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MANAGEMENT OF CARDIAC DYSFUNCTION INDUCED BY IBRUTINIB THERAPY

Diana MIHALCEA[1,2]

[1]University and Emergency Hospital, Bucharest, Romania
[2]University of Medicine and Pharmacy Carol Davila, Bucharest, Romania
Corresponding author: Ass. Prof. Diana Mihalcea MD, PhD, University of Medicine and Pharmacy Carol Davila, University and Emergency Hospital, Splaiul Independentei 169, Bucharest 050098, Romania, Tel: + 40 21 3180576; Fax: + 40 21 3180576, Email: dyddy_free@yahoo.com

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Ibrutinib is a Bruton's tyrosine kinase inhibitor used for the treatment of refractory hematological neoplasia, that improves overall survival and outcome. Despite its effectiveness, ibrutinib has a high risk of cardiac dysfunction, which can lead to increased morbidity and mortality. The most common cardiac side effects secondary to ibrutinib are arrhythmias (especially atrial fibrillation) and arterial hypertension. Moreover, ibrutinib generates a high bleeding risk by a direct inhibition of platelet functions and has important interactions with drugs metabolized on the same cytochrome CYP3A4. Concomitant administration of ibrutinib, antihypertensive therapy, anticoagulation therapy, and rate or rhythm control treatment for atrial fibrillation additionally increases the bleeding risk and ibrutinib exposure. This review will discuss the practical management of patients with cardiac dysfunction related to ibrutinib therapy and will emphasize the essential role of a multidisciplinary team for a safe and correct approach of these special patients.

Key words: ibrutinib, atrial fibrillation, hypertension, anticoagulation therapy.

INTRODUCTION

Ibrutinib is a new molecule used in the treatment of refractory chronic lymphocytic leukemia, small lymphocytic lymphoma, mantle cell lymphoma and Walderstörm macroglobulinemia, improving clinical outcome and overall survival [1]. His mechanism of action involves the inhibition of Bruton's tyrosine kinase, an essential molecule for B-cell receptor signaling crucial for cell survival and proliferation [2]. Although highly efficient, well tolerated in the elderly and having good compliance, ibrutinib has adverse events that may alter the quality of life, increasing morbidity and mortality [3]. These complications can be divided into several categories: digestive, infectious, hematological and cardiac.

The most common digestive side effects, often mild and transient, are diarrhea, nausea, inflammation of mouth and lips and constipation [4]. Septic complications due to ibrutinib include sinusitis, urinary and upper respiratory tract infections or pneumonia that can lead to sepsis and death [4]. Hematologic toxicity is represented by neutropenia, that can favor the occurrence of infectious, anemia or thrombocytopenia, with increased risk of hemorrhage [4]. Bleeding due to ibrutinib may occur up to 50% of patients and is often minor, comprising bruising, ecchymosis and petechiae; life-threatening bleeding are rare (2% of the patients) and include intracranial or severe gastrointestinal haemorrhages [4,5]. Bleeding can be determined not only by cytopenia secondary to the hematological disease or chemotherapy, but also by a platelet dysfunction (activation, adhesion, aggregation) induced by ibrutinib. More than that, the risk of bleeding is higher in patients receiving ibrutinib and concomitant treatment with anticoagulant or antiplatelet agents [4].

Cardiovascular dysfunction represents the most feared side effect of anticancer drugs, with a growing incidence, up to 30% [6]. Cardiotoxicity may vary from asymptomatic forms, with electrocardiographic or echocardiographic alterations, to different forms of arrhythmias or structural cardiomyopathies and irreversible heart failure [7]. By increasing life

expectancy in cancer survivors, it is essential that chemotherapy should be safe [8]. Ibrutinib favors the occurrence of hypertension and supraventricular or ventricular heart rhythm disturbances in 20% of the patients; atrial fibrillation is the most common arrhythmia induced by ibrutinib [4,9]. Data about a possible structural systolic or diastolic cardiac dysfunction secondary to ibrutinib are scarce.

Management of cardiac dysfunction induced by ibrutinib can be challenginggiven the need for anticoagulation of the patient with atrial fibrillation, optimal antihypertensive treatment, the risk of bleeding and potential interactions of different drugs with the hematological treatment. Therefore, ibrutinib therapy in hematological neoplasia requires a close follow-up by a multidisciplinary team, including a hematologist, a cardiologist and a pharmacologist in order to reduce the risk of cardiotoxicityand to apply early preventive or therapeutic measures [4].

This review will focus on the mechanisms and the management of ibrutinib-induced cardiac and vascular toxicity in hematological diseases.

IBRUTINIB-INDUCED CARDIAC DYSFUNCTION

Definition. Incidence. Cardiac dysfunction related to chemotherapy is known since 1960s, when it was named as "toxicity that affects the heart" [10]. In 2016, the position paper of cancer treatments and cardiovascular toxicity, defined cardiotoxicity as a decrease of left ventricular ejection fraction (LVEF) with more than 10 percentage points below the value of 50% [7]. This decrease needs to be confirm by a cardiac imaging method 2–3 weeks after the initiation of the citotoxic drugs [7]. The incidence of cardiac dysfunction varies depending on the chemotherapeutic drugs used (Table 1) [7].

Classification. According to LVEF value, cardiac dysfunction induced by chemo- or radiotherapy can be categorized in reversible (LVEF is improving with at least ±5 percentage points of the baseline value), partial reversible (LVEF is arising with more than 10% but remaining with at least 5% percentage points below the baseline value) and irreversible (LVEF is improving with less than 10% or it decreases) [11]. More than that, cardiac dysfunction can be asymptomatic or symptomatic [7]. Depending on the occurrence of the symptoms, cardiotoxicity can be acute, subacute or chronic. Acute cardiotoxicity appears in the first two weeks from initiation of chemotherapy, subacute cardiotoxicity develops after two weeks and chronic cardiotoxicity manifests either in the first year (early chronic cardiotoxicity) or after the first year of treatment (late chronic cardiotoxicity) [6,12]. Often, late cardiotoxicity determines irreversible structural myocardial dysfunction, leading to heart failure and death [7,11].

Cardiovascular complications of cancer therapy can be classified in: direct toxic effect leading to myocardial dysfunction and heart failure, coronary artery disease, aggravation of preexisting valvular heart disease, arrhythmias, pericardial disease, arterial hypertension, peripheral and cerebral vascular disease, pulmonary hypertension and thromboembolic disease [7]. Most often, ibrutinib favors the occurrence of arterial hypertension and arrhythmias [4]. Data about direct toxic cardiac side effects are scarce, although systemic hypertension and heart rhythm disturbances induce left ventricular hypertrophy, left atrial dilatation, diastolic and late systolic dysfunction and finally heart failure.

Table 1

The incidence of cardiac dysfunction induced by different chemotherapeutic drugs [7]

Chemotherapy drugs	Incidence (%)
Anthracyclines	
- Doxorubicin	48
- Idarubicin	18
- Epirubicin	11
- Mitoxantrone	2
Alkylating agents	
- Cyclophosphamide	28
- Ifosfamide	17
Tyrosine kinase inhibitors	
- Sunitinib	19
- Sorafenib	8
- Dasatinib	4
- Lapatinib	1.5
- Nilotinib	1
Antimicrotubule agents	
- Docetaxel	13
- Paclitaxel	1
Monoclonal antibodies	
- Trastuzumab	20
- Bevacizumab	4
- Pertuzumab	1.2
Proteasome inhibitors	
- Carfilzomib	25
- Bortezomib	5

Risk factors for cardiac dysfunction secondary to chemotherapy can be divided in two categories: individual and oncological. The first category

includes conventional cardiovascular risk factors (hypertension, smoking, diabetes, dyslipidemia, age over 65 years, family history of premature cardiovascular diseaseunder the 50 years), preexisting cardiovascular disease (various arrhythmias, coronary artery disease, cardiomyopathy, valvular heart disease, heart failure) and hygienic-dietary factors (alcohol or drug abuse, obesity, sedentary habit). The risk for cardiotoxicity is higher if the patient has previous or concomitant radiotherapy involving the heart, previous or concomitant various classes of chemotherapy; moreover, it depends on the cumulative dose of the cytotoxic drugs [5,7,11,13].

Atrial fibrillation induced by ibrutinib therapy. Atrial fibrillation (AF) is associated witha high risk of all cause-mortality due to stroke, sudden death or heart failure [14]. Moreover, this supraventricular arrhythmia determines an increased morbidity by cardiac dysfunction, heart failure, hospitalizations, stroke, cognitive decline and vascular dementia [14]. Significant reduction of morbidity and mortality in AF patients is achieved by the use of anticoagulation with vitamin K antagonists (VKA) or nonVKA oral anticoagulants(NOAC). Rhythm or rate control may improve AF symptoms and quality of life but has no effect on reducing long-term mortality [14,15].

Mechanisms. AF is the most frequent arrhythmia related to ibrutinib therapy [4]. It occurs in up to 16% of the hematological patientsand 75% of them develop AF in the first year of treatment [4,5]. The mechanism of the AF secondary to ibrutinib is not fully elucidated. Comparing cardiac messenger RNA in AF and sinus rhythm in patients receiving ibrutinib, McMullen *et al.* identified a higher expression of Bruton's tyrosine kinase and other tyrosine kinases of T cell signaling in atrial tissue of AF patients [16]. In experimental models, in rat atrial myocytes with AF exposed to ibrutinib, the same group found a reduced expression of PIK3-Akt signaling, an essential cardioprotective pathway, that plays also an important role in B-cell receptor cascade16. Moreover, 18% of oncological patients by comparison with only 5% of patients without cancer develop AF, associated with a high serum level of C reactive protein, suggesting that inflammation can be a trigger for cardiac arrhythmias [6,17].

Classification. Current guidelines define four types of AF [14]. *Paroxysmal AF* lasts less than 27 days and often it is self-terminating. *Persistent AF* duration is greater than 7 days, regardless it is self-terminated or by cardioversion (electrical or pharmacological). *Long-standing persistent AF* is continuous for at least 1 year and the preferred strategy is rhythm control. Contrary, in *permanent AF*, an arrhythmia accepted by the doctor and patient, the cardioversion is not performed, but only rate control. *First diagnosed AF* is defined, irrespective of duration and the presence of symptoms, when it has not been identified at a medical check-up before [14].

Diagnosis. AF generates different symptoms, such as palpitations, dyspnoea, chest pain, fatigue, dizziness, sleeping disorders, which alter the quality of life, but it can be also asymptomatic [14,18]. European Heart Rhythm Association (EHRA) established a scale to evaluate symptom severity in AF patients (Table 2) [14,18]. The diagnosis of AF is made by electrocardiogram or prolonged electrocardiogram monitoring (24–72 hours), for paroxysmal episodes, and its duration has to be at least 30 seconds [14].

Frequently, ibrutinib therapy favors the occurrence of paroxysmal or persistent AF, with clinical indication for cardioversion, asymptomatic or with 1 and 2a EHRA symptom score. Thereby, AF is generally manageable using the recommendations of the current guidelines and ibrutinib therapy will not be discontinued [9].

Table 2

EHRA symptom scale in AF [14]

EHRA score	Symptom severity	Clinical description
1	Absent	AF has no symptoms
2a	Mild	AF does not affect normal daily activity
2b	Moderate	Frequently AF does not affect normal daily activity, but the patient can be disturbed by symptoms
3	Severe	AF disturbs normal daily activity
4	Disabling	AF discontinues normal daily activity

AF: atrial fibrillation; EHRA: European Heart Rhythm Association.

Treatment. The treatment goals for ibrutinib-induced AF are: (1) identifying hemodynamic instability or 3 and 4 symptoms on EHRA scale; (2) diagnosis of precipitating factors (sepsis, cytopenia, thyroid dysfunction, electrolyte disturbance); (3) the need for anticoagulation; (4) rhythm control; (5) rate control [7,14].

(1) Always, AF with hemodynamic instability, regardless of its onset, has a firm indication of urgent electrical cardioversion [14].

(2) More than that, identification and prompt treatment of extracardiac factors, that can favor the occurrence and maintenance of AF is mandatory, in order to restore the sinus rhythm or to obtain a good rate control14.

(3) Prevention of ischaemic strokes or other embolic events with anticoagulation (OAC) therapy isessential in AF patients because it prolongs life and improvesits quality [14,19]. OAC has proven its superiority to aspirin or no treatment in thromboembolic prophylaxis, with a risk of bleeding [14,19]. However, the risk of embolic stroke exceeds the risk of bleeding even in special patients with psychiatric and degenerative neurological diseases, frailty or elderly [14,20]. The bleeding risk of antiplatelet agents is similar to bleeding risk of OAC therapy, but only OAC reduces mortality in AF patients by preventing thromboembolic events14. Moreover, cancer may predispose to both prothrombotic and bleeding conditions and this can make the decision for long-term OAC a challenge.

After cardioversion, an episode of AF requires a minimum 4 weeks of OAC therapy [14]. The indication for long-term OAC therapy, by estimating the stroke risk in AF patients is based on CHA2DS2-VASc score (Table 3) [14]. A CHA2DS2-VASc score of 2 or more in men and 3 or more in women requires the need for OAC therapy [14]. A CHA2DS2-VASc score 0 for men and 1 for women (by sex category) do not benefit for long-term OAC therapy [14]. For a CHA2DS2-VASc score of 1 in men and 2 in women the OAC treatment should be considered, by an individualizedpatient's profile, balancing the risk for stroke and bleeding and patient preferences [14].

In cancer population, CHA_2DS_2-VASc score has not been validated, considering the permanent prothrombotic state of the disease itself and of the chemotherapy, but in clinical practice it is generally used. OAC is considered at a CHA_2DS_2-VASc score of 2 or more when the platelet count exceeds 50000/mm^3 and no significant active bleeding are recorded [7,21]. Also, for low-risk hematological patients with AF, OAC prophylaxis should be considered, knowing the additional risk for venous thromboembolic events at this category of patients [7]. Cardiac biomarkers, such as high-sensitivity troponin or N-terminal pro-B-type natriuretic peptide (NT-pro-BNP) may become in the future important tools for a better stratification of patients for stroke risk [14,23]. Moreover, cardiac biomarkers can diagnose asymptomatic cardiac dysfunction induced by chemotherapy. Troponin level is high secondary to myocardial injury and NT-pro-BNP increases in heart failure with high filling pressure [7,13,24]. Thereby, they can be used in ibrutinib-induced AF as markers for early structural myocardial alterations andalso they can guide specific cardiac therapeutic measurements [7].

Table 3

CHA_2DS_2-VASc score for indication of OAC therapy in AF patients [14]

Risk factors for stroke	**Points**
Congestive heart failure	+1
Hypertension	+1
Age ≥ 75years	**+2**
Diabetes	+1
Stroke, transient ischaemic attack, thromboembolism	**+2**
Vascular disease (myocardial infarction, peripheral vascular disease, aortic plaque)	+1
Age 65-74 years	+1
Sex category (female)	+1

AF: atrial fibrillation; OAC: anticoagulation.

The OAC therapy includes therapeutic low-molecular-weight heparin (LMWH), VKA (with regular international normalized ratio – INR monitoring) and NOAC. In hematological patients, LMWH is the preferred option, due to INR variation pronounced by the neoplasia and target chemotherapy [7,14,25]. NOAC includes direct thrombin inhibitor (dabigatran) and factor Xa inhibitors (apixaban, rivaroxaban, edoxaban) [14]. Compared to warfarin, NOAC significantly reduces all embolic events (including stroke) with 19% and mortality with 10% [14,26]. In addition, this new class of OAC halves the risk of intracranial haemorrhage, but with more frequent gastrointestinal non-fatal bleeding [14,27]. However, NOAC was not yet studied in valvular AF (moderate and severe mitral stenosis and mechanical heart valve); thereforeAVK therapy is requiredfor this category of patients [14].

Although not strongly recommended in cancer population, new studies suggest a better safety profile for NOAC versus AVK; thereby, these new anticoagulation class should be safe [7]. Recently, Kim *et al.* demonstrated that NOAC determines lower incidence of stroke, bleeding and all-cause mortality in comparison with warfarin in cancer patients newly diagnosed with AF, over a 1.8 years follow-up period [28]. Moreover, Ording*et al*. identified the same thromboembolic and bleeding risk with NOAC or warfarin in AF patients with or without cancer [29]. In Nam *et al.* study, NOAC had similar outcome and safety with LMWH in an active cancer population with stroke secondary to AF [30].

NOAC administration in ibrutinib-induced AF patients requires careful monitoring, because ibrutinib, apixaban and rivaroxaban are metabolized on the same cytocrome, CYP3A4 [5]. Thereby, NOAC may increase the patient exposure to ibrutinib, favouring an additional risk of bleeding and other side effects [5,31].

To assess the risk of bleeding for OAC therapy, current guidelines recommend various scales: HAS-BLED, ORBIT (Outcome Registry for Better Informed Treatment of Atrial Fibrillation) or ABC (age, biomarkers, clinic history) [14]. The most widely score used in daily practice is HAS-BLED, not yet validated in cancer population (Table 4) [14,32]. A HAS-BLED of 3 or more does not contraindicate the initiation of OAC therapy, but it requires a close monitoring of the patient [14]. The risk factors for bleeding can be divided in three categories: modifiable, potentially modifiable and non-modifiable (Table 5) [14]. They should be promptly identified and corrected, when possible [14].

The risk of bleeding in patients with ibrutinib therapyremainshigh even without association of OAC or antiplatelet agents, because ibrutinib favors a primary platelet dysfunction [5]. By inhibition of Bruton's tyrosine kinase, ibrutinib blocks collagen receptor glycoprotein IV (GP IV) and interaction between von Willebrand factor and glycoprotein Ib-IX-V, resulting an altered activation, adhesion and aggregation of platelets [5,33]. More than that, the hematological disease itself may favor the occurrence of anemia or thrombocytopenia, with increased risk of bleeding [34]. Not least, the occurrence of arterial hypertension or worsening of preexisting hypertension, secondary to ibrutinib therapy, with uncontrolled values, can have an additional role in increasing the risk for haemorrhages [34,35].

Table 4

HAS-BLED score for bleeding risk of OAC therapy in AF patients [14,32]

Risk factors	Points
Hypertension	+1
Abnormal renal /hepatic function	+1 each
Stroke	+1
Bleeding history or predisposition	+1
Labile INR	+1
Eldery (age>65 years)	+1
Drugs/alcohol	+1 each

AF: atrial fibrillation; OAC: anticoagulation.

(4) Restoration and maintenance of sinus rhythm is another important goal in AF treatment for symptoms improvement, without any effect on mortality [14]. Rhythm control therapy is made by electrical or pharmacological cardioversion and it is applicable for paroxysmal, persistent or long-term persistent AF [14]. Early cardioversion, performed in the first 48 hours from the onset of AF, can be done without a transesophageal echocardiography [14].

Electrical cardioversion is urgently indicated in hemodynamic instability AF cases [14]. Pharmacological cardioversion can be made with antiarrhythmic agents of class Ic (propafenone, flecainide – "pill in the pocket"), class III (amiodarone) or vernakalant, depending on the presence of coronary artery, structural heart disease or blood pressure values [14,36].

Table 5

Risk factors for bleeding of OAC therapy in AF patients [14]

Modifiable risk factors	Potentially modifiable risk factors	Non-modifiable risk factors
Hypertension (> 160 mmHg)	Anaemia	Age > 65 years
Labile INR	Abnormal liver function	History of significant bleeding
Antiplatelet agents	Abnormal renal function	History of stroke
Anti-inflammatory drugs	Abnormal platelet function	Cancer
Alcohol abuse	Reduced platelet count	Chronic kidney disease (dialysis)
		Cirrhotic liver disease
		Genetic factors

AF: atrial fibrillation; OAC: anticoagulation.

Long-term therapy for maintenance of sinus rhythm and prevention of AF recurrence is done after evaluating all comorbidities (including the presence of cancer), cardiovascular risk factors, ischemic or structural heart disease [14,37]. The commonly used drugs are antiarrhythmic agents of class III (amiodarone, sotalol), class I (propafenone), dronedarone, class II (beta-blockers) or, less often, class IV (calcium channel-blockers, such as verapamil or diltiazem) [14,37]. In selected cases, refractory to maximal pharmacological therapy, AF ablation with the isolation of pulmonary veins is recommended [14,37].

Most often, rhythm control therapy and prevention of recurrence in ibrutinid-induced AF was done with beta-blockers, calcium-blockers or amiodarone [5,38]. However, ibrutinib, amiodarone, diltiazem and verapamil have a common CYP3A4 metabolism pathway, increasing the patient exposure to ibrutinib [5].

Furthermore, current guidelines recommend the addition, when clinically indicated, of non-antiarrhythmic drugs with antiarrhythmic effects. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB) may prevent new episodes of AF in patients with systemic hypertension which associates LV hypertrophy or LV dysfunction [14,39]. Also, in heart failure patients with reduced LVEF, beta-blockers demonstrated a protective role against new-onset AF [14,40].

In cancer population, besides primary or secondary prevention of AF, beta-blockers, ACE inhibitors and ARB demonstrated an essential cardioprotective role in early cardiac dysfunction induced by chemotherapy [7,11,13,41].

(5) Rate control is an integral part of AF treatment, when there is no indication for cardioversion [14]. The optimal heart rate is below 80bpm at rest and below 110 bpm at moderate exercise [14]. This goal is obtained by single agent or combination therapy [14,42]. The choice of optimal pharmacological treatment is done considering the value of LVEF, the presence of heart failure, coronary artery disease or structural heart abnormalities [39]. A good rate control can be achieved with beta-blockers, calcium channel-blockers(diltiazem and verapamil) and digoxin [14]. Amiodarone also can be used for acute control of heart rate in patients with depressed LVEF or with hemodynamic instability [14,42]. In patients with high heart rate, unresponsive to maximal combination rate therapy, atrioventricular nod ablation and VVI pacemaker implantation should be considered [14].

In cancer patients, AF rate control is achieved frequently with beta-blockers and digoxin [5,22]. Association of ibrutinib and digoxin favors the risk of increased levels of serum digoxin, since both compete on the same substrate, represented by p-glicoprotein [5].

Ventricular arrhythmias related to ibrutinib therapy. Besides AF, in less than 2% of patients, ibrutinib may favor the occurrence of ventricular arrhythmias (isolated premature beats, ventricular tachycardia, torsade de pointes, ventricular fibrillation), without any QT interval prolongation [17,43,44]. In cultured myocytes, through an unknown kinase pathway, ibrutinib causes alteration of various phases of the action potential, increases late sodium current, leading to high ventricular automaticity [45]. In experimental models, Tuomi*et al*. showed that atrial and ventricular arrhythmias are more common in mice exposed to a single high dose of ibrutinib compared to chronic therapeutic dose [46]. Treatment of ventricular arrhythmias follows the recommendation of the current guidelines [47].

Regarding brad arrhythmias only one case of sinoatrial arrest secondary to ibrutinib therapy was reported in the literature so far [48].

Arterial hypertension induced by ibrutinib. Chemotherapy favors increased arterial stiffness, leading to hypertension, LV hypertrophy and coronary artery disease [7,11,49]. Arterial stiffness is an essential marker for early diagnosis of subclinical cardiovascular disease and became an independent predictor of cardiovascular mortality [49]. Pulse wave velocity represents the most used method in clinical practice for the assessment of arterial stiffness, recommended by current guidelines [49,50].

Hypertension occurs in up to 45% of oncological patients as a side effect of chemotherapy. The main mechanism involves the decrease of nitric oxide (NO) by inhibition of NO-synthase, leading to vasoconstriction and high peripheral resistance [6,12,13]. However, different chemotherapeutic regimens can exacerbate the preexistent hypertension7. Ibrutinib-related hypertension was identified in 20% of patients for a period of 3-years follow-up5. Hypertension-related to ibrutinib treatmentincreases the risk for AF, ischaemic stroke and intracranial hemorrhage and affects the risk-benefit balance for anticoagulation between thromboembolic prophylaxis and bleeding [5].

First-line therapy for chemotherapy-induced hypertension, with maintained blood pressure

values below 140/90mmHg, is ACE inhibitors or ARB, with their cardiac anti-remodeling effectand demonstrated cardioprotective role [7,51]. Dihydropyridine calcium-channel blockers represents another good option. Diuretics should be avoided due to the risk of electrolyte disturbance [7,13].

Direct toxic myocardial effect related to ibrutinib. Data about direct myocardial dysfunction induced by ibrutinib are scarce. Though, Wallace et al. reported an isolated case of cardiomyopathy with reduced LVEF and ventricular tachycardia, without coronary artery disease, after 4 months of ibrutinib therapy in a relapsed non-Hodgkin lymphoma. However, it cannot be excluded a late cardiotoxicity induced by anthracyclines therapy, since the patient received 2 years ago R-CHOP treatment (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) [52].

Conclusions. Ibrutinib represents an effective target therapy for various refractory hematological neoplasia, with significant improved outcome and survival of the patients. The occurrence of cardiac side effectsrepresents a challenge for a safe and correct management of ibrutinib therapy. A multidisciplinary approach for surveillance of these patients is required, in order to avoid unnecessary discontinuation or reduced-dose period for ibrutinib and to establish an optimal cardiovascular therapy with low risk of side effects and pharmacological interactions.

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