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Atrial Fibrillation in Patients with Cancer

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Abstract

Atrial Fibrillation (AF) is considered a rising epidemic in the world with an estimated 33.5 million cases world-wide in 2010, and the number of cases is expected to increase by atleast 5% per year.

AF has been related with major cardiovascular events containing stroke, progressive congestive heart failure and also sudden cardiac death, with the subsequent disability and higher mortality rate, and one of the most common etiologies of dementia, even seizure and also depression in the elderly. AF has been shown to confer a five-fold increase in the probability of cerebrovascular events in all ages and accounts for 15% of all strokes.

Introduction

Atrial Fibrillation (AF) is considered a rising epidemic in the world with an estimated 33.5 million cases world-wide in 2010, and the number of cases is expected to increase by atleast 5% per year. Also, the number of patients with AF in the United States (US) is expected to raise from 2.3 million in 2001 to 5.6 to 6.3 million in 2050. But, the dimension of the actual problem would be underestimated in the light of sub-clinical and clinical disease.

AF has been related with major cardiovascular events containing stroke, progressive congestive heart failure and also sudden cardiac death, with the subsequent disability and higher mortality rate, and one of the most common etiologies of dementia, even seizure and also depression in the elderly. However, stroke is the most dangerous complication of AF, According to the 2015 Report from the American Heart Association, about 795,000 strokes are reported each year in the US.

AF has been shown to confer a five-fold increase in the probability of cerebrovascular events in all ages and accounts for 15% of all strokes. This has tremendous impact on the elderly. However the other populations with an elevated risk are females, patients with diabetes mellitus, hypertension, heart failure, vascular disease, and everyone with a previous history of cerebrovascular disease.

Atrial Fibrillation and Malignancy

Traditionally several chronic conditions like valvular heart disease (particularly mitral valve disease), hypertension and coronary artery disease and cardiomyopathies, as well as hyperthyroidism, are linked to the development of AF, but malignancy is not regarded as one of its risk factors. To assist the prediction of thromboembolic events in patients with AF there are many different clinical scores, but generally cancer is not a part of them. However, in some studies malignancy is a part of bleeding risk scores used in the guidance of anti-thrombotic therapy in patients with AF [1].

Inspite of this, we know of an increasing body of scientific evidence establishing the association of malignant disease and AF in recent decades. Compared to general population, there seems to be a higher association between cancer and elevated prevalence of AF as evidenced by large epidemiological studies.

An incidence of up to 28% of post-operative AF has been reported for esophageal, colorectal and lung cancer, which is greater when compared to similar populations experiencing surgery for non-neoplastic conditions. Finally, there is evidence from a retrospective study comparing cardiovascular outcomes in patients with AF receiving therapy for colorectal, breast, and cervical cancers which indicates a greater tendency to thromboembolic events [2].

The underlying mechanism responsible for the association between AF and malignancy is not well understood. Usually there are other comorbidities in cancer patients which can make them more susceptible to developing AF. Additionally, the augmented inflammatory response seen in patients affected by neoplastic processes, the hyper-adrenergic state with the characteristic

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autonomic nervous system imbalance, and the common metabolic and electrolyte derangements typical of this patients have been proposed as the perfect substrate for electrical disturbances of the cardiovascular system. Another probable mechanism might be the induction of AF by chemotherapeutic agent. Other postulated factors are a direct contribution of the tumor due to primary or metastatic involvement of the cardiac structures or adjacent organs, as well as paraneoplastic syndromes.

Cancer Treatments and AF

As previously stated, the burden of cardiovascular comorbidities in patients with cancer is elevated, promoting a trial and pulmonary vein dilatation and a trial fibrosis, pathophysiological conditions considered to be the substrate required for creating and maintenance of AF. Some of the cancer therapeutics has been linked to developing AF, most likely through generation of ectopic activity or due to their effect on the electrical properties of the atrial tissue.

The most common trigger of AF generation is delayed after depolarizations, considered to be the most important mechanism associated of ectopic atrial activity. Additionally, activation of the autonomic nervous system (parasympathetic and sympathetic) has been associated with changes in the action potential, refractoriness, and repolarization of the atrial tissue leading to pro-arrhythmic activity.

Drug-induced AF related to antineoplastic agents have been reported especially for anti-microtubule agents (paclitaxel and docetaxel) in 1% of the patients, interleukin-2 (4% to 8%), alkylating agents (cyclophosphamide, cisplatin), antimetabolites (5-fluorouracil), and anthracyclines (doxorubicin and mitoxantrone) in 10.3% of patients; paroxysmal AF manifested early after infusion being the most common form reported. Similarly, corticosteroids, predominantly high dose methylprednisolone, have been reported in clinical trials to be associated with AF; although evidence is not conclusive.

On the other hand, there are other factors commonly present in most patients receiving antineoplastic therapy, like multi-drug cancer therapies used as part of the therapeutic approach against malignant disease, the presence of medical conditions in most of the patients that are predisposed to cardiac events, the prominent systemic inflammation, and the elevated psychosocial stress.

Management of AF and Prevention of Stroke

Medications are recommended for rate control, including β-blockers, non-dihydropyridines calcium channel blockers, and digoxin. Possible drug interactions with concomitant antineoplastic agents should be evaluated to avoid side effects. A common finding is QT interval prolongation as a result of antiarrhythmic therapy (i.e., amiodarone, sotalol), as well as therapies for cancer or antiemetics (frequently used as supportive treatment during chemotherapy. It sounds wise then to pay special attention to electrocardiographic changes when prescribing medications that cause QT prolongation, including tyrosine kinase inhibitors (i.e. dasatinib, sunitinib), the BRAF inhibitor vemurafenib, and arsenic trioxide; though no formal recommendations have been made.

Preventing cardioembolic events and stroke in the cancer patient is one of the most challenging issues of AF management. As previously discussed, malignant disease may increase the risk of thromboembolic complications in patients with AF *via* inducing a hypercoagulable state, favoring the starting of antithrombotic therapy. However at the same time, the cancer patients are frequently prone to hemorrhagic complications, especially in those suffering from hematological malignancies (such as myeloproliferative or myelodysplastic disorders), profound thrombocytopenia related to cancer or secondary to cancer treatment, and intracranial tumors. In this context, an individually tailored approach should be adopted after a judicious evaluation of the each clinical situation to determine the risk-benefit relationship of anticoagulation or antiplatelet medications before making therapeutic decisions.

This was elucidated in a large epidemiological study that included cancer patients in which the incidence of thromboembolism could not be predicted *via* CHADS2 score in patients with new-onset AF compared to patients with known AF. Finally, the risk assessment must include the antineoplastic therapy used, especially when medications with probable thromboembolic complications, such as alkylating agents (i.e. cisplatin), hormonal therapy (i.e. tamoxifen), or angiogenesis inhibitors (i.e. bevacizumab or sunitinib), are administered [3-5].

Finally, better management of hemorrhagic events may be achieved through controlling its modifiable predisposing factors which is facilitated by the bleeding scoring systems which provide an estimation of the bleeding risk. The HEMORR2 HAGES score (which includes malignancy as a risk factor) seems to be more accurate for the prediction of hemorrhagic complications in patients with cancer; however, this hypothesis needs to be further evaluated in clinical trials.

The use of antiplatelets is not recommended by the current AHA/ACC guidelines as part of the therapeutic strategy for stroke prevention in patients with AF. Similarly, in 2012 the ESC recommended anti-platelet therapy only in cases where patients who are at risk of stroke refuse any systemic anticoagulation. Also, ASA monotherapy is recommended only in patients with excessive risk of bleeding not taking anticoagulation therapy.

Vitamin K antagonists have been the corner stone of stroke prevention in high-risk patients during recent decades. However, special attention is required to avoid pharmacological interaction with concomitant cancer therapy that might lead to an unpredictable anticoagulant effect, especially in the setting of frequent gastrointestinal symptoms (diarrhea, vomiting), liver dysfunction, and metabolic disturbances seen in patients with malignant diseases. Effective prevention against stroke mandates a close follow-up of the International Normalized Ratio (INR), which might be challenging in this population. Some evidence indicates the elevated risk of hemorrhagic events in patients with cancer (compared to the general population) who received warfarin due to venous thromboembolism. However, formal recommendations to address this concern are not currently possible due to lack of conclusive evidence.

Though the Novel Oral Anticoagulants (NOACs) have demonstrated a better safety profile due to less intracranial hemorrhage with non-inferior preventive effect as opposed to stroke patients with non-valvular AF, the experience in cancer patients is limited at this time. Unfortunately, recent clinical trials evaluating the efficacy for stroke prevention of the NOACs containing dabigatran (RE-LY), apixaban (ARISTOTLE), and rivaroxaban (ROCKETAF) excluded patients with cancer. Additionally, there are concerns about the safety of NOACs regarding the higher risk of bleeding in patients with active malignancy, especially in the setting of potential

drug interactions with chemotherapeutic agents metabolized by the CYP3A4 enzyme and/or P-glycoprotein transporter, as well as the relatively common metabolic disturbances with changing liver and renal function, and the lack of effective reversal strategies for this group of medications. The semedications should be used with caution in patients with active malignancy until solid evidence regarding efficacy and safety is derived from clinical studies. In the same way, there is no clinical experience of the role of left atrial appendage closure devices in cancer populations.

Conclusion

AF is a common entity in patients with cancer. Due to the higher risk of bleeding and thrombosis in this population, AF Management and preventing stroke are challenging. Developing new clinical tools for assessing the risk of stroke and predicting hemorrhagic complications is required. ASA is not recommended at this time for prevention of thromboembolic events even in low-risk patients. As a final point, larger studies are necessary for assessment of NOACs and more advanced therapies in patients suffering from malignant diseases.

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