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Cardiotoxicity of Tyrosine Kinase Inhibitors: A Case Report

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Abstract **Case Report**

Chronic myeloid leukemia (CML), considered a fatal disease, is characterized by the presence of an acquired cytogenetic abnormality, resulting in the formation of an abnormal chromosome 22. Its prognosis has changed markedly following the advent of Tyrosine Kinase Inhibitors (TKIs), and overall survival is now approaching that of the general population, However, TKIs are responsible for a wide range of adverse effects, and the safety evaluation of these drugs has highlighted cardiotoxicity, the frequency and severity of which vary from one agent to another. The pathophysiological mechanisms by which TKI inhibitors increase the risk of cardiac damage remain unknown to this day, and several hypotheses have been put forward. This question has been widely discussed in the scientific literature. We propose to explore this issue through the analysis of a patient's clinical case. A review of the literature completes the clinical case to better clarify the current dangers and study the mechanisms of action of cardiotoxicity of these drugs.

Keywords: Atrioventricular block, tyrosine kinase inhibitors, chronic myeloid leukemia, cardiotoxicity, Nilotinib.

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INTRODUCTION

The BCR-ABL tyrosine kinase is a key molecule responsible for the pathophysiology of CML. Tyrosine kinase inhibitors (TKIs) directed against BCRABL are currently the cornerstone of treatment for CML patients. New data suggest that the three tyrosine kinase inhibitors used to treat CML patients - imatinib, dasatinib and nilotinib - have potentially serious cardiotoxic effects. The mechanisms underlying these side effects are still unclear. Reported cardiac side effects include palpitations, arrhythmia, QT prolongation, pericardial effusions, myocardial ischemia, myocardial infarction and congestive heart failure. For example, compared with dasatinib and nilotinib, severe congestive heart failure and left ventricular dysfunction are rare but prominent with imatinib treatment, particularly in patients receiving high doses [1]. Compared with imatinib, QT interval prolongation is relatively frequent in patients treated with dasatinib or nilotinib. In contrast to nilotinib, pericardial effusions are observed with imatinib and dasatinib. These data suggest that assessment of cardiac status, use of concomitant medications and potential risk factors should be taken into account in the management of CML. Good management of adverse events from the outset of treatment is necessary to avoid switching to another TKI, especially in good responders. Initiate a low-salt diet for all TKIs and a low-carbohydrate diet, especially for Nilotinib, and don't rush to stop the TKI, to ensure good therapeutic adherence [2].

CLINICAL INFORMATION

Observation

Mrs. I.A., aged 52, with no modifiable cardiovascular risk factors of note, and with a history of chronic myeloid leukemia initially treated for one year with an oral tyrosine kinase inhibitor Imatinibe, a first-generation TKI, had to be changed to Nilotinibe following adverse effects such as hydrosodic retention and edema of the lower limbs and face. She had been in remission for 5 months prior to the last admission, with a BCR ABL transcript level of less than 0.1% (= 0.0098%). Her history dated back two months prior to her consultation, with the occurrence of several brief episodes of loss of consciousness, preceded by prodromal symptoms of palpitations, profuse sweating and visual fog, without chest pain, with ad integrum recovery without urine leakage or tongue biting. The course was marked by recurrence and worsening of the symptoms. On admission, the patient was hemodynamically and respiratory stable, BP=122/63 mmgh both limbs symmetrical, HR= 46 bpm, FR= 16 cycle/min, with SaO2= 95% on room air. Heart sounds were clear, with no audible murmurs or noises added to the cardiovascular examination. The pleuropulmonary examination was unremarkable, with no auscultatory

rales, an unremarkable abdominal examination and, above all, no detectable splenomegaly. The 12-lead electrocardiogram performed on admission showed a regular sinus rhythm with a mean ventricular rate of 50 beats per minute, a normal cardiac axis, a constant and normal PR space of 160 ms, with the presence of a right delay extrasystole, and a QT interval corrected to 524 ms by the FREDERICIA formula (Figure 1). Biologically, blood form counts, ionograms, renal function and thyroid function tests were without abnormality, while Pro Bnp cardiac markers were slightly elevated at 232pg/ml, with us troponins at 10ng/l. Transthoracic echocardiography was without structural abnormalities (Figure 2).

A 24h holter ECG recording was performed for further investigation, and in the absence of arguments explaining our patient's symptomatology, which showed a regular, sinusoidal basal rhythm, with a switch to atrial fibrillation (Figure 4) with sinus bradycardia at 45 beats per minute and a prolonged QT interval and a transition to compeltal BAV.

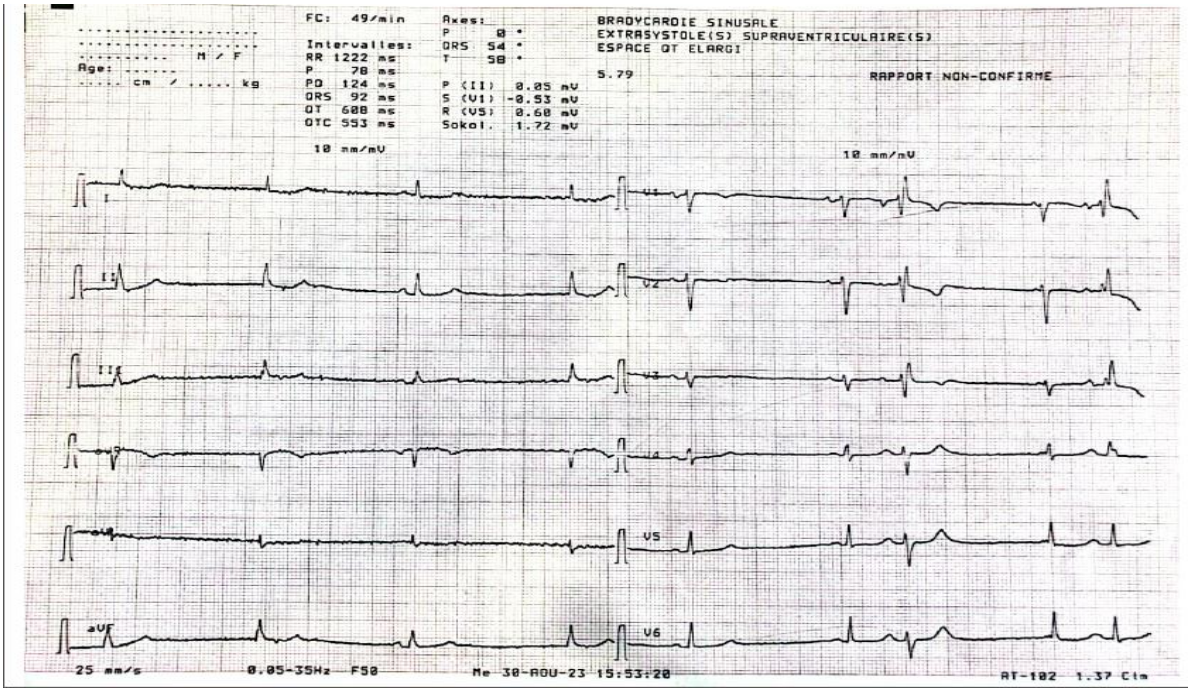

Figure 1: 12-lead electrocardiogram

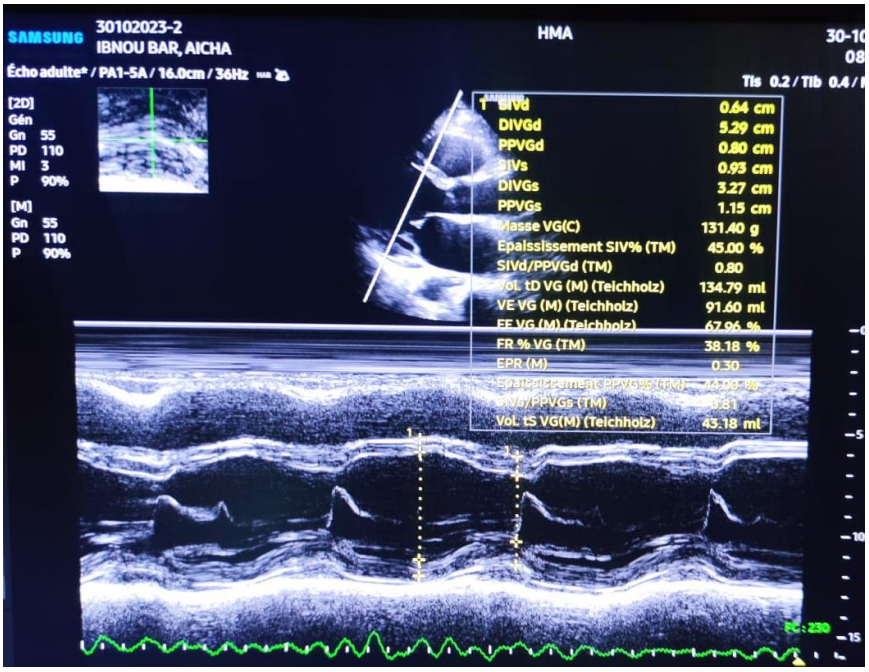

Figure 2: Transthoracic echocardiography

Therapeutic strategy

Unfortunately, even on Nilotinibe, our patient developed rhythmic side effects. A transition to sustained paroxysmal AF was documented on the 24h HOLTER ECG, with a CHA2DS2VASc of 1 (female gender), and so the indication for anticoagulation was not maintained. As far as bradycardia was concerned, the multidisciplinary discussion was in favour of discontinuing treatment in the first instance, with no improvement in symptomatology and no regression of rhythmic disturbances on the follow-up holter ecg. To overcome this problem, we decided to implant a dual-chamber pacemaker.

DISCUSSION

CML is a chronic myeloproliferative syndrome characterized by the presence of an acquired cytogenetic abnormality, resulting in the formation of an abnormal chromosome 22, known as the Philadelphia chromosome (Ph). A molecular marker, the BCR-ABL fusion gene, induces the production of a chimeric protein (oncoprotein tyrosine kinase bcr-Abl) which, through its uncontrolled tyrosine kinase activity, deregulates cell proliferation, reduces leukemic cell adhesion to the bone marrow stroma, and protects leukemic cells from normal programmed cell death (apoptosis), which is responsible for the disease. Left untreated, CML passes through three phases: an initial indolent chronic phase that can last 5 to 6 years, with spectacular results when treatment is initiated; an accelerated phase; and a blast phase with a very poor prognosis, leading to acute leukemia.

Considered a fatal disease, the prognosis has changed markedly with the advent of Tyrosine Kinase Inhibitors, and overall survival is now on a par with that of the general population. Three generations of TKIs have been described, depending on their efficacy and spectrum of action: 1st-generation TKIs (Imatinib, Mesylate), 2nd-generation TKIs (Nilotinib, Dasatinib, Bosutinib, Radotinib), and 3rd-generation TKIs (Ponatinib).

Managing the adverse effects of TKIs is therefore crucial in both the short and long term. While side effects are largely determined by the spectrum of protein kinase or non-kinase inhibition of each TKI, potential drug interactions, possible comorbidities and inter-individual environmental and genetic differences are likely to help explain variations in the incidence or severity of certain side effects for a given TKI. Most TKI side-effects are mild, resolving spontaneously or with appropriate measures including symptomatic treatment, dosage reduction or change of TKI. Others, however, can be life-threatening or functionally disabling [3].

An article published in ONCO Target and Therapy in 2018 on the mechanisms of cardiotoxicity of tyrosine kinase inhibitors, objective that these remain unknown to this day and several hypotheses are put forward. The proposed mechanisms of cardiotoxicity vary and appear to be drug-specific. Disruption of mitochondrial function within the cardiomyocyte has been implicated. In a preclinical study, tyrosine kinase inhibitors disrupted the action potential in the hERG potassium channel of certain Purkinje fibers, especially with dasatinib, nilotinib and imatinib, causing arrhythmias. Toxicity is likely to be due to receptor kinase binding both on and off target, reflecting a lack of specificity of TKIs [4]. This study showed that fluid retention was most frequent with dasatinib, hypertension with sorafenib, and reduced LVEF with lapatinib. This implies that cardiotoxicity is not due to a single mechanism for the TKI class, but varies from agent to agent. Pooled safety data suggest minimal risk of cardiotoxicity for dasatinib and lapatinib. A review of professional guidelines and recommendations shows that systematic monitoring of cardiac function during treatment and identification of at-risk patients prior to treatment are key steps in the prevention of cardiovascular events, regardless of the agent used [4]. In an article published in BMC Medicine in 2023, studies carried out on the cardiomyocyte in vitro revealed oxidative stress at the endoplasmic reticulum leading to apoptosis, especially with imatinib and nilotinib, but the activation of this stress and how this cardiotoxicity is regulated remain unknown [5].

In the journal of hematology published in 2009, the cardiotoxic effects of TKIs in CML were described in detail, and ranged from simple palpitations, arrhythmia, QT prolongation and pericardial effusion to more serious effects such as myocardial infarction and heart failure, pericardial effusion, to more adverse effects such as myocardial infarction and heart failure. In the same review, the focus was on nilotinib, which primarily causes QT prolongation, with a risk of progression to torsade de pointes and sudden death [6].

What do the ESC 2022 cardio oncology guidelines say about TKI toxicity? Firstly, they concur with previous studies concerning the mechanism of TKI toxicity. Second-generation TKIs, and more specifically nilotinib, are responsible, in order of frequency, for arterial hypertension, corrected QT prolongation, atrial fibrillation and, more rarely, pleural or pericardial effusion. European guidelines recommend that, before starting patients on TKIs, the patient should always be examined first, blood pressure taken and a baseline electrocardiogram performed; echocardiography is indicated in class IIa. A repeat ECG and QTc calculation are recommended after two to four weeks of nilotinib introduction, and every two weeks after any dose increase [7].

CONCLUSIONS

Most patients treated with TKIs for CML have a normal life expectancy, provided they maintain an optimal response. According to the national cancer institute, for patients on nilotinib, treatment can only be discontinued after three years on TKIs with a satisfactory

molecular response. However, some TKIs increase the risk of cardiotoxicity, particularly in patients already at high or very high risk. Determining baseline and on-treatment cardiovascular risk, and implementing preventive measures, are therefore important, in collaboration with the general practitioner and cardiovascular medicine specialists. Further research into the mechanisms underlying these effects is needed, as it could ultimately lead to more specific prevention strategies.

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