-established therapeutic option for the treatment of symptomatic, predominantly paroxysmal and drug-refractory AF.<sup>[25]</sup> However, it has not been studied in cancer patients. Maze procedure is another modality for individuals undergoing cardiac or thoracic surgery which can be considered in patients undergoing lung resection.<sup>[26]</sup> If the above-mentioned measures fail to control AF, AV node ablation with permanent pacing is reserved as a last resort strategy to mitigate the symptoms and hemodynamic effects of refractory rapid AF.<sup>[27]</sup>

## ANTICOAGULATION

### Risk-Benefit Decisions Regarding Anticoagulation

The use of anticoagulant medications always requires consideration of both the benefits and complications, especially bleeding risk, associated with their use. It has been well established that AF is a risk factor for arterial thromboembolism. It is also well established that many patients with AF benefit from the use of anticoagulant medications.<sup>[16,28,29]</sup> It is important to point out however that both the very old (> 85 years) and patients with cancer were underrepresented in the large trials that established

Table 3 Antiarrhythmics in atrial fibrillation.

Drug	Metabolism and Dosing	Non cardiovascular adverse effects	Cardiovascular adverse effects
Flecainide	Renal/hepatic CYP2D6; 50–100 mg twice a day, maximum dose 300–400 mg/day.	Dizziness, headache, visual blurring	Atrial flutter with 1:1 conduction; ventricular tachycardia; may unmask Brugada-type ST elevation; contraindicated with coronary disease
Sotalol	Renal: 80–120 mg twice a day; maximum dose 240 mg twice a day.	Bronchoconstriction	Bradycardia, Torsades de pointes
Amiodarone	Hepatic; half-life 50 day: oral load 10 g over 7–10 day, then 400 mg for 3 week, then 200 mg/day for atrial fibrillation; maintenance dose of 400 mg/day for ventricular tachycardia; dose-reduced load for bradycardia or QT prolongation; intravenous: 150–300 mg bolus, then 1 mg/min infusion for 6 h followed by 0.5 mg/min thereafter.	Pulmonary (acute hypersensitivity pneumonitis, chronic interstitial infiltrates); hepatitis; thyroid (hypothyroidism or hyperthyroidism); photosensitivity; blue-gray skin discoloration with chronic high dose; nausea; ataxia; tremor; alopecia	Sinus bradycardia
Ibutilide	Hepatic CYP3A4; 1 mg intravenous over 10 min; repeat after 10 min if necessary.	Nausea	Torsades de pointes
Dofetilide	Renal/hepatic CYP3A4; CrCL >60 (500 µg twice a day), CrCl 40–60 (250 µg twice a day), CrCl 20–39 (125 µg twice a day).	None	Torsades de pointes



this benefit. The need for anticoagulation therapy in the setting of AF is commonly determined by a risk assessment tool such as the CHA<sub>2</sub>DS<sub>2</sub>-Vasc score where heart failure, hypertension, older age, diabetes mellitus, stroke and vascular disease are considered risk factors.<sup>[30]</sup> Each risk factor is given a point score; one point for each of the risk factors, except for age over 75 years and a history of stroke which are each assigned two points. A patient with two points or more warrants anticoagulation unless there is a high risk of bleeding.<sup>[16]</sup> It is notable that even though cancer is often associated with a propensity for thrombosis, cancer or a history of cancer is not a listed risk factor in CHA<sub>2</sub>DS<sub>2</sub>-Vasc.

The decision to use anticoagulation for patients who have AF and cancer is determined primarily by AF related risk factors such as those addressed by a CHA<sub>2</sub>DS<sub>2</sub>-Vasc score. Based on this type of risk assessment most older patients will be determined to benefit from the use of anticoagulant treatment. However, some older patients with cancer including those between 65 and 75 years who do not have other risk factors may not be recommended to take an anticoagulant medication and may remain at high risk for embolic events. There are also data that indicate that patients who have both AF and cancer for whom anticoagulation is indicated based on AF factors alone are less likely to be anticoagulated in comparison to AF patients without cancer.<sup>[31]</sup>

Bleeding risk always needs to be assessed when considering the use of anticoagulation. There are two risk scores, HAS-BLED and HEMORR2HAGES that are commonly used to assess bleeding risk from anticoagulation therapy. Both scores are available as web-based calculators which can be used to guide care.<sup>[32,33]</sup> Older age is considered a risk for increased bleeding in both tools and HEMORR2HAGES includes a history of malignancy and thrombocytopenia as bleeding risks. Metastatic disease, luminal gastrointestinal cancers, chronic kidney disease  $\geq$  stage III, and platelets  $< 100,000 \times 10^9/L$  have all been shown to increase bleeding risk for cancer patients on anticoagulants.<sup>[34]</sup> Moreover, older adults often take antiplatelet agents for primary or secondary prevention of cardiovascular disease, which may further exacerbate the bleeding risk.<sup>[35,36]</sup>

For some older adults with cancer and AF, there

may be a legitimate contraindication to prescribing anticoagulation. Cancers and cancer treatments may cause thrombocytopenia. A platelet count below 20,000 per microliter and less than 50,000 per microliter are absolute and relative contraindications, respectively, for therapeutic anticoagulation.<sup>[37]</sup> However, some older adults with AF are not initiated on anticoagulation or have anticoagulation discontinued, when the benefits of anticoagulation are greater than the perceived.<sup>[29]</sup> For example, fall risk or a history of falls may be cited as a reason for not starting anticoagulation or stopping an anticoagulant when the risk benefit for most of these patients favours anticoagulation.<sup>[38]</sup>

In the vast majority of cases, the left atrial appendage (LAA) is thought to be the origin of embolic strokes in non-valvular AF.<sup>[39]</sup> Therefore, in cases in which anticoagulation may be contraindicated such as a history of intracranial haemorrhage or high bleeding risk, LAA closure or exclusion is thought to be an alternative. It is a safe, durable and effective method performed as an adjunct to cardiac surgery, or as a stand-alone procedure.<sup>[40]</sup> However, the benefit in cancer patients with AF are unknown since they have been excluded in clinical trial conducted to test this intervention.

### Choice of Anticoagulant Medication

Vitamin K antagonists (VKA) and direct oral anticoagulants (DOACs) have similar efficacy in preventing thrombo-embolic events in cancer patients with AF.<sup>[41,42]</sup> Although low molecular weight heparin (LMWH) is often used in patients with cancer for the treatment of thromboembolism, data on its use for stroke prevention in patients who also have AF and cancer is lacking.<sup>[43]</sup> Warfarin therapy can be challenging due to frequent INR monitoring, interaction with foods containing vitamin K, and many potential drug to drug interactions (DDIs). Warfarin use can be particularly problematic in cancer patients as they have increased INR variability due to concomitant use of chemotherapeutic agents that affect VKA metabolism, frequent nausea or vomiting, inconsistent dietary intake, low body weight, reduced albumin levels, and nutritional supplements.<sup>[42]</sup> For these reasons, DOACs are usually a better choice for patients with both AF and cancer.<sup>[43]</sup>



However, when prescribing DOACs for patients with cancer, close surveillance of DDIs is required; especially when used concurrently with chemotherapy or immunotherapy that induces or inhibits the permeability glycoprotein (P-gp).<sup>[44]</sup> There are many potential DDIs and many new cancer treatments that an online tool should be used when prescribing DOACs to cancer patients who are receiving chemotherapy or immunotherapy.<sup>[45]</sup> A clinical pharmacist can also be a very helpful resource when making these complex clinical decisions.<sup>[46]</sup>

## THE MANAGEMENT OF AF FOR CANCER PATIENTS NEAR THE END-OF-LIFE

There is very little data to guide the management of AF in older adults with cancer who are near the end of their life. In a study looking at polypharmacy at the end of life for patients who were thought to have less than one year to live, more than one third of these primarily older patients with cancer, were on fifteen or more medications.<sup>[47]</sup> Though avoiding polypharmacy in older adults is always a good idea, it is important to note that older adults with AF and cancer who have a limited life expectancy, may still benefit from both rate control and anticoagulation therapy. Embolic complications can be particularly painful and disabling. A very rapid heart rate may cause a sudden deterioration in cardiac function, which may or may not be congruent with comfort care, depending on the patient's immediate prognosis.

## CONCLUSIONS

Older adults are at an increased risk for both AF and cancer. Both conditions frequently occur concurrently in this population. Older adults with AF and cancer can benefit from both rate control and rhythm control. Special consideration should be given to the increased prevalence of side effects from antiarrhythmic medications in older adults with both AF and cancer. Decisions regarding the risk-benefit ratio of anticoagulation and the choice of anticoagulant medication can be challenging for older adults with AF and cancer. These patient population has an increased risk of both thromboembolic

and bleeding complications. DDIs are common between medications used to treat cancer and medications used to treat AF. An individualized approach is warranted to address the continued use of antiarrhythmic medications and anticoagulant medications for older adults with both AF and cancer who are near the end-of-life.

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