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EDITORIAL COMMENT

Anticoagulation in Cancer Patients With Atrial Fibrillation or Atrial Flutter

Are There Gaps in Care?*

Andrea M. Russo, MD

Atrial fibrillation (AF) is the most common sustained arrhythmia, affecting 3 to 6 million people in the United States in 2010, and the prevalence is estimated to rise to 12 million or more by 2050 (1,2). The incidence of AF increases with age and at any given age group, the incidence is higher in men than in women (1). AF in cancer patients may be pre-existing or could be precipitated by some antineoplastic agents. It is well established that AF or atrial flutter (AFL) increase the risk of stroke and practice guidelines recommend thromboembolic risk assessment using the CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism, vascular disease, age 65-74 years, sex category) score (3,4). There may be hesitancy to initiate or continue anticoagulation in patients with cancer, particularly when actively receiving chemotherapy, due to potential increased risk of bleeding.

In this issue of *JACC: CardioOncology*, Fradley et al. (5) evaluated patterns of anticoagulation use in cancer patients with AF or AFL based on risk for stroke and bleeding in a retrospective single-center analysis. They found that 44% of patients with cancer and AF or AFL who had an elevated risk of stroke but low risk of bleeding did not receive anticoagulation. The authors used a CHA_2DS_2-VASc score of ≥2 and HAS-BLED (hypertension, abnormal renal or liver function, stroke, bleeding, labile international normalized ratio, elderly, drugs or alcohol) score of <3 to define stroke risk warranting anticoagulation and low bleeding risk. Data were analyzed from 2016, and use of this CHA_2DS_2-VASc score was consistent with guideline recommendations for thromboembolic risk assessment in men and women at that time (4). Patients were required to have both a cancer diagnosis and documented 12-lead electrocardiography showing AF or AFL to be included in this analysis of 472 patients, representing 4.8% of 9,857 eligible cancer patients.

With advancements in screening and improvements in cancer therapy, there has been significant improvement in survival rates from many cancers (6,7). As the number of cancer survivors continues to grow with an aging population, more patients will be alive to develop AF. In addition, chemotherapeutic agents may lead to cardiovascular adverse effects, and as patients continue to live longer following cancer treatment, these cardiovascular complications may become important predictors of outcomes (8). Although many patients may have pre-existing AF, others may be asymptomatic and AF may not be detected until evaluation for cancer is underway. Therefore, the magnitude of the problem and importance of studying AF and stroke prevention in cancer patients should not be underestimated.

In the current study, 44% of patients deemed to be good candidates for anticoagulation did not receive anticoagulation (5). In multivariable analysis, older age, hypertension, prior stroke, prior AF, and venous thromboembolism history were all associated with

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anticoagulation usage while current chemotherapy, thrombocytopenia, nonsteroidal anti-inflammatory drug use, brain metastases, prior history of major bleeding, and presence of perioperative AF were inversely associated with anticoagulation usage.

Patients with AF and cancer may be at increased risk for bleeding (9). In the ORBIT-AF (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation) registry, antithrombotic therapy, rates of stroke or other thrombotic events, and cardiac death were similar in AF patients with or without a history of cancer, while patients with cancer were at higher risk of major bleeding (9). Patients with malignancy, particularly while receiving antineoplastic therapy, may be at increased risk for bleeding due to concomitant thrombocytopenia and may have pre-existing anemia. Bleeding risks may change during the course of therapy, and certain drugs used to treat cancer may interact with anticoagulants.

Current thromboembolic risk prediction models in cancer patients are extrapolated from guidelines in the general population that recommend use of the CHA_2DS_2-VASc score, but this scoring system was validated in patients without cancer (10). In fact, a retrospective analysis of 2,037 patients with cancer and pre-existing AF suggested that the $CHADS_2$ (heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism) score may be more predictive of increased stroke risk than the CHA_2DS_2-VASc score in this population (11). In a large national Danish registry that included 122,053 patients with incident AF who were not on anticoagulation, the association of CHA_2DS_2-VASc score and risk of thromboembolism and bleeding differed between AF patients with and without recent cancer, leading the authors to recommend that the CHA_2DS_2-VASc score be used with caution in patients with recent cancer (12). The American College of Cardiology/American Heart Association/Heart Rhythm Society guidelines currently recommend use of the CHA_2DS_2-VASc score for thromboembolic risk assessment, recommending anticoagulation for women with a CHA_2DS_2-VASc score of ≥3 and men with a score of ≥2, and no specific recommendations are given for patients with and without cancer (3,4).

When examining choice of anticoagulant, 54% of patients received direct oral anticoagulants (DOACs) in the current study. In a recent review of anticoagulation for cardiovascular conditions in cancer patients, DOACs, specifically apixaban and edoxaban, were felt to be safe in cancer patients with AF or AFL, demonstrating fewer bleeding complications and thromboembolic events compared with warfarin (13). Although cancer patients were excluded or underrepresented in the large randomized trials that compared DOACs with warfarin, a comparative effectiveness study that examined 16,000 patients with active cancer and oral anticoagulation therapy for nonvalvular AF showed that the incidence of ischemic stroke was similar between DOAC and warfarin users (14). The rate of severe bleeding was significantly lower among apixaban compared with warfarin and rivaroxaban users, whereas the rate was similar in dabigatran and rivaroxaban compared with warfarin users (14). Potential drug-drug interactions between cancer therapies and oral anticoagulants should also be considered prior to selection of specific agents in individual patients, in addition to the standard consideration of other factors that can impact on anticoagulant selection and dosing, such as renal function.

In patients who are not considered long-term candidates for anticoagulation, left atrial appendage devices are now available to reduce thromboembolic risks in patients with AF. The 2019 American College of Cardiology/American Heart Association/Heart Rhythm Society guidelines state that “percutaneous LAA occlusion may be considered in patients with AF at increased risk of stroke who have contraindications to long-term anticoagulation,” with a Class IIb recommendation (3). In studies that led to approval of the Watchman device (Boston Scientific, Marlborough, Massachusetts), oral anticoagulation with warfarin was utilized for a period of time following device insertion (typically warfarin and aspirin for 45 days with subsequent use of antiplatelet agents depending on transesophageal echocardiography findings) (15,16). Although trials that led to device approval actually studied patients who were candidates for warfarin, additional study is underway to evaluate patients who are not currently candidates for oral anticoagulation.

As acknowledged by the authors, this is a retrospective single-center study and potential confounders cannot be excluded. Owing to the relatively small sample size, it was not powered to determine thromboembolic events in those who did receive anticoagulation versus those who did not. As a 12-lead electrocardiography showing AF or AFL was required for inclusion, many patients with paroxysmal AF or persistent AF that was pre-existing and well controlled on medical therapy were likely excluded. Therefore, this study likely underestimates the occurrence of AF in this cohort and instead selects a higher risk cohort with more persistent AF and higher AF burden. AF burden is one factor not included in the CHA_2DS_2-VASc score that

impacts on thromboembolic risk (17). In addition, nonpharmacological therapies for AF were not discussed, including pre-existing percutaneous left atrial occlusion or surgical occlusion, the latter of which is now more commonly performed in patients undergoing cardiac surgery. Although a large percentage of eligible patients did not receive anticoagulation, factors such as frailty or contraindications to anticoagulation may also influence prescription for anticoagulation and cannot be evaluated in this retrospective analysis.

In short, there appears to be a gap in care related to treatment of AF or AFL in cancer patients, with a low usage of thromboembolic therapy, not prescribed in 44.3% of patients who have high risk for stroke with acceptable bleeding risks. Although gaps in care were previously described for the general population of patients with AF, more recent investigation has shown that those gaps have greatly narrowed, and oral anticoagulation is not prescribed in <4% of eligible patients in a quality improvement registry (18).

With therapeutic advancements, many cancer patients have improved long-term outcomes, and additional studies are needed to better assess long-term risks and benefits of anticoagulation. Specific guidelines or care pathways should be considered to help guide thromboembolic risk assessment and stroke prevention strategies in cancer patients. Additional study is also needed to determine if risk assessment algorithms other than the CHA_2DS_2-VASc score should be developed for patients with both cancer and AF. This study is important in that it raises awareness of the complexity of decisions related to oral anticoagulation recommendations in these patients, highlighting the need for an integrated and multidisciplinary approach to treatment to assure delivery of the highest-quality care.

AUTHOR DISCLOSURES

Dr. Russo has reported that she has no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr. Andrea M. Russo, Cooper Medical School of Rowan University, Cooper University Hospital, Dorrance #393, 1 Cooper Plaza, Camden, New Jersey 08103, USA. E-mail: russo-andrea@cooperhealth.edu. Twitter: @AndreaRussoEP.

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