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Optimizing antithrombotic therapy for atrial fibrillation in cancer

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ABSTRACT

Atrial fibrillation (AF) may be a pre-existing disease before cancer diagnosis, may be a direct effect of the neoplasm or, more often, appears as a post-surgical complication, especially after thoracic surgery. AF may also develop as a consequence of chemotherapy or radiotherapy. The management of the anticoagulation in cancer patients with AF is challenging, and data on these patients are lacking. 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/or changes in renal or hepatic function. Low molecular weight heparins and direct oral anticoagulants (DOACs) could be preferred. However, the possible pharmacological interactions of DOACs with anti-cancer and anti-arrhythmic drugs and the bleeding risks in thrombocytopenic patients should be considered. Based on these considerations, a careful evaluation of the antithrombotic strategy with the best efficacy/safety ratio is always needed in cancer patients and anticoagulation for AF should be tailored individually. An ongoing consultation of oncologists/hematologists with cardiologists and coagulation experts in a multidisciplinary approach, with a periodic re-assessment of the benefits of anticoagulation with changes in cancer status/advancement and treatment plans is needed.

1. Introduction

Atrial fibrillation (AF) is the most common cardiac rhythm disorder and affects about 1.5–2% of the general population. Patients experiencing AF have a 5-fold increased risk of ischemic stroke, a 3-fold increased risk of heart failure, and a 2-fold increased rate of mortality [1]. Cancer patients may experience a wide spectrum of cardiac arrhythmias, including AF [1–3]. Data on the prevalence of AF in the setting of cancer are very limited. However, the prevalence of AF reported so far appears to be up to 20% in oncologic patients, in various types of cancer [4,5]. In a large epidemiological retrospective cohort study conducted in Taiwan, of 24,125 cancer patients, 2.4% of patients were already affected by AF at the time of cancer diagnosis and 1.8% developed new onset AF during the course of the cancer treatments [4]. In this study, AF was associated with higher incidence of thromboembolism and heart failure in cancer patients, compared with patients with cancer but without AF [4]. Evidence suggests that AF could be the consequence of cancer and/or anti-cancer therapies, but also could precede the development of cancer (mostly in the first 3 months following a diagnosis of AF) or be a marker of occult cancer. However, data on this latter aspect are contrasting [5]. In any case, these two conditions may share common risk factors, such as advanced age, obesity, diabetes mellitus, inflammation, and cigarette smoking [5]. New onset AF in oncologic patients is associated with negative prognosis and difficult therapeutic management [4]. Among patients with new onset AF, active cancer appears to be associated with 11-fold increased risk of 30-day mortality [6]. The management of the anticoagulation in cancer patients with AF is challenging and influenced by many complicating factors (thrombocytopenia, changes in renal or hepatic function, malnourishment) and the lack of solid evidence on treatment strategies. The purpose of this review is to summarize the evidence on the association between AF and cancer and to provide some practical considerations about the management of anticoagulation in this setting.

2. AF in cancer patients: risk factors and mechanisms

Although AF may be a pre-existing disease before cancer diagnosis, multiple causes can induce new onset AF in oncologic patients [6]. AF may be due to a direct effect of the neoplasm, in the case of intra-cardiac cancers or due to extra-cardiac compression, or a post-surgical complication, especially after thoracic (lung, esophageal cancer) or abdominal surgery (colon cancer) [6]. Factors such as aging, electrolyte

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abnormalities and malnourishment contribute to the onset of AF in cancer patients. AF may develop also during/after cancer chemotherapy, including treatments with novel "targeted" drugs, or radiotherapy [3,7,8]. Anti-cancer drugs may induce AF through multiple and partially uncertain mechanisms, including: 1) the release of cytokines, 2) abnormalities in calcium homeostasis and also 3) direct myocardial damage, creating an arrhythmogenic substrate [9]. Additional arrhythmogenic conditions in cancer patients include: coronary vasospasm, through the inhibition of endothelial nitric oxide (NO) synthesis, oxidative vessel damage, and a direct toxic effect on the atrial conduction system [9]. Treatments with anthracyclines may increase, for example, cardiomyocyte susceptibly to reactive oxygen species (ROS) interfering with the production of endogenous antioxidants, catalase, glutathione-peroxidase and superoxide dismutase [6,7]. AF associates with increased levels of C-reactive protein, suggesting a key role of an inflammatory state in AF development/maintenance [10]. Anthracyclines and alkylating agents (in particular cisplatin) are the drugs mostly associated with new-onset AF in oncologic patients [11–15]. Ifosfamide, melphalan, cyclophosphamide, 5-fluorouracil, capecitabine, monoclonal antibodies and also bisphosphonates can also induce AF [16–26]. Ibrutinib, an inhibitor of Bruton kinases, approved for chronic lymphatic leukemia, Waldenstrom's macroglobulinemia and mantle cells lymphoma, is responsible for newly onset AF, in particular in the first six months of treatment [27–29]. Also, rituximab was reported to be associated to new onset AF, reversible upon the discontinuation of the drug [30]. Reversible arrhythmias have been reported also in patients treated with interferons and interleukin (IL)-2. In a phase II trial of patients with metastatic renal cell cancer treated with subcutaneous IL-2 plus interferon-alpha, two cases of AF developed in 5-years of follow-up [31]. Tyrosine kinase inhibitors (TKI) may produce important cardiotoxicity. In patients with metastatic renal cell carcinoma treated with sorafenib after sunitinib failure, 1/3 patients experienced AF within the first 2 weeks of treatment [32]; this occurred also with sunitinib plus lenalidomide [33]. Literature reports describe the occurrence of AF with azathioprine, docetaxel, mitoxanthrone and trastuzumab [34–40]. Despite the lack of definitive data, it is conceivable that also radiotherapy could induce AF through the development of heart failure [41].

3. Optimizing antithrombotic therapy for AF in cancer

A new diagnosis of AF in oncologic patients is associated with difficult therapeutic management [4,8]. The anticoagulation of cancer patients experiencing AF is challenging, because of the need to balance the thromboembolic and the bleeding risk. These two risks are both increased in relation to the neoplasm itself and the effects of anti-cancer treatments [3]. Cancer is associated to a prothrombotic state due to release of pro-coagulants by tumor cells, platelet activation and endothelial dysfunction. The risk of thrombosis is highest in metastatic disease and in the most aggressive malignancies [42–44]. On the other side, the bleeding tendency of intracranial and hematologic neoplasms and drug-induced thrombocytopenia are concomitant complicating factors. Also, the need for frequent surgery or other invasive procedures and other factors such as advanced age, anemia, renal failure, frailty, and gastrointestinal (GI) cancers increase the bleeding risk in oncologic patients [42–44]. Moreover, current clinical scores for the prediction of thromboembolism (CHA_2DS_2-VASc) and bleeding (HAS-BLED) have not yet been validated in this context [3]. The recent ESC Position Paper on cardiovascular toxicity stated that the decision on antithrombotic therapy for stroke prevention in AF may be quite challenging and should not be based only on the risk assessment scores used for the general population [3]. In any case, anticoagulation is universally considered to have a positive risk benefit ratio in patients with a CHA_2DS_2-VASc score ≥ 2 and a platelet count $\geq 50 \times 10^9$/L [3].

There is also controversy as to which anticoagulant is the best. The use of vitamin K antagonists (VKAs) in cancer patients with AF is problematic, mainly because of the difficulty in maintaining a stable international normalized ratio (INR) resulting from multiple factors, including variable dietary intake due to vomiting or nausea, low body weight and drug interactions [45]. The response to VKAs and the bleeding risk are unpredictable in this context and also in relation to possible changes in renal and/or hepatic function. In a recent retrospective study of 2168 consecutive patients with AF and cancer followed 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, and pulmonary embolism) or major bleeding in patients treated with VKAs, when compared to those who were not anticoagulated. However, only 12% of patients on VKA therapy achieved a therapeutic INR, and the difficulty of maintaining effective anticoagulation likely contributed to the lack of treatment benefit [46]. In a large population of veterans taking VKAs for AF or for VTE, warfarin laboratory control worsened significantly over a period of 6 months following a new diagnosis of cancer, compared to no oncologic patients [47].

The use of low molecular weight heparins (LMWHs), widely studied in cancer patients experiencing VTE [48,49], is not recommended/approved for AF in the general population (no phase 3 studies support long term use) [1]. A short to intermediate use of LMWHs could be considered in AF in patients with cancers at high bleeding risk, including patients with luminal GI cancers [3], or unable to tolerate oral route of administration, or peri-operatively (bridging therapy) [50]. In some studies, LMWHs showed also an anti-angiogenic role, which has been considered theoretically beneficial against cancer progression [51].

Direct oral anticoagulants (DOACs) present advantages because of their short half-life, less food and drug interaction than VKAs, and absence of a routine monitoring. The current European AF guidelines recommend these drugs over VKAs in patients with AF [1]. High quality data on the efficacy and safety of DOAC therapy in cancer patients is limited to randomized trials in oncology patients with VTE [52–55], good information on the use of DOACs for cancer patients with AF is lacking [1,56]. However, recently, some important evidence on the use of DOACs in patients with cancer and AF has been produced. In a Danish population-based cohort study, the absolute risks of thromboembolic or bleeding complications were nearly the same in AF patients with and without cancer, and treated with VKAs or DOACs [57]. A post-hoc analysis from the ARISTOTLE trial showed that, compared with warfarin, apixaban was associated with a greater reduction in the risk of stroke, systemic embolism, myocardial infarction, and death in patients with cancer (Hazard Ratio -HR-, 0.30; 95% CI, 0.11–0.83) versus no cancer (HR, 0.86; 95% CI, 0.78–0.95) [58]. In an 8-year cohort study, the use of DOACs compared with warfarin in cancer patients with AF was associated with a significantly lower risk of stroke and systemic embolism (HR 0.42, 95% CI 0.24–0.74) and major bleeding (HR 0.26, 95% CI, 0.09–0.76); furthermore, at 1 year, no intracranial bleeds in patients treated with DOACs were reported. There was no difference between the DOAC and warfarin groups in GI bleeding and death from any cause at 6 months and one year [59]. A study of the Market Scan databases compared the safety and effectiveness of DOACs and warfarin in 16,096 AF patients with active cancer. Compared with warfarin, risks of bleeding were similar in patients treated with rivaroxaban and dabigatran, whereas apixaban use was associated with significantly lower rates of bleeding (HR 0.37, 95% CI 0.17–0.79) [60]. Two meta-analyses showed a reduction in stroke/embolism and intracranial bleeding in patients with cancer treated with DOACs compared to VKAs [61,62], while no difference in major bleeding between the two groups was found. A large registry including 196,521 AF patients with active cancer showed a lower 1-year mortality in the DOAC group (dabigatran 25%, $p < 0.001$; rivaroxaban 24.4%, $p < 0.001$; apixaban 30%, $p < 0.001$) as compared with VKA group (44.9%) [63].

Moreover, in cancer patients with AF, the risk of VTE is lower with DOACs compared with warfarin, as evidenced in the large population of the MarketScan databases [60]. It should also be emphasized that the prescription of oral anticoagulation after ischemic stroke in AF cancer

patients has increased since the introduction of DOACs [64].

Although these findings generate enthusiasm, caution is warranted when considering use of DOACs in cancer patients with AF. First of all, caution is needed in patients with gastrointestinal malignancies, who may be predisposed to major GI bleeding. In this regard, it is important to consider the characteristics of the different DOACs in cancer patients. Treatment with edoxaban or rivaroxaban has been associated with an increased risk of GI bleeding in oncologic patients with VTE, as compared with LMWH [52,53], while apixaban is not associated with increased GI bleeds [54]. However, it should be emphasized that there are no head-to-head trials with DOACs for this outcome. Gastric protection with proton pump inhibitors or H2 blockers should always be considered in patients with cancer and high bleeding risk [56].

Second, possible pharmacological interactions between DOACs and anti-cancer therapies should be taken into account [65–69]. However, the extent to which each DOAC interacts with each anti-cancer drug and the clinical relevance of these interactions is not clear. Strong glycoprotein-P or CYP3A4 inducers or inhibitors should be avoided, but a majority of anti-cancer drugs have small or moderate effect on glycoprotein-P or CYP3A4, and therefore many interactions are not clinically relevant. Further data on this point are needed and will certainly become available in the future.

Third, in randomized clinical trials of DOACs, patients with platelet count $<100 \times 10^9$/L were excluded. Thrombocytopenia is common during chemotherapy or it can be developed by tumor invasion of the bone marrow, or by an immune-mediate mechanism. There is no contraindication to anticoagulation in case of platelet count $\geq 50 \times 10^9$/L, in the absence of other bleeding risk factors. In patients with severe thrombocytopenia ($<50 \times 10^9$/L), considering the lack of data on DOACs in this clinical setting, reduced doses of LMWHs may represent a valid choice for treatment [70,71]. In patients with platelet count between 25 and 50×10^9/L, half doses of LMWH may be safe. In the case of platelet counts $<25 \times 10^9$/L, treatment decisions should be individualized [70,71].

Finally, DOACs are safe in AF cancer patients with creatinine clearance >30 ml /min. They can also be used cautiously and with close monitoring until creatinine clearance is 15 ml /min. Dehydration, sepsis and drugs can worsen renal function in cancer patients and dose adjustments may be needed [65]. Close monitoring for bleeding signs/symptoms is also needed in patients with chronic liver failure [65].

4. Conclusions and perspectives

In cancer patients the incidence of AF is increased. Patients with both AF and cancer require a multidisciplinary approach to face the problems associated with this arrhythmia. Patients at high risk for AF should be managed, for example, by choosing anti-cancer drugs which are less associated with the risk of AF. Common stroke risk and bleeding risk stratification scores are not validated in these patients, and an individualized stratification for this specific population is necessary. The choice of anticoagulant is also a challenge in cancer AF patients. Since VKAs interact with several oncologic treatments, in patients with active cancer undergoing chemotherapy, coagulation experts traditionally prefer LMWHs (in general as a short- to intermediate-term treatment), especially in patients with high bleeding risk (including intraluminal GI malignancies) or in the case of metastatic disease. When choosing an oral anticoagulant strategy (VKA or DOAC), patient characteristics, comorbidities and also preferences should be considered and a careful follow-up needs to be adopted. A complete clinical examination for bleeding symptoms/signs, a regular laboratory evaluation of renal/hepatic function, as well as periodic full blood counts, including platelets, should be performed. The choice of any DOAC should always be guided by the renal and hepatic function, and the interactions with anti-cancer and anti-arrhythmic drugs, and the safety of anticoagulation should be periodically reassessed.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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