AF in Cancer Patients: A Different Need for Anticoagulation?

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Abstract

Cancer and cancer therapies might be a risk factor for developing Atrial Fibrillation (AF). It remains unclear if one is the cause or consequence of the other, or if they simply coexist. An unpredictable response to anticoagulation can be expected, as a result of the lack of information in oncology patients. The balance between thromboembolic and bleeding risks of AF in these patients is particularly challenging. Little is known about whether embolic and bleeding risk scores used for the general population can be applied in oncologic patients. Cardiology involvement in the management of these patients seems to be associated with favourable AF-related outcomes.

Keywords

Anticoagulation, cancer, cardio-oncology, vitamin K antagonist, direct oral anticoagulants, bleeding risk, embolic risk

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Search Strategy

An independent literature search was performed on the topic 'AF in cancer patients' with the assistance of professional librarians. The search terms included anticoagulation, cancer, cardioncology, vitamin K antagonist, direct oral anticoagulants, bleeding risk and embolic risk. An electronic search was conducted using a minimum of two major databases (Cochrane Registry, MEDLINE) to identify relevant systematic reviews, randomised clinical trials and high-quality observational studies about the topic.

AF and Cancer

AF is the most common sustained cardiac arrhythmia, with an estimated prevalence of 3% in adults aged 20 years, and higher in older people.[1] An association between AF and malignant cancer has been reported, but is incompletely defined.[2]

Cancer is one of the chronic pathologies whose survival has increased in past decades. The onset of AF may be related to comorbidities, direct tumour effects, or it can be triggered by paraneoplastic conditions, left ventricular dysfunction or toxic effects of cancer treatment. It remains unclear if cancer acts as a risk factor or a marker of the arrhythmia, and the relationship between AF and cancer seems to be bidirectional. It has even been suggested that AF may act as a marker for occult cancer.[3]

In surgical patients admitted with a new diagnosis of colorectal or breast cancer, AF was twice as common (3.6% versus 1.6%) compared with patients admitted for non-neoplastic surgery.[4] The highest incidence of cancer-related AF has been described in postoperative in patients undergoing lung resection.[5] In the large Women's Health Study cohort, the authors reported that the incidence of cancer was significantly higher in women with AF than in women without AF. The risk of cancer was threefold greater within 3 months of AF diagnosis and still elevated beyond 1 year. On the other hand, the risk of incident AF after diagnosis of cancer was 20% higher in the first 3 months after diagnosis of cancer, but not beyond.[6]

In the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF), it was found that approximately one in four AF patients had a history of cancer.[7] Patients with both diagnoses had a higher burden of cardiovascular risk factors and concomitant cardiovascular disease.

Specific Risks of AF in Cancer Patients

Cancer is a prothrombotic state leading to increased risk of stroke.[8] Moreover, stroke in patients with cancer has been associated with worse outcomes, including prolonged hospitalisation and disability, when compared with cerebrovascular events in patients without cancer.[9] Some anticancer therapies have been associated with both thromboembolic complications and increased risk of bleeding events.[10]

Traditionally, anticoagulant therapy with warfarin has been the mainstay of treatment for stroke and systemic thromboembolism prevention in patients with AF. Its dose is adjusted by monitoring the international normalised ratio (INR). Maintaining INR at target is generally more difficult in cancer patients as a result of drug–drug interactions between warfarin and cancer treatment, changes in renal and hepatic function, dietary/nutritional status, chemotherapeutic toxicity and disease state. There are no current INR monitoring guidelines for patients with AF and concurrent malignancy.[11]

In the ORBIT-AF trial, AF patients with history of cancer treated with warfarin required more INR checks to obtain the target INR, compared with patients who did not have a history of cancer, but overall time in

therapeutic range was similar.[7] In this study, the risk of stroke, systemic embolism, heart failure and cardiovascular death was similar between those with and without a history of cancer, but patients with a history of cancer were at higher risk of major bleeding.

Risk Scores in Cancer Patients

A European Society of Cardiology position paper admits that the embolic-haemorrhagic risk balance can be modified in AF and cancer, and points out the lack of validation of the main risk prediction scales CHA_2DS_2-VASc and HAS-BLED. When proposing anticoagulant treatment for cancer patients with AF, the same recommendations are followed as in non-oncological patients, despite the lack of specific evidence.[12]

Patell et al. found $CHADS_2$ and CHA_2DS_2-VASc predicted risk of ischaemic stroke in cancer patients with baseline AF.[13] $CHADS_2$ score was more predictive of increased risk of stroke in patients with cancer and AF than CHA_2DS_2-VASc. Similarly, Hu et al. showed that in patients with cancer and pre-existing AF, increasing $CHADS_2$ was predictive of new thromboembolism ($CHADS_2$ 0–1: 6.7%, $CHADS_2$ 2–3: 15.8%, $CHADS_2$ 4–6: 27.0%; p=0.004).[14] Patell et al. also found that a higher $CHADS_2$ score was associated with increased mortality (HR 1.24; 95% CI [1.17–1.32]; p<0.001).[13] However, Hu et al. found that $CHADS_2$ was not associated with mortality ($CHADS_2$ 0–1: 32.0%, $CHADS_2$ 2–3: 34.2% and $CHADS_2$ 4–6: 35.6%; p=0.560).[14]

A Different Treatment for Cancer Patients?

The selection of antithrombotic therapy in patients with AF and cancer is challenging. European clinical practice guidelines for the management of AF make no distinctions in patients with concomitant oncological pathology, applying the same criteria for the use of antithrombotic treatment as in the general population.[15]

Little is known about how patients with AF and cancer are routinely treated in clinical practice and whether their risk for embolic or bleeding events is higher than patients without cancer. A study by O'Neal et al. aimed to examine the relationship between early cardiology involvement after AF diagnosis in patients with cancer.[16] They found that cardiology involvement was less likely to occur among patients with a history of cancer than those without. Patients with a history of cancer were less likely to fill prescriptions for anticoagulants than those without cancer. Cardiology involvement was associated with increased anticoagulant prescription fills and favourable AF-related outcomes in AF patients with cancer (reduced risk of stroke without increased risk of bleeding).[16]

Patients with AF and a history of cancer carry a high burden of cardiovascular risk factors and frequently have cardiovascular disease. They appear to be similarly treated with antithrombotic and anticoagulant therapy, but in some studies they experience a higher risk of major bleeding than AF patients without cancer.[7] Ning et al. followed 1,807 cancer patients for 7 years, noting that the cause of death in 51% was cancer, but in up to 33% it was cardiovascular disease that was the first cause of death not related to cancer.[17] This shows the importance of cardiovascular disease in cancer patients. It is essential to try to optimally manage both pathologies, especially embolic and bleeding risk in AF.

Patients with cancer may experience erratic control of INR. Therefore, vitamin K antagonists (VKAs) may not be the optimal anticoagulants for cancer patients, especially during chemotherapy. Both nutritional factors and concomitant medications can influence VKA activity in patients with cancer and maintaining INR at target is challenging.[18] A higher rate of thrombotic events has been described, regardless of the indication for anticoagulation.[19]

Low-molecular-weight heparins seem to have a more favourable profile in this group of patients, and potential antitumour and antimetastatic effects have been suggested in some studies, although these effects have not been confirmed.[20] There is a clear reduction in quality of life associated with long-term administration of subcutaneous drugs.

The advent of direct-acting oral anticoagulants (DOACs) – dabigatran, apixaban, rivaroxaban and edoxaban – has led to a revolution in the antithrombotic treatment of AF. In pivotal studies, a dosage of 150 mg twice daily of dabigatran reduced stroke and systemic embolism compared with warfarin, without significant differences in bleeding events, while dabigatran at a dosage of 110 mg twice daily was non-inferior to warfarin for prevention of stroke and embolism, with less bleeding. In this study, patients with a diagnosis of cancer were excluded.[21]

A dosage of 5 mg twice daily of apixaban also decreased the rate of bleeding and mortality – with greater protection against strokes and embolisms – than warfarin. Patients with a life expectancy of less than a year were excluded.[22]

Rivaroxaban once daily proved non-inferior to warfarin for the prevention of strokes and embolisms, with a lower incidence of intracranial bleeding. Patients with a life expectancy of less than 2 years were excluded, so it is hard to obtain conclusions valid for cancer patients.[23]

In the Global Study to Assess the Safety and Effectiveness of Edoxaban versus Standard Practice of Dosing With Warfarin in Patients With Atrial Fibrillation (ENGAGE-AF-TIMI 48), more than 21,000 patients with non-valvular AF were randomised to warfarin or edoxaban. Edoxaban 60 mg once daily was non-inferior to warfarin, but it significantly reduced bleeding events and cardiovascular death.[24]

While all of these drugs have been tested in the general population, available information in patients with cancer and AF is scarce. Although cancer did not constitute an absolute contraindication for participation in the clinical trials, patients with a short life expectancy were excluded. As such, we do not have specific data on the safety and efficacy of DOACs in patients with AF and cancer. In the pivotal clinical trials of DOACs for patients with deep vein thrombosis, the number of patients with cancer was also small, between 2.6% and 6.0%. In addition, information on the type of cancer, the stage and the concomitant use of chemotherapy were not collected. These are retrospective analyses of the original trails, and the number of patients with cancer was too low to obtain solid conclusions.[21–24]

The relationship between stroke and cancer is complex. Stroke is common in cancer patients, and cancer patients with ischaemic stroke often show different risk factors, stroke biomarkers and stroke aetiology compared with non-cancer patients with ischaemic stroke.[25] There has been controversy in regard to the risk factors in the pathogenesis of stroke in cancer patients. The presence of a hypercoagulable state and increased D-dimer levels are common.[26,27] In a subanalysis of the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in

Atrial Fibrillation (ROCKET-AF), after adjusting for competing risks, the estimated 1-year cumulative incidence of ischaemic stroke in patients with cancer and AF was 1.4% (95% CI [0.0–3.4]).[28]

In a subanalysis of the Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation (ARISTOTLE) trial, the subgroup of patients with cancer showed no significant associations between history of cancer and stroke/systemic embolism, major bleeding or death.[29] The safety and efficacy of apixaban versus warfarin were preserved among patients with and without active cancer. Apixaban was associated with a greater benefit for the composite of stroke/systemic embolism, MI and death in active cancer (HR 0.30; 95% CI [0.11–0.83]) versus without cancer (HR 0.86; 95% CI [0.78-0.95]).

In contrast, there is another analysis in regard to the behaviour of patients with cancer from ENGAGE-AF-TIMI 48.[30] In the original trial there were 21,105 patients with AF randomised to edoxaban or warfarin.[24] Patients with active malignancy – defined as a post-randomisation new diagnosis or recurrence of remote cancer – were followed for clinical events over a median 2.8 years. Patients with active malignancy, compared with those without, had increased death (12.0% per year versus 3.6% per year; univariate HR 3.3; 95% CI [3.0–3.7]) and major bleeding (7.4% per year versus 2.5% per year; HR 2.9; 95% CI [2.4–3.4]), but not stroke or systemic embolism (HR 0.8; 95% CI [0.6–1.2]).

In the analysis by subgroup of ROCKET-AF and the Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY) trial, the risk of bleeding in cancer patients was two- to six-times higher than in patients without cancer.[21,23] This is probably because the pathology of our patients (breast cancer) does not confer a special tendency to bleeding, and in these studies the few patients with cancer who were analysed included other types of cancer with greater predisposition to bleeding, such as colorectal cancer. Also, the study by Zhang et al. showed a trend towards greater intracranial bleeding in patients with cancer and AF.[31]

No specific clinical trials have been conducted comparing the use of DOAC versus VKA in cancer patients; all we have are observational studies. In the study by Shah et al., which included 16,000 patients with AF and cancer, the risk of major bleeding was significantly lower in patients taking apixaban than in patients taking VKA, rivaroxaban or dabigatran.[10]

With the available data, the lack of evidence for the use of DOACs in cancer patients means that their use must be discussed in each patient. Fluctuations in renal and hepatic function may affect the levels of these drugs and dose adjustments may be required. The pharmacokinetic properties of cancer therapies should be taken into account when considering the use of DOAC in patients having active chemotherapeutic treatment, although data on the clinical relevance of the interactions are scarce.

Until clinical trials are conducted to verify the efficacy and usefulness of DOAC specifically in oncological patients, the clinician should rely on observational studies, as more robust evidence is not available.

Conclusion

The management of antithrombotic therapy for stroke prevention in oncologic patients with AF is challenging and it can determine their outcomes in terms of bleeding and embolic events. It requires involvement of cardiologists and oncologists to individualise the treatment for each case and offer the best therapy. Specific clinical trials are needed to assess the best treatment for these patients. Given the available data from observational studies, DOACs seem to be a safe choice for this group of patients. ■

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