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HOW TO

How to Manage Atrial Fibrillation Secondary to Ibrutinib



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Atrial fibrillation (AF) is the most common cardiac arrhythmia and a significant cause of cardiovascular morbidity and mortality worldwide (1). Ibrutinib is a covalent irreversible inhibitor of Bruton's tyrosine kinase (BTK) used in the treatment of B-cell cancers such as chronic lymphocytic leukemia and mantle cell lymphoma. It is estimated that up to 16% of patients develop ibrutinib-induced AF, which can be a therapy-limiting side effect. The mechanisms are not clear but may relate to direct inhibition of BTK, which is expressed in cardiac tissue (2). In this primer, we use a clinical case of a patient with chronic lymphocytic leukemia to demonstrate the challenges and management considerations of AF secondary to ibrutinib.

CASE PRESENTATION

A 68-year-old man with hypertension and hyperlipidemia presents to the hematology clinic for follow-up of his chronic lymphocytic leukemia. He had initially been treated with 6 cycles of cyclophosphamide and rituximab with a partial response. This was subsequently followed by ibrutinib 420 mg once daily. At his follow-up clinic appointment, he complained of palpitations and intermittent shortness of breath. His pulse was 77 beats/min and regular, his respiratory rate was 18 breaths/min, and his blood pressure was 137/78 mm Hg. His chest was clear, he had normal heart sounds, and there was no evidence of pedal edema. His electrocardiogram (ECG)

demonstrated normal sinus rhythm with a normal axis. Laboratory investigation demonstrated a normal hemoglobin, urea and electrolytes, bone profile, and magnesium. He was referred to the cardiology clinic for further management.

This patient has several risk factors for AF including age, hypertension, and exposure to cardiotoxic chemotherapy (cyclophosphamide and rituximab) (3). We recommend a 12-lead ECG at baseline before ibrutinib initiation. Ibrutinib treatment increases his risk of AF, and it is prudent to have a high index of suspicion for this in the context of his reported palpitations. A 12-lead ECG may capture AF, but as this case demonstrates, more prolonged monitoring is often required. The importance of emerging technologies such as smartwatches as diagnostic tools to diagnose asymptomatic AF has been demonstrated; it would be reasonable to use this strategy for more prolonged monitoring (4). However, not all patients own such devices. In this case, referral to cardiology can help facilitate 72-h ambulatory ECG monitoring and an echocardiogram. A cardiologist with a subspecialty interest in cardio-oncology is best placed to guide patient management.

CASE CONTINUED

The patient proceeded to have 72 h of ambulatory ECG monitoring, which demonstrated a 10% burden of AF with a rapid ventricular response. The patient reported symptoms of palpitations and shortness of

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breath that coincided with these events. His transthoracic echocardiogram demonstrated a moderately enlarged left atrium and normal left ventricular function and valvular structures. Following this diagnosis of paroxysmal AF, he was treated with apixaban and bisoprolol.

HOW DO WE MANAGE AF SECONDARY TO IBRUTINIB?

The main considerations when managing AF are:

1. Rhythm control versus rate control
2. Anticoagulation

HOW DO WE DECIDE ON RATE CONTROL VERSUS RHYTHM CONTROL?

There is a paucity of randomized controlled trial data addressing the question of rate versus rhythm control in patients with hematologic malignancy. We typically advise a rate control strategy, because maintenance of sinus rhythm may be less likely in patients being treated with proarrhythmogenic cancer therapies. In specific populations, rhythm control may be more appropriate; for example, in young patients without structural heart disease who have completed proarrhythmogenic therapy or patients who are unable to tolerate their symptom load. When using a rate control strategy, we advise beta-blockers as first-line therapy. This is due to interactions between ibrutinib and calcium channel blockers (diltiazem and verapamil), which have a CYP3A4 inhibitory effect resulting in increased levels of ibrutinib and resultant exacerbation of AF and bleeding. Digoxin is also known to have P-glycoprotein interactions resulting in increased plasma levels of digoxin and so should be avoided whenever possible. If there are no other options, we suggest a lower dose of digoxin to be given 6 h before or after ibrutinib (2).

In our case, a decision was made for a rate control strategy based on: 1) patient's age; 2) need for ongoing Ibrutinib treatment; 3) low symptom burden reported by the patient; and 4) left atrial enlargement on echocardiogram suggesting that a rhythm control strategy was less likely to be successful.

HOW DO WE MANAGE ANTICOAGULATION?

The decision to start anticoagulation includes consideration of stroke and bleeding risk, and the most validated and commonly utilized risk stratification strategy includes the CHA₂DS₂-VASc and HAS-BLED scores. However, these scoring systems do not consider cancer-specific high-risk bleeding features

such as intracranial metastasis, severe thrombocytopenia, and actively bleeding high-risk malignancies. This was recognized in a European Society of Cardiology position paper that advised that treatment should not hinge solely on the utility of scoring systems derived from and validated in the general population (3). Therefore, treatment decisions should be personalized to the individual patient and cancer type.

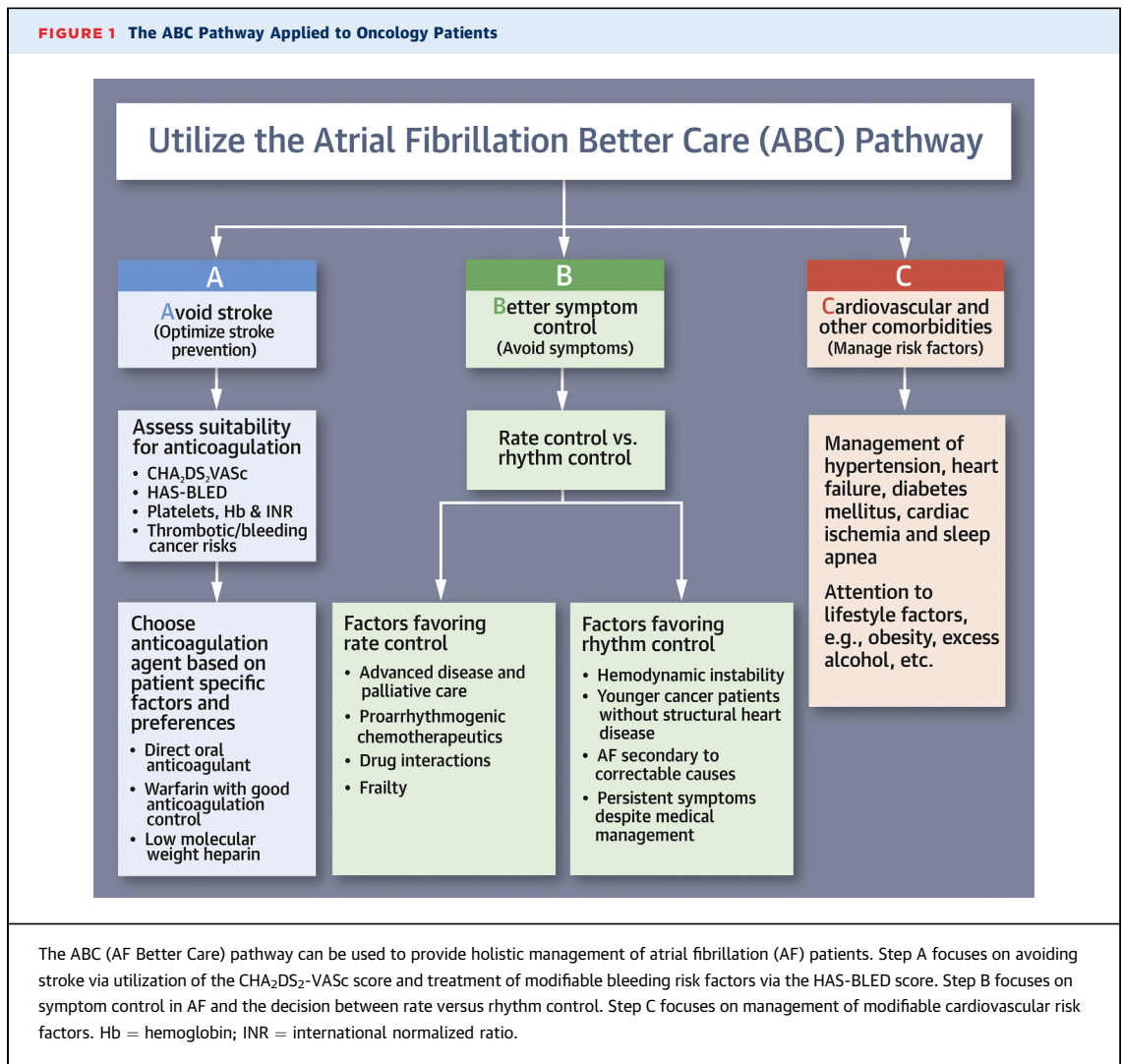
Vitamin K antagonists such as warfarin have traditionally been used for stroke prevention in patients with both AF and cancer. Close monitoring is required, and the likelihood of achieving optimal time in the therapeutic window can be reduced during cancer treatment. Therefore, low molecular weight heparin (LMWH) may be a more suitable option in these circumstances.

Injectable subcutaneous LMWH is a frequently used treatment option due to a large evidence base supporting its utility in the treatment of venous thromboembolism in cancer patients. Studies derived from patients treated in everyday practice have shown that over 50% of treated patients with AF and cancer are on LMWH, but with a large proportion on prophylactic doses rather than treatment doses (5).

The introduction of the direct oral anticoagulants (DOACs) has resulted in a paradigm shift in the management of AF. However, the role of DOACs in AF patients with cancer is less clear, because many of the pivotal trials for these medications excluded cancer patients and/or patients with limited life expectancies. A 2020 meta-analysis of randomized controlled trials and cohort studies that included subgroup analyses of cancer patients from the ROCKET-AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibitor Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation), ENGAGE AF-TIMI 48 (Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis In Myocardial Infarction 48), and ARISTOTLE (Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation) trials demonstrated that compared to vitamin K antagonists, DOACs have a similar incidence of systemic embolism (odds ratio [OR]: 0.70; $p = 0.11$), stroke (OR: 0.71; $p = 0.42$), venous thromboembolism (OR: 0.91; $p = 0.86$) and all cause death (OR: 1.02; $p = 0.13$). The rate of intracranial bleeding was significantly lower with DOACs (OR: 0.11; $p = 0.01$) (6). Furthermore, data from 16,096 AF patients with cancer treated with DOACs demonstrated that these patients experienced lower or similar rates of bleeding and stroke as compared with warfarin

ABBREVIATIONS AND ACRONYMS

- AF** = atrial fibrillation
BTK = Bruton's tyrosine kinase
DOAC = direct oral anticoagulant
ECG = electrocardiogram
LMWH = low molecular weight heparin
OR = odds ratio



users (1). However, given that DOACs are relatively newer medications, there is less information on their interactions with cancer therapies, and this should be noted before their use.

SPECIAL CONSIDERATIONS WITH ANTICOAGULATION AND IBRUTINIB

The management of ibrutinib-induced AF is complicated by: 1) an increased risk of bleeding due to inhibition of collagen induced platelet aggregation (7); and 2) drug pharmacokinetics owing to metabolism by cytochrome PCYP3A4 and P-glycoprotein inhibition. Ibrutinib is known to interact with several of the medications utilized in the management of AF including calcium channel blockers, digoxin, amiodarone, and DOACs (7).

There are limited anticoagulation options in this cohort, with most of the evidence derived from small retrospective studies. Further complicating anticoagulation is the increased bleeding risk inherent to ibrutinib therapy. It is well recognized that up to 44% of patients on ibrutinib experience some form of bleeding event during their treatment course (7). Most bleeding is minor and limited to events such as epistaxis, hematuria, ecchymosis, and mucosal bleeding. However, major bleeding has been seen in up to 7% of patients after a year (7). Therefore, patients should be counseled with regards to bleeding risks before ibrutinib initiation. Furthermore, there is strong evidence implicating concurrent ibrutinib and warfarin therapy with an increased risk of intracerebral bleeding, particularly in the mantle cell population (7). This is possibly mediated via CYP3A4 drug

interactions leading to higher levels of warfarin. Therefore, warfarin is generally reserved for patients previously on warfarin before initiation of ibrutinib and unable to take DOACs. Generally, a DOAC is recommended with close monitoring for any side effects. We recommend utility of a factor Xa inhibitor (apixaban, rivaroxaban, edoxaban) and avoidance of the direct thrombin inhibitor dabigatran due to P-glycoprotein interactions. We advise starting a DOAC at a low dose for 10 to 14 days in patients with HASBLED scores ≥ 3 before increasing it to a maintenance dose (7). In patients at even higher risk of bleeding, we would advise a short-term reduction in the dose of ibrutinib until the patient is stabilized. Alternatively, LMWH is also an option in some patient groups. In the event of a clinically significant major bleeding event, we advise discontinuation of ibrutinib and transfusing the patient with platelets \pm red blood cells until the bleeding event has terminated.

In view of the limited treatment options and the increased risk of bleeding in this patient cohort, we recommend that patients with ibrutinib-induced AF are managed by a cardio-oncologist. Populations at high risk of AF (elderly, those with cardiovascular disease, chronic lung disease, and cardiomyopathy) should undergo baseline cardiovascular risk stratification and aggressive risk factor management before starting ibrutinib (2,8). We suggest that oncologists are aware of the importance of cardiovascular disease risk factor management and refer to a cardio-oncologist as needed.

CASE CONTINUED

Six months later, the patient was tolerating his anti-coagulation and beta-blocker, and was asymptomatic.

It is important to follow patients with new AF. This is particularly important if the proarrhythmogenic treatment is continuing because their symptom load may increase. If this patient started complaining of increasing palpitations and shortness of breath, it would be prudent to increase his rate control medication. If his symptoms were refractory to maximal medical therapy, he would then be considered for a rhythm control strategy, which can include medications, or more invasive management such as atrio-ventricular node ablation and pacemaker insertion or radiofrequency ablation. If a rhythm control strategy is pursued, it is advisable to avoid CYP3A4 inhibitors such as amiodarone, diltiazem, and verapamil. Generally, it is accepted that Class 1B and 1C antiarrhythmic drugs are the least likely to cause drug-drug

interactions with ibrutinib (9). An electrical cardioversion strategy can also be considered. An alternative rhythm control strategy could potentially involve acalabrutinib. This is a second-generation BTK inhibitor that is more selective and has thus far demonstrated lower rates of AF and bleeding (10).

Our treatment decisions throughout the case were guided by the AF Better Care (ABC) pathway, which our group has pioneered (Figure 1). The ABC pathway proposes a streamlined approach to holistic AF management that is applicable to primary and secondary care: A, Avoid stroke/Anticoagulation; B, Better symptom management, with patient-centered symptom-directed decisions on rate or rhythm control; and C, Cardiovascular risk factor and Comorbidity management, including addressing lifestyle factors.

CONCLUSIONS

AF is a common condition seen in the cancer population due to multiple shared risk factors and proarrhythmogenic cancer treatments. The main decisions in the treatment of AF are: 1) choice of anticoagulation; and 2) rate versus rhythm control. In both these aspects, there is a paucity of evidence guiding clinical practice in cancer patients. Furthermore, there are a plethora of pitfalls including a higher risk of bleeding and drug interactions. Oncologists should take a pragmatic case-by-case approach and use a multidisciplinary team that incorporates cardio-oncologists to generate treatment decisions with an acceptable risk profile to the patient while modifying risk factors. Moving forward, high-quality trials are required to generate evidence-based guidance for clinicians on the best management strategies in this population.

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