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Mechanism and Management of Ibrutinib-Associated Atrial Fibrillation

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1. Abstract

Ibrutinib is one of the kinase inhibitors that can be used in the treatment of mantle cell lenfoma (MCL), Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL), Waldenström's Macroglobulinemia (WM) and Marginal Zone Lymphoma (MZL). Although ibrutinib is well tolerated by patients, the cardiovascular side effects of the drug are an important problem. One of the most feared side effects of ibrutinib is atrial fibrillation. The most important concern in atrial fibrillation is thromboembolism. It is a known situation that the risk of thromboembolism in cancer patients is higher than the normal population. In patients using ibrutinib, the drug interacts with drugs used in atrial fibrillation and causes bleeding by disrupting platelet functions on its own, complicating atrial fibrillation management. The purpose of this article is to reveal the ibrutinib-associated atrial fibrillation mechanism and to review the treatment options.

2. Introductıon

Ibrutinib is a tyrosine kinase inhibitor and it is used in the treatment of hematologic malignancies including Mantle Cell Lenfoma (MCL), Chronic Lymphocytic Leukemia (CLL)/ Small Lymphocytic Lymphoma (SLL), Waldenström's Macroglobulinemia (WM) and Marginal Zone Lymphoma (MZL) [1]. It is the primary oral covalent inhibitor of Bruton's Tyrosine Kinase (BTK) [2] Ibrutinib blocs the autophosphorylation of BTK and its immediate substrate phospholipase C-y2, as well as ERK and SYK pathways [3] Thus, proliferation of B cells is inhibited and their survival are shortened by ibrutinib [4].

The fact that ibrutinib improves the prognosis in B-cell lymphomas has made it very popular. In randomized phase III clinical trials ibrutinib monotherapy was more effective than chlorambucil in the first-line treatment in older patients (RESONATE-2) and more effective than ofatumumab in previously treated adults (RESONATE) [14, 15]. Furthermore, a combination of ibrutinib, bendamustine and rituximab was more effective in previously treated adults than bendamustine plus rituximab in a phase III placebo-controlled study (HELIOS) [16]. Despite its well tolerability and efficacy; it has several side effects such as cutaneous side effects, hypertension and Atrial Fibrillation (AF) [8].

Data from clinical trials suggest that ibrutinib is associated with increased risk of both Atrial Fibrillation (AF) and bleeding [5]. Mainly, Phosphoinositol-3-Kinase (PI3K) /Akt pathway is important in preventing stress-related cardiomyopathy [6]. It is shown in rats that ibrutinib significantly reduces PI3K-Akt activity in cardiac cells at a concentration of 0.1 to 1 mM and it is claimed that reduced PI3K-Akt activity is responsible for increased rates of AF in patients treated with ibrutinib (Table 1) [7].

BTK has an important role in glycoprotein VI signalling pathway, and inhibition of BTK has been shown to block collagen-mediated platelet aggregation [5]. Thus, ibrutinib impairs platelet functions, leading to increased bleeding risk. Additionally; ibrutinib not only affects platelet functions but also it affects platelet counts. Patients treated with ibrutinib have increased bleeding risk due to both impaired platelet functions and reduced platelet counts [1].

AF is a major problem especially in cancer patients. In one study, it is revealed that newly diagnosed AF in cancer patients causes 2-fold increased risk of thromboembolism and 6-fold higher risk of heart failure [9]. Cancer itself is also a prothrombic process therefore thromboembolic risk increases with AF. On the other hand,

ibrutinib impairs platelet functions and causes tendency for bleeding [11]. Several drugs are used in AF for rhythm control, rate control and anticoagulation which are metabolised via microsomal enzymes such as CYP3A, and CYP2D6. Ibrutinib is also metabolized via CYP 450 enzymes therefore interacts with common medications used for the management of AF (Table 2) [10].

Table 1: Advers Effects of Ibrutinib

Side Effects	Frequency in Patients
Cutaneous Side Effects	2–27%
Hair and Nail Toxicities	26 -66%
Bleeding	2,72-11,6%
Atrial Fibrillation	9-16%
Hypertension	25%

Table 2: Interaction Between Ibrutinib and Common Medications of AF

Medication	Level of Interaction	Effect	Mechanism of Interaction
Diltiazem/verapamil	Major	Increases plasma level of ibrutinib (6- to 9-fold)	CYP450 3A4 inhibition by diltiazem/ verapamil
Digoxin	Moderate	Increases plasma level of digoxin	P-glycoprotein inhibition by ibrutinib
Amiodarone/dronedarone	Major	Increases plasma level of ibrutinib (6- to 9-fold)	CYP450 3A4 inhibition by amiodarone/ dronedarone
Factor Xa inhibitör (rivaroxaban, apixaban, edoxaban)	Moderate	Increases plasma level of factor Xa inhibitors	CYP450 3A4 induction and P-glycoprotein inhibition by ibrutinib
Direct thrombin inhibitor	Major	Increases plasma level of dabigatran	P-glycoprotein inhibition by ibrutinib

CYP450 = cytochrome P450.

The recommended dose of ibrutinib for patients on concomitant use of moderate CYP3A4 inhibitor drugs, such as diltiazem, verapamil and amiodarone, is 140 mg (i.e. 33% of full dose) [10]. Apixaban and rivaroxaban are also metabolized by CYP3A4. In addition, ibrutinib can function as a p-glycoprotein inhibitor, and thereby increases the plasma levels of digoxin, dabigatran, and to a lesser extent apixaban and rivaroxaban [11].

Since the risk of developing AF continues under ibrutinib treatment, rate control rather than rhythm control is the most appropriate approach in patients with stable hemodynamics. Ibrutinib does not interact with beta blockers, so beta blockers can be used as first-line treatment in rate control. If rate control cannot be achieved with beta blockers, calcium channel blockers can be added to the treatment by reducing the dose of ibrutinib [12]. Smaller doses of digoxin, taken either 6 h prior to or after taking ibrutinib, should be considered with close follow-up of digoxin levels [13]. If the patient is hemodynamically unstable, electrical cardioversion should be performed. However, due to there is a need for anticoagulation after electrical cardioversion, the patient's clinical condition should be evaluated while making this choice.

The most important complication of atrial fibrillation is thromboembolism. Thromboembolism risk in AF is evaluated with CHA-2DS2VASc [Congestive Heart Failure, Hypertension, Age≥75 Years, Diabetes Mellitus, Prior Stroke or Transient Ischemic Attack or Thromboembolism, Vascular Disease, Age 65 to 74 Years, Sex Category] score and bleeding risk is assessed with HASBLED [Hypertension, Abnormal Renal and Liver Function, Stroke, Bleeding, Labile International Normalized Ratio, Elderly, Drugs or Alcohol] score but that scores may not predict the risk accurately in patients with cancer [13]. For that reason, anticoagulation treatment is a major problem in this group of patients due to high risk of adverse drug interaction between ibrutinib and commonly used anticoagulants and even fatal bleeding events can occur as a result of concomittant use of ibrutinib together with anticoagulants. Grade 3 or higher bleeding events (subdural hematoma, gastrointestinal bleeding, hematuria and post procedural hemorrhage) occurred in up to 6% of patients treated with ibrutinib [1]. However, anticoagulation of patients using ibrutinib is not an absolute contraindication provided that the patient's thromboembolism risk and bleeding risk is evaluated carefully at the same time. Warfarin should be used in the first line since its blood levels can be monitored easily and it has an effective antidote in case of a major bleeding event. Low molecular weight heparin should be used with caution, as there is a possibility of impaired renal function in patients with cancer. Factor Xa inhibitors, on the other hand, do not have an antidote and therefore should not be used at the first line. There is no experience of AF ablation or left atrial appendage closure devices in this patient population [13].

3. Conclusion

Ibrutinib is used in the treatment of many B cell lymphomas and it is well tolerated in general. However, the fact that ibrutinib causes AF in 9-16% of patients should also be taken into consideration. Approach to the ibrutinib-associated AF is individualized on the patients basis. High possibility of drug interactions and increased risk of bleeding is the main concern in the management of ibrutinib related AF. Rate control should be preferred in patients who are hemodynamically stable. For this purpose, beta blockers that do not interact with ibrutinib in the first stage should be used first. If rate control is not achieved, calcium channel blockers can be used by reducing the ibrutinib dose. Digoxin can be added to the treatment with close follow-up. If the patient is hemodynamically unstable, cardioversion should be applied. Drug discontinuation may be required if the patient has a serious bleeding or drug refractory symptomatic AF. Vitamin K antagonists should be preferred as first line anticoagulant treatment.

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