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ATRIAL FIBRILLATION CAUSED BY THE DISEASE OF CANCER

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Abstract. Cancer patients have a higher risk of atrial fibrillation (AF) than the general population. The pathophysiological mechanisms involve the pro-inflammatory status of the immune system in these patients and the exacerbated inflammatory response to cancer treatment and surgeries. Adequate management and prophylaxis for its occurrence are important to reduce morbidity and mortality in this population. There is a challenge in predicting thromboembolic and bleeding risk in these patients, as standard stroke and hemorrhagic prediction scores are not validated for them. The CHA2DS2-VASc and HAS-BLED scores, commonly used in the general population, are also used for these patients. In this review, we demonstrate the correlated mechanisms of AF occurrence in cancer patients, as well as the therapeutic challenges in managing AF in this population.

Keywords: atrial fibrillation, cancer, anticoagulation, cardiotoxicity, drug-drug interaction

Introduction. Atrial fibrillation (AF) in cancer patients is closely linked to several predisposing factors and involves multiple mechanisms. The incidence of AF in cancer patients is high, affecting around 20% of this population [1]. The pathophysiology of AF in these patients is associated with the pro-inflammatory status of the immune system, as well as with treatments such as the inflammatory response to cancer surgery and the cardiotoxic effects of anti-cancer drugs and radiotherapy [2].

It's crucial to understand the mechanisms that cause and sustain this heart rhythm disorder in cancer patients, in order to establish preventive measures and effective treatments. Proper management and prevention of atrial fibrillation can reduce hospital admissions, illness, and death among these patients. This should be tailored to each individual, taking into account the specific characteristics of cancer patients [3].

Epidemiology. Epidemiological evidence is typically limited, but it shows that cancer patients have a higher risk of atrial fibrillation (AF) than the general population [4]. Atrial fibrillation occurs in around 1.5–2% of the general population [5], but in the cancer population, the incidence of AF is around 30%. The prevalence of AF in the cancer population may vary depending on the type of cancer,

chemotherapy treatment, and surgical procedures.

The mechanisms by which certain cancer treatments trigger arrhythmia are unclear, but individual risks vary depending on the treatment, the patient's clinical circumstances, and tumor- induced metabolic and inflammatory changes.

The risk of AF is higher in patients older than 65 years and may occur in 2 out of 3 patients with cancer and those with pre-existing cardiovascular diseases [6].

Table 1

Anti-cancer drugs related to atrial fibrillation.

Alkylating agents:
Nitrogen mustards: Melphalan, Cyclophosphamide
Platinum complexes: Cisplatin.
Antimetabolites: Capecitabine, 5-Fluorouracil, Gemcitabine.
Anthracycline agents: Doxorubicin. Bruton tyrosine kinase: Ibrutinib Taxanes: Docetaxel, Paclitaxel HER2 inhibitors: Trastuzumab
Monoclonal antibodies: Alemtuzumab, Cetuximab, Ipilimumab, Obinutuzumab, Ofatumumab, Rituximab.
Small molecules: Sorafenib, Sunitinib.
Vascular endothelial growth factor inhibitors: Bevacizumab Histone deacetylase inhibitors: Dacinostat, Belinostat, Romidepsin Proteasome inhibitors: Carfilzomib, Bortezomib
Immunotherapy: Interleukin 2
Hormones:
Gonadotropin-releasing hormone (GnRH) antagonist: Degarelix
Androgen Synthesis Inhibitors: Abiraterone
Aromatase inhibitors
Glucocorticoids: high doses of Dexamethasone.

Postoperative atrial fibrillation (AF) is the most common type of AF linked to cancer. Its prevalence ranges from 16 to 46% for cardiothoracic surgery and 0.4–12% in non-cardiothoracic surgery [2,8]. AF occurs in about 5.6–28% of cases of lung resection in lung cancer, according to a systematic review [5]. As a result, it may have a negative impact on the prognosis of these patients and may increase postoperative mortality, hospitalization time, and hospital costs [7].

When it comes to anticancer drugs, the incidence of atrial fibrillation (AF) as a side effect of treatment ranges between 2.2% and 16.7%. Many cytotoxic agents,

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such as alkylating agents (like Cisplatin, Cyclophosphamide, Ifosfamide, and Melphalan), anthracyclines, tyrosine kinase inhibitors (such as Ibrutinib, Sorafenib, and Sunitinib), antimetabolites, taxanes, and topoisomerase II inhibitors, have been found to significantly increase the risk of AF-related heart problems [2, 6] (see Table 1). Additionally, cancer patients using direct oral anticoagulants (DOACs) are twice as likely to experience hemorrhagic and thromboembolic events compared to the general population [1].

PATHOPHYSIOLOGY

Atrial fibrillation (AF) in cancer patients is influenced by several risk factors. These include traditional risk factors seen in the general population, such as hypertension, diabetes mellitus, hypercholesterolemia, smoking, alcohol consumption, heart failure, myocardial ischemia, chronic pulmonary disease, thyroid dysfunction, chronic kidney disease, and advanced age. Additionally, inherent factors related to cancer, like electrolyte imbalances, hypoxia, and metabolic disorders, can contribute to AF [11]. Other cancer-related risk factors include autonomic nervous system (ANS) imbalance, which can be caused by increased sympathetic stimulus due to pain or other forms of physical or emotional stress. Cancer treatments such as surgery, chemotherapy, and radiation, as well as the presence and progression of malignancies, can also contribute to extreme inflammatory stress, potentially leading to the development of AF[12].

Figure 1

Pathophysiology of AF in cancer patients.

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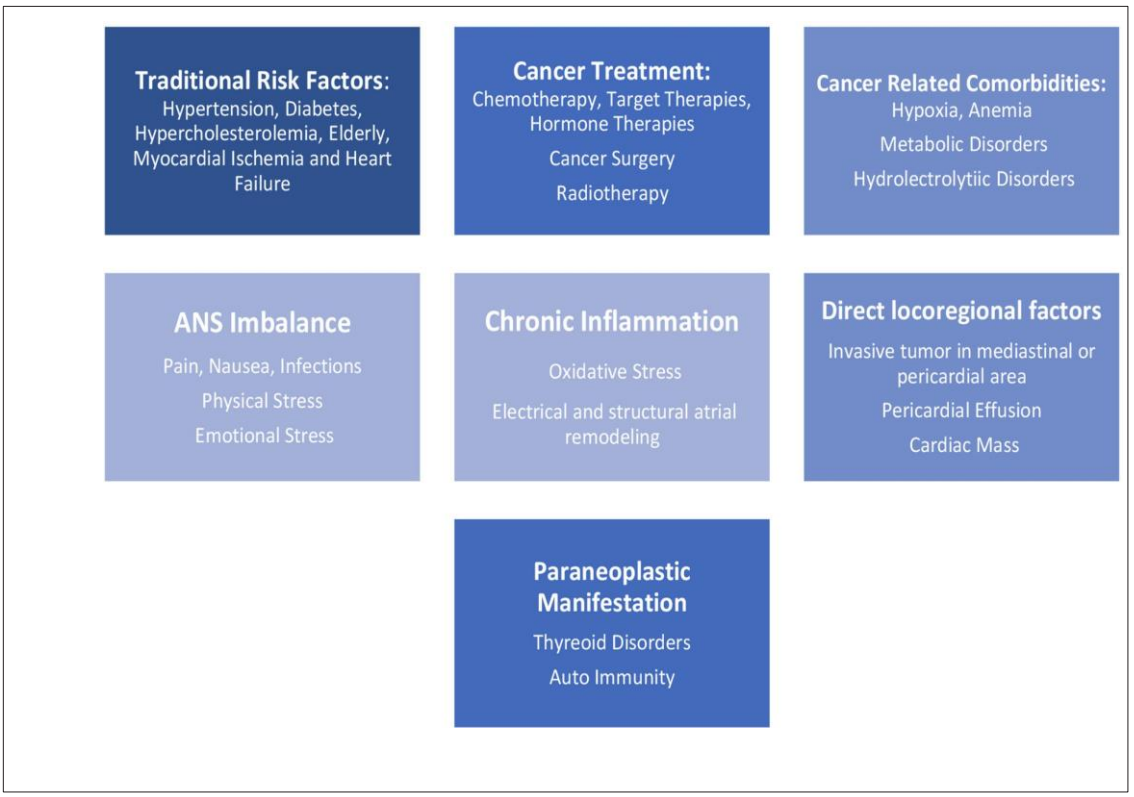


Cardiotoxicity is a significant side effect of cancer treatment, leading to increased illness and death. Additionally, the inflammatory stress from cancer and its treatment raises the risk for those with a history of cardiovascular disease. Various cancer treatments, including chemotherapy, radiotherapy, hormone therapy, and targeted therapy, are linked to cardiotoxicity [2, 4, 10] (see Table 1), and this association increases the risk of atrial fibrillation.

The higher prevalence of atrial fibrillation (AF) in cancer patients is believed to be caused by the systemic inflammation resulting from malignancy, which promotes the occurrence of AF by causing restructuring of the atria. This idea is supported by the increased levels of inflammatory markers such as C-Reactive Protein (CRP), Tumor Necrosis Factor α (TNF α), and Interleukins and that are found in cancer patients and are associated with the risk of developing this arrhythmia[13].

The immune system's involvement has also been hypothesized as an autoimmune paraneoplastic syndrome sustained by antibodies directed against tumor antigens. This may lead to an immune reaction against atrial structures, possibly triggering atrial fibrillation [12].

TREATMENT

At present, there are no specific guidelines for managing atrial fibrillation (AF)

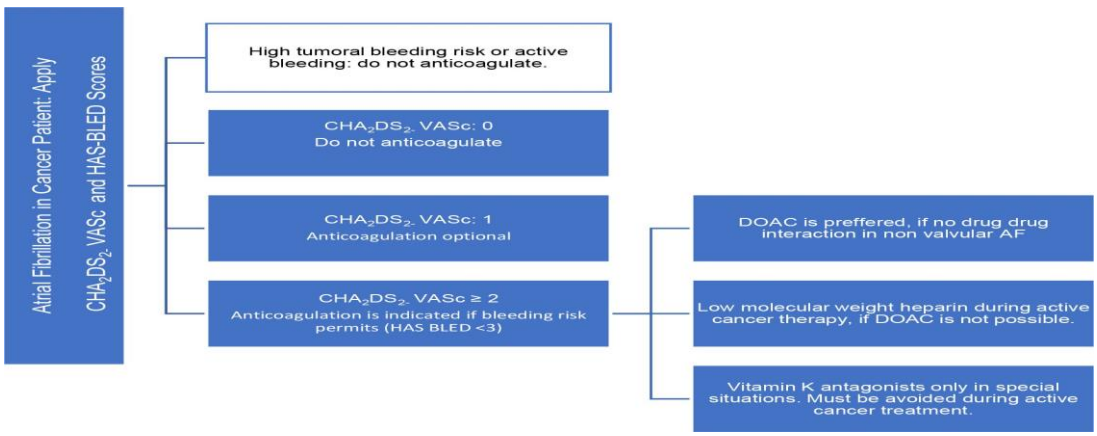
in cancer patients. The treatment aligns with the general population, aiming to improve symptoms, control arrhythmia, and prevent stroke and systemic embolism, as recommended by the current guidelines in ESC and ACC/AHA.

Anticoagulation Therapy

The cancer patient has certain characteristics, such as an increased tendency for blood clotting and a higher risk of blood clots due to certain anticancer treatments. Additionally, they also have an increased risk of bleeding. These risks are not fully explained by the CHA2DS2 – VASc score or the HAS-BLED score.

Table 2

Thromboembolic and bleeding risk assessment score.



Therefore, due to the limitations of these scores, when analyzing cancer patients at risk of developing AF, the decision of whether to initiate anticoagulation treatment should be tailored to each individual, taking into consideration the balance of risks and benefits. It is essential to assess the patient's treatment goals and preferences, potential drug interactions, performance status, and cancer prognosis.

It is significant to carefully consider the choice of anticoagulants for treating atrial fibrillation (AF) in cancer patients within the field of cardio-oncology. Unlike general cardiologists who often treat anticoagulation similarly to patients without cancer, it is essential to recognize that cancer patients may have limitations with vitamin K antagonists (VKA), especially when their creatinine clearance is above 30 ml/min. VKAs can still be used when creatinine clearance is above 15 ml/min, but close monitoring is necessary, as factors such as dehydration, sepsis, and cancer drug nephrotoxicity can lead to deteriorating renal function. Therefore, renal dose

adjustment is crucial [4,9].

Thrombocytopenia

Nausea and vomiting are common side effects of cancer therapy, particularly during chemotherapy. They are often accompanied by poor food intake and can also be caused by drug interactions. Currently, the percentage of time spent within the therapeutic range is low, making it difficult to manage invasive procedures or episodes of thrombocytopenia due to the delayed onset and prolonged duration of action [16].

Direct oral anticoagulants (DOACs) have several advantages over VKA, including fast onset of action, short half-life, and fewer food/drug interactions. Routine blood tests are not necessary to ensure that the patient is within the therapeutic window of anticoagulation when using DOACs. However, it's important to note that all DOACs are influenced by the P-glycoprotein (P-gp) system and can also be affected by the CYP3A4 system in the liver, particularly Apixaban and Rivaroxaban [15]. The use of DOACs alongside drugs that inhibit or induce P-gp/CYP3A4 can lead to anticoagulation levels outside of the therapeutic range. It's not recommended to coadminister DOACs with cancer drugs and adjunctive therapies that are strong P-gp inducers or inhibitors, which poses a significant limitation to their use in cancer patients, as many chemotherapy agents fall into this category [13].

If DOAC is not permitted, low molecular weight heparin (LMWH) is preferable over vitamin K antagonists during active cancer treatment, with more favorable results concerning interactions and therapeutic anticoagulation. The disadvantage of this medication is cost, discomfort in the application of the medication and prolonged use due to active cancer.

Basically, vitamin K antagonists are reserved in valvular AF, during non-active cancer treatment, period that has less drug-drug interaction and oral intolerance, and for renal impairment <15 ml/min [14].

Antiplatelet Therapy

This combination therapy is recommended for cancer patients undergoing treatment who also have acute coronary syndrome (ACS) or are undergoing elective percutaneous coronary intervention (PCI). It is important to evaluate both the risk of ischemia and the risk of bleeding for each patient, especially individuals with gastrointestinal, genitourinary or central nervous system cancer [4]. Triple therapy, which includes aspirin (AAS), clopidogrel, and oral anticoagulation (OAC), should be administered for at least 1 month in patients with ACS and can be extended to 3–6 months for those with a high risk of ischemia and low risk of bleeding [12]. In cases of elective PCI, triple therapy is reserved for only 1 month if the risk of ischemia is

greater than the risk of bleeding. If the risk of bleeding is higher, double therapy with clopidogrel and OAC is administered post-PCI. Double therapy, consisting of clopidogrel and OAC, should be continued for the full 12 months. After completing 12 months of treatment, oral anticoagulation alone can be continued for cancer patients with AF who experienced ACS or underwent elective PCI [15].

It is important to know that Clopidogrel is preferred over others P2Y12 in combination therapies because it has a lower bleeding risk. If the only oral anticoagulation possible is VKA therapy, rigorous monitoring of INR values is needed. DOACs is preferred. Some recent trials in the general population, PIONEER AF-PCI , REDUAL PCI and AUGUSTUS trials, support the safety of Rivaroxaban, Dabigatran, and Apixaban as respective alternatives for dual therapy with Clopidogrel after percutaneous coronary intervention (PCI).

Chronic Liver Dysfunction

Patients with CLD were excluded from randomized clinical DOAC trials, leading to a lack of safety data in this population. Current recommendations for the use of DOAC therapy are based on data in pharmacokinetic studies and small observational studies. Rivaroxaban and Edoxaban can be prescribed with caution in patients with mild liver impairment and must be avoided in moderate or severe liver impairment. Apixaban and Dabigatran can be used with caution in mild and moderate liver impairment and must be avoided in severe impairment [14, 15]. Close monitoring for signs and symptoms of bleeding is needed in these patients. Further studies are needed.

Antiarrhythmic Therapy

The decision about antiarrhythmic therapy is part of AF treatment. Initially, treat AF triggers, as hydro electrolytic disturbance, fever, sepsis, pain and hypoxemia [4], during cancer therapy is important because sinus reversion can occur spontaneously. In an echocardiogram, it is possible to assess other potential triggers such as acute ventricular disfunction, pulmonary thromboembolism, pericardial effusion, and cardiac tamponade, tumor invasion e endocarditis. If AF persists, the decision of rate control or rhythm control must be based in check potential interactions between antiarrhythmics and cancer drugs, and also contraindications to long-term anticoagulation therapy. Ablation therapy in patients with AF and cancer is not well-defined.

CONCLUSION

Atrial fibrillation has a higher incidence in cancer patients. Cancer medical treatment and surgery contribute to its occurrence, although an increased incidence of AF is observed in these patients even in the absence of treatment. This suggests

that the pro-inflammatory status in cancer predispose the arrhythmia.

Common risk stratification scores, as CHA2DS2VASc and HASBLED, are not validated to this population, once do not take cancer as a variable account. An individualized stratification tool for this specific population to have a better evaluation of thrombotic and bleeding risk in cancer patients is necessary.

The anticoagulation decision is also a challenge due to drug-drug interactions and special situations as thrombocytopenia. It is a challenge to manage stroke prevention in patients with AF and cancer with antithrombotic therapies due to a lack of evidence and guidelines to guide the ideal treatment, given the complexity of these patients.

AF brings an increase in the morbidity and mortality of these patients, in addition to affecting the prognosis, the therapeutic effects, increasing the costs of hospitalization and disability of these patients. Future studies are needed to orientate better care in AF related to cancer.

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