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Recommendations on cardiac safety during ibrutinib therapy

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Abstract

In November 2022, an update of the Summary of Product Characteristics for Imbruvica® (ibrutinib) was published, containing new risk minimization measures, including dose modification recommendations, due to the risk of serious cardiac events in patients receiving ibrutinib.

A team of experts composed of developed practical guidelines aimed at increasing cardiac safety and optimizing the care of patients treated with Bruton's tyrosine kinase inhibitors. The document was based on the recommendations of the European Society of Cardiology.

Key words: ibrutinib, cardio-oncology, hypertension, heart failure, atrial fibrillation

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Introduction

There are currently insufficient data to create separate cardiac algorithms for ibrutinib and acalabrutinib. Based on current experience and available publications, it seems that the profile and incidence of cardiac complications may be similar for both therapies and are probably related to the class effect of Bruton's tyrosine kinase (BTK) inhibitors.

It should be highlighted that the high effectiveness of therapy with BTK inhibitors significantly outweighs the risk of substantial toxicity. Additionally and importantly, decisions regarding patients with risk factors for cardiac events should always be made on an individual basis, after assessing the risk-benefit ratio, before starting treatment of ibrutinib.

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Recommendations for cardiac initial assessment and monitoring during the use of BTK inhibitors in accordance with the recommendations of the European Society of Cardiology (ESC) from 2022 (prepared in cooperation with European Hematology Association) [1]

General remarks

1. At present, there are insufficient data to create separate cardiac algorithms for ibrutinib and acalabrutinib — the profile and incidence of cardiac complications appear to be similar for both drugs.
2. BTK inhibitors are used for treatment of lymphoid malignancies, which are common in elderly people with underlying cardiovascular disease. While chronological age alone is not a significant predictor of serious cardiac events (including cardiac death), significant coexisting cardiovascular diseases and reduced patient fitness increase the risk, and thus the likelihood of cardiac complications.
3. Patients taking ibrutinib may be at increased risk of developing hypertension, atrial fibrillation, heart failure, ventricular arrhythmias not associated with QTc prolongation.

European recommendations

In a patient treated with a BTK inhibitor:

1) it is recommended to measure blood pressure at each clinical visit (class I recommendation, level B evidence);
2) weekly home blood pressure monitoring during the first 3 months of treatment and monthly thereafter should be considered (class IIa recommendation, level C evidence);
3) baseline cardiac echocardiography is recommended in high-risk patients (class I recommendation, level C evidence);
4) cardiac echocardiography is recommended for all patients who experience atrial fibrillation (class I recommendation, level C evidence);
5) pulse assessment or ECG is recommended at each clinical visit (class I recommendation, level C evidence).

Practical guidelines developed by a Polish experts panel

1. **Cardiac baseline assessment and optimization of cardiac treatment:**
   a) **high-risk** patient — any patient with a history of heart disease — for such a group of patients it is recommended to perform an echocardiography and echocardiogram (ECG), as well as to order a cardiological consultation;
   b) a patient **of at least intermediate risk** — a patient with arterial hypertension or diabetes or cardiac arrhythmias — for such a group of patients it is recommended to perform an ECG. In addition, echocardiography and cardiological consultation should be considered.
2. **Monitoring during treatment with ibrutinib:**
   a) blood pressure measurements at each clinical visit, it is also worth recommending home measurements
      → in the case of elevated blood pressure, modification of antihypertensive treatment is indicated;
   b) assessment of the pulse at each clinical visit and heart rate at least during auscultation, it is optimal to perform an ECG;
   c) informing the patient about the need to report any new symptoms, such as: dyspnea, decrease in exercise tolerance or feeling of irregular heart rhythm
      → in the case of the above symptoms, it is advisable to perform an ECG;
      → if arrhythmias are diagnosed, echocardiography is indicated.
3. **Ibrutinib dosage modifications:**
   a) discontinuation of ibrutinib or dose reduction occurs after the diagnosis of cardiac complications specified in the table I [2]. Consultation with a cardiologist is then recommended. Treatment may be restarted according to the new dose modification recommendations [3];
   b) a cardiologist evaluating each ibrutinib-related cardiac complication should additionally refer his diagnostic decisions to the latest definition of cancer therapy-related cardiovascular toxicity (CTR-CVT) proposed by the International Cardio-Oncology Society [4] and accepted by the European Society of Cardiology. In the aspect of cancer therapy related cardiac dysfunction (CTRCD), it is possible to implement preventive strategies at very early stages of myocardial damage (even asymptomatic ones), which may prevent cardiac events, the occurrence of which necessitates the discontinuation of ibrutinib or reduction of his dose;
   c) the Summary of Product Characteristics (SmPC) of Imbruvica® does not contain contraindications for patients with hypertension or cardiac comorbidities. Ibrutinib has been studied in a broad patient population worldwide, including patients with underlying cardiac comorbidities or cardiac risk factors. There are also available data suggesting that dose reduction will not have a significant impact on the efficacy of ibrutinib [3].

Table I. Diagnostic criteria proposed by the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5 [3] and proposed rules for dose reduction or discontinuation of ibrutinib for cardiac reasons

Type of complication	Definition of a complication	Recommendations for the use of ibrutinib
Grade 4 heart failure	Life-threatening condition — urgent hospitalization, intravenous administration of drugs, *etc.*	Discontinuation of the drug after the first occurrence
Grade 4 arrhythmia	Life-threatening condition: hemodynamic disorders, thrombus in the heart cavities	
Grade 3 heart failure	Dyspnea at rest or with minimal activity	
Grade 3 arrhythmias	Symptoms of arrhythmia require urgent intervention	• First occurrence → dose reduction by 140 mg • Second occurrence → drug discontinuation
Grade 2 heart failure	Dyspnea occurs with moderate activity	• First and second occurrence → dose reduction by 140 mg • Third occurrence → drug discontinuation

Authors' contributions

SS — preparation of the draft version of the manuscript. IH, KG, KJ, TR — critical, independent evaluation of manuscript. SS, IH, KG, KJ, TR — acceptance of the final version of the manuscript.

Conflict of interest

SS — fees for lectures or Advisory Board or support for attending meetings from companies: Amgen, Angelini, Astellas, AstraZeneca, Bayer, BMS, Gilead, Janssen-Cilag, Pfizer, Teva. IH — fees for lectures and advisory meetings: Janssen, AstraZeneca, Abbvie, Roche. KG — honoraria and research grants from companies Janssen-Cilag, AstraZeneca, Abbvie, BeiGene, Roche, Sandoz. KJ, TR — no conflict of interest reported.

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Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform Requirements for manuscripts submitted to Biomedical journals.

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