Ibrutinib in patients with atrial fibrillation – the challenge of thromboembolic prophylaxis

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Ibrutinib is a novel drug used in haematological malignancies. Its use is associated with an increased risk of atrial fibrillation (AF), which, in turn, exposes patients to embolic risk, including stroke. Reducing this risk requires anticoagulant therapy which is a matter of concern in the context of the increased bleeding risk of patients with haematological malignancies. In this context the presence of thrombocytopenia related to haematological disorder, ibrutinib-anticoagulants and ibrutinib-platelets interactions contribute to the amplification of the problem. The correct assessment of the thrombosis vs. haemorrhage balance represents a significant challenge for the clinician.

In this paper we discuss practical issues related to anticoagulation in patients treated with ibrutinib and incident AF.

Key words: ibrutinib, atrial fibrillation, anticoagulation, thromboembolic prophylaxis, haemorrhagic risk.

What is new, what is important?

- AF is a worrying adverse reaction to ibrutinib treatment.
- Ibrutinib carries an increased bleeding risk compared to standard chemotherapy.
- Ibrutinib-related AF management is a therapeutic challenge. The current options for thromboembolic prophylaxis are NOACs.
- Thrombotic and haemorrhagic risk scores are required to guide antithrombotic therapy; those recommended (CHA₂DS₂-VASc, HAS-BLED) for AF are not validated in the ibrutinib population.

INTRODUCTION

Ibrutinib is the first bruton kinase inhibitor (BTKi) approved in several B-cell malignancies, including chronic lymphocytic leukemia (CLL), mantle cell lymphoma (MCL), Waldenström’s macroglobulinemia and marginal zone lymphoma [1]. Chronic lymphocytic leukemia is the most common type of leukemia, with a median age at diagnosis of 72 years and a ratio 2:1 men: women [2].

AF, hypertension and excessive bleeding are cardiovascular side effects of ibrutinib [3].

AF is the most common hospitalized rhythm disorder, with an incidence on the rise. It generates a high rate of cardiovascular and cerebrovascular mortality and morbidity, translated into major health care costs [4]. AF is an independent risk factor for thromboembolism [5], which also depends on the presence of demographic, clinical, biological and

echocardiographic factors [6]. Validated risk scores for initiating thromboembolic prophylaxis in AF commonly include advanced age, high blood pressure, heart failure, diabetes, previous stroke, vascular disease, female gender [7]. The use of anticoagulant therapy such as antithrombotic K agents or novel oral anticoagulants (NOACs) significantly reduces embolic risk and mortality (exemplifying “A” from ABC pathway [8]) [6]. Implementation of the ABC algorithm has improved the prognosis of patients with AF [8]; in the ibrutinib population the concomitant disease/associated pathology certainly influences general management (“C” – detection and management of Cardiovascular risk factors and Concomitant diseases [8]). Some data indicate that patients with CLL are at higher risk for AF regardless of ibrutinib use, even after adjusting for age and sex [9].

The incompletely elucidated mechanisms behind the interaction of ibrutinib and

anticoagulants may generate challenges for the practitioner.

The risk of AF in neoplastic patients treated with ibrutinib

Globally, cancer is a risk factor for AF. A cohort of nearly 15,500 patients (REGARDS) reported a 20% higher adjusted risk of AF in patients with cancer compared to those without cancer [10]. Moreover, the prognosis of patients with AF and cancer is worse and the risk of thromboembolism is higher than in those with AF but without cancer. In addition, the first category of patients has a six-fold higher adjusted risk for heart failure, which also increases the embolic risk [10,11]. Despite the growing association between AF and cancer, there are no specific guidelines for therapeutic behaviour.

AF is a worrying adverse reaction to ibrutinib treatment, affecting 2 to 16% of these patients [12]. This incidence is higher than expected in the general population (1–2% for patients >65 years) and cancer patients (4%) [13].

Several studies have attempted to identify risk factors for AF during ibrutinib therapy. Although limited by the small number of cases, several predictive factors have been reported for the occurrence of AF, including diabetes mellitus, hypertension, prior history of AF [12] and acute infections [14]. Intensifying the cardiological follow-up of this subgroup of patients is an important consequence.

Mechanism of ibrutinib-induced AF

The mechanism of the ibrutinib-induced AF has not been clarified yet. There are several hypotheses trying to explain this association. The most commonly mentioned mechanism is related to phosphoinositide-3-kinase-protein kinase B/Akt (PI3K-PKB/Akt) inhibition by ibrutinib. PI3K-Akt plays a role in cardiac protection under stress conditions, being an intracellular signalling pathway targeting multiple cellular functions, including cell proliferation and survival, angiogenesis, increased metabolism [13, 15, 16]. The PI3K inhibition could result in AF by activation of late sodium channels [17]. This may lead to prolongation of cardiac action potential duration (APD) and so increased vulnerability to early depolarization that in turn may increase the risk of both atrial and ventricular arrhythmias [3]. In general, increasing and not decreasing APD

favors AF [18], but the early after-depolarization promotion by ibrutinib may increase the possibility of triggering AF.

It has been observed that decreased cardiac PI3K activity increases the susceptibility of AF in mice [19, 20]. Also, human heart samples from patients with and without AF were compared and reduced cardiac PI3K activity was observed in those with AF [19, 20]. Moreover, in an experimental model of rat myocytes exposure to ibrutinib resulted in less PI3K expression and therefore may predispose to AF [21]. However, these findings cannot be extrapolated to humans, their applicability being questionable. Moreover, there is no evidence confirming inhibition of PI3K by ibrutinib *in vitro* or *in vivo* [15]. As of yet, no evidence of ibrutinib's functional effect on cardiac myocytes has been demonstrated [15].

Other potential mechanisms refer to structural remodelling and calcium handling disorders in the atrium [22] or to reduced activity in tyrosine kinase pathways other than PI3K-Akt [23].

The underlying mechanisms remain unclear, further research being needed to elucidate them.

The haemorrhagic risk in patients treated with ibrutinib

Ibrutinib, an effective therapeutic agent for multiple B-cell mediated lymphoproliferative disorders, carries an increased bleeding risk compared to standard chemotherapy and is also associated with an increased risk of AF which often requires anticoagulation [24]. This clinical situation leads to complex decisions regarding stroke vs. bleeding risk, for which evidence-based data is currently lacking.

In clinical trials ibrutinib has been found to be associated with approximately 50% risk of bleeding [25], the majority of these events being low grade such as subcutaneous or mucosal bleeding, including epistaxis, haematuria, petechial bleeding, contusions, or ecchymosis [24]. Major haemorrhage has been reported between 1 and 10% in major trials [25] with fatal bleeding occurring in less than 1% of patients [26, 27].

Mechanisms of ibrutinib-induced haemorrhagic risk

The mechanisms behind ibrutinib's increased bleeding risk are manifold, including Bruton's tyrosine kinase (BTK) and other intracellular molecules inhibition, ibrutinib-induced thrombo-

cytopenia or enhancement of CLL-induced platelet function impairment [28].

Ibrutinib inhibits irreversibly BTK and related TEC (tyrosine expressed in hepatocellular carcinoma) kinases [29], both molecules being involved in downstream signalling of collagen receptor glycoprotein VI (GPVI) and C-type lectin-like receptor 2 (CLEC-2). GPVI is responsible for platelet activation [30]. CLEC-2 is a platelet transmembrane receptor which enhances thrombus stability after platelet adhesion to damaged endothelium [28].

Ibrutinib also interferes with platelet GPIb-mediated platelet functions. GPIb binds to von Willebrand factor, this interaction leading to the attachment of platelets to the damaged vascular wall and stimulating multiple platelet pathways and platelet cytoskeletal reorganization. BTK is essential in von Willebrand factor – induced signalling and GPIb-dependent thrombus formation [24, 31]. Therefore, BTK inhibition increases haemorrhagic risk. Also, the inhibitory effect of ibrutinib on von Willebrand factor – GPIb interactions may explain the bleeding mostly in the microvasculature where shear stress is elevated [32].

Ibrutinib also inhibits platelet adhesion to fibrinogen, blocking the interaction fibrinogen – integrin $\alpha\text{IIb}\beta_3$, which involves BTK [33]. Physiologically fibrinogen binds to this integrin on the platelet membrane, triggering platelet adhesion, spreading and clot retraction [28].

Furthermore, patients with CLL have mild defects of platelet function which can be exacerbated by ibrutinib via inhibition of collagen-dependent platelet aggregation [34]. Adding, patients with CLL often have significant thrombocytopenia and ibrutinib also causes cytopenias, including thrombocytopenia [15].

Baseline abnormalities in platelet function (activation, adhesion and aggregation), combined with drug-related effects, boost bleeding risk in patients on ibrutinib.

Considering the effects on platelets, the question arises whether ibrutinib could confer some cardiovascular protective properties. To date, there is no data regarding the effect of ibrutinib on the thromboembolic risk of AF [35]. It appears that after mechanical arterial injury, GPVI inhibition could reduce thrombotic risk, protecting against platelet adhesion, thrombus extension, as well as against leukocyte recruitment and neointimal hyperplasia [36, 37]. Also,

GPVI inhibition may limit plaque-induced thrombus formation [24, 38, 39]. In vascular disease, inhibition of the von-Willebrand-GPIb axis is a potential antithrombotic target [40]. Despite the interaction of ibrutinib with GPVI and with von Willebrand factor-GPIb axis, there are insufficient data to support the possible efficacy of ibrutinib in reducing cardiovascular risk [24].

Ibrutinib therapy in patients with B cell malignancy results in high response rates and long progression-free survival. Despite the haemorrhagic risk, especially when combined with an antithrombotic, its continuation remains important [14].

Anticoagulation in AF patients receiving ibrutinib

Because of the increased haemorrhagic risk of ibrutinib treated patients, the decision to anticoagulate is challenging.

The decision to anticoagulate the patient with AF is based on the CHA₂DS₂ -VASc score (congestive heart failure/left ventricular dysfunction, hypertension, age ≥ 75 years (2 points), diabetes, stroke (2 points), vascular disease, age 65–74 years, and female sex category), which is the best validated scale for stroke risk in patients with AF. The European Society of Cardiology recommends initiation of anticoagulant therapy in men with a CHA₂DS₂ -VASc score ≥ 1 and in women with a score ≥ 2 [8]. For patients with a CHA₂DS₂ -VASc score of 0 or 1 for women, no antithrombotic therapy is required [8].

However, CHA₂DS₂ -VASc was not evaluated in patients on ibrutinib or in patients with pathology manageable by ibrutinib [41]. Moreover, the neoplastic context increases thrombotic risk depending of cancer type [41, 42]. At this time, there is no specific score to help establish the anticoagulation indication in patients with AF treated with ibrutinib.

Estimation of haemorrhagic risk in patients treated with oral anticoagulants can be performed using several scores.

Among all, the HAS-BLED score was the most validated and is recommended in patients with AF [42, 8]. However, the HAS-BLED score does not take into account the platelet count, the functional status of platelets and the therapy with ibrutinib which, as shown above, increases the risk of bleeding. So, this score underestimates the haemorrhagic risk [41].

Another useful tool for monitoring and managing the bleeding tendency could be the quantitative assessment of RIPA (ristocetin-induced platelet aggregation), which might thereby increase the prediction of bleeding [43], but this assay has not been validated in AF patients on oral anticoagulant.

Although in the general AF population a HAS-BLED score above 3 does indicate an increased bleeding risk however it does not contraindicate anticoagulant therapy, in patients on ibrutinib there are several different recommendations, most of them based on expert opinion [44]. It is recommended not to anticoagulate the patient with ibrutinib-related AF if the CHA₂DS₂-VASc score is less than or equal to HAS-BLED score [44]. If the CHA₂DS₂-VASc score is higher than HAS-BLED score the recommendation is to administer an anticoagulant, preferring NOAC (non-antivitamin K anticoagulant) over VKA (antivitamin K anticoagulant) and to consider alternative anti-lymphoproliferative disorder treatment options [14,44]. This last recommendation could compromise progression-free survival and overall survival in these patients. Withholding ibrutinib when atrial fibrillation develops does not seem to prompt a higher resolution rate of the rhythm disorder [14].

Forgoing anticoagulation for AF may be a reasonable option even if the CHA₂DS₂-VASc score is ≥ 2 in patients on ibrutinib and a high risk of bleeding, in patients with limited life-expectancy (< 12 months) [41].

Control of modifiable risk factors for bleeding as hypertension, alcohol consumption or comedication predisposing to bleeding is mandatory [45].

Ultimately, the anticoagulation decision should be made by a multidisciplinary team consisting of cardiologist, haematologist/ oncologist with the patient fully informed about the thrombotic and haemorrhagic risks [44].

Oral anticoagulants use in AF patients treated with ibrutinib

The standard options for thromboembolic prophylaxis in AF are NOACs (novel oral anticoagulants) and anti-vitamin K anticoagulants [45].

Patients on warfarin were excluded from most trials with ibrutinib because of the initial observations of major bleeding. [24] To date, there is a paucity of safety data regarding concomitant

use of these drugs [35]. Currently, ibrutinib is contraindicated in patients on anti-vitamin K anticoagulants, but NOACs were allowed in pivotal ibrutinib trials [46].

Ibrutinib is metabolized in the liver, primarily by cytochromes P450 and 3A4 (CYP3A4) [24] and to a lesser extent by CYP2D6 [47], to active metabolite. Also, ibrutinib is an inhibitor of the transporter P-glycoprotein (P-gp), but this inhibition is not fully established *in vivo*. However, the increased risk of bleeding in these patients is not caused by the increased plasma levels of the anticoagulant but by the additional risk generated by ibrutinib [28].

NOACs have less drug interactions than warfarin. Many drug interactions with NOACs occur in the intestine, involving the P-gp, particularly for dabigatran. All NOACs are substrates of the P-gp, which as previously mentioned, is inhibited by ibrutinib. Rivaroxaban and apixaban are metabolised extensively by CYP3A4 [48], whereas dabigatran and edoxaban are not [49].

Therefore, ibrutinib may increase the plasma concentration of these anticoagulants and thus the risk of bleeding.

Evidence from drug-drug interactions and antiplatelet effects of ibrutinib show that thromboembolic prophylaxis in ibrutinib-related AF is challenging. Expert recommendations are limited as they are based on small scale, retrospective studies. Options for anticoagulant therapy are oral factor X_a inhibitors that have clinically insignificant CYP3A4 interactions with ibrutinib, while the use of warfarin and low-molecular-weight heparin is recommended to be avoided [50].

Regarding the doses to be used, currently low-doses of oral factor X_a inhibitors are recommended for the first 7–10 days from therapy initiation, with the possibility of further increase depending on the patient's response [50]. As ibrutinib is a P-glycoprotein inhibitor and dabigatran (especially 150 mg b.i.d) is a potent substrate for P-gp, their association is discouraged [50].

Current anticoagulant therapy recommendations for thromboembolic prophylaxis in ibrutinib-related AF, in patients with normal renal function, in the absence of other drug-drug interactions are summarized in Table 1. Furthermore, temporary dosage reduction but not withdrawing ibrutinib may be considered when initiating a NOAC [29].

Table 1

Anticoagulant therapy in ibrutinib – related AF [50, 29]

Antithrombotic therapy	Initial dose	Maintenance dose
Apixaban	2,5 mg b.i.d	5 mg b.i.d
Rivaroxaban	15 mg o.d	20 mg o.d
Edoxaban	30 mg o.d	60 mg o.d

Figure 1. Interrelation ibrutinib – AF – haemorrhage.

Alternatives to anticoagulant therapy

In patients who cannot receive anticoagulant therapy, **left atrial appendage occlusion** should be considered [41]. Special devices are approved for reducing long-term anticoagulation requirements in AF patients [51]. However, a major disadvantage is the need to combine anticoagulant with antiplatelet therapy during endothelialisation process into the appendage, to prevent thrombus formation on the device itself [52]. In addition, antithrombotic therapy after occlusion has not been yet evaluated in randomized trials [8]. If patients cannot receive antiplatelet therapy, the options to consider are epicardial catheter approach or thoracoscopic clipping of the left atrial appendage [8]. However, if there is an absolute contraindication for anticoagulation, according to the ASAP study, post-procedural

dual antiplatelet therapy (aspirin plus clopidogrel) could be used for 6 months or even for 1 to 3 months for patients at very high risk of bleeding [53]. More studies are needed to test the outcomes of left atrial appendage occlusion in such patients.

CONCLUSION

The optimal thromboembolic prevention in AF patient under chemotherapy is challenging.

Ibrutinib, used in chronic lymphocytic leukemia, mantle cell lymphoma, Waldenström's macroglobulinemia and marginal zone lymphoma is associated with increased haemorrhagic risk and AF rising yet unsolved therapeutic issues.

The ibrutinib-related AF anticoagulation decision does not yet have extensive scientific

support. The classic risk scores from AF (CHA₂DS₂-VASc and HAS-BLED) are used without being validated in this population. Thus, the anticoagulation of patients with a CHA₂DS₂-VASc score higher than HAS-BLED is preferred. However, if the bleeding risk is very high, left atrial appendage occlusion may be considered. The therapeutic options are limited to NOACs, especially apixaban, rivaroxaban and edoxaban, with doses adapted to the neoplastic context. NOACs are often a

safe alternative to antivitamin K anticoagulants in cancer associated AF [41].

Stopping or replacing ibrutinib may not be profitable for patients with haematological conditions. Therapeutic decisions must be individualized and patient-centered, with an accurate estimation of benefits. The Cardiologist-Hematologist team [54] should optimize decisions by integrating stroke risk from AF with the cancer context, response to treatment and prognosis.

Ibrutinibul este un medicament nou folosit în patologii maligne hematologice. Este asociat cu un risc crescut de apariție a fibrilației atriale, care, la rândul ei, expune pacienții la risc embolic, inclusiv accident vascular cerebral. Reducerea acestui risc necesită terapie anticoagulantă, care constituie o problemă în contextul riscului hemoragic crescut al pacienților cu patologie malignă hematologică. Prezența trombocitopeniei din cadrul patologiei hematologice, interacțiunile ibrutinib-anticoagulante și ibrutinib-trombocite contribuie la amplificarea problemei. Aprecierea corectă a balanței tromboză vs. hemoragie reprezintă o provocare semnificativă pentru clinician. În acest articol discutăm provocările practice legate de anticoagulare la pacienții tratați cu ibrutinib și având fibrilație atrială.

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