Critical Reviews in Oncology/Hematology 107 (2016) 190–198

Contents lists available at ScienceDirect

Critical Reviews in Oncology/Hematology

journal homepage: www.elsevier.com/locate/critrevonc

Proposal for a tailored stratification at baseline and monitoring of cardiovascular effects during follow-up in chronic phase chronic myeloid leukemia patients treated with nilotinib frontline

Massimo Breccia (MD)[a,*], Eleonora Arboscello[b], Andrea Bellodi[b], Gioia Colafigli[a], Matteo Molica[a], Micaela Bergamaschi[b], Fulvio Massaro[a], Luisa Quattrocchi[a], Matteo Sarocchi[b], Paolo Spallarossa[b], Giuliana Alimena[a]

[a] Department of Cellular Biotechnologies and Hematology, Sapienza University, Rome, Italy
[b] IRCSS AOU San Martino – IST di Genova, Italy

Contents

ARTICLE INFO

Article history:
Received 10 January 2016
Received in revised form 24 August 2016
Accepted 11 October 2016

Keywords:
Chronic myeloid leukemia
Nilotinib
Cardiovascular risk
Prognosis

ABSTRACT

Nilotinib was approved for chronic myeloid leukemia patients in chronic phase or accelerated phase after resistance to imatinib or as frontline treatment. The drug, as other tyrosine kinase inhibitor has a specific safety profile with possible occurring metabolic side effects, such as increased glycaemia and cholesterol level, that may result, in predisposed patients, in an increased rate of cardiac and vascular disorders.

The objectives of this paper were to focus on the optimal procedures to perform at diagnosis in order to identify patients at risk of possible events and the correct monitoring procedures in order to prevent and manage metabolic and cardiovascular adverse events. Several national haematologist and cardiologist reviewed the literature, analysed levels of evidence for each topic and, after extensive discussions presented their proposals based on current international guidelines.

1. Introduction

The pivotal role of *BCR-ABL1* in the pathogenesis of CML provided the rationale for the design of inhibitory agents specifically targeting oncoproteins constitutive kinase activity. The first drug tested, namely imatinib mesylate (IM) is an inhibitor of ABL1,

* Corresponding author at: Department of Cellular Biotechnologies and Hematology, Sapienza University, Via Benevento 6, 00161 Rome, Italy.
E-mail address: breccia@bce.uniroma1.it (M. Breccia).

http://dx.doi.org/10.1016/j.critrevonc.2016.10.002
1040-8428/

BCR-ABL1 and other tyrosine kinases (Goldman and Melo, 2003; Yeung and Hughes, 2012). IM provides effective and durable therapy for CML. Indeed, a 8-year follow-up of the phase III International Randomized IFN versus STI571 (IRIS) study, showed 85% overall survival (OS) rates, but reported that 30% of patients had unfavourable outcomes, mostly due to primary (17%) or acquired resistance (15%) (Deininger et al., 2009). Hence, second generation TKIs (dasatinib and nilotinib) were introduced in the pharmacological armamentarium successfully rescuing about 50% of IM-resistant patients (Shah et al., 2010; Giles et al., 2013). Dasatinib and nilotinib were then tested in frontline setting and now can be prescribed after the results of DASISION and ENESTnd randomized phase III trials, respectively (Larson et al., 2012; Kantarjian et al., 2012).

In particular the results at 6 years of follow-up of ENESTnd trial and the recent results of ENEST1st at 2 years of follow-up showed that nilotinib was able to induce higher rate of early molecular response at 3 months, higher rate of deep molecular responses (MR4 and MR4.5) and reduce the progression rate as compared to imatinib (Hughes et al., 2016; Hochhaus et al., 2016). Nilotinib, as dasatinib and imatinib, has a specific safety profile that limits possible prescription for all patients. In particular all second-generation tyrosine kinase inhibitors (TKIs) increased the potential risk for cardiovascular complications and which impose baseline identification according to cardiovascular pre-existing profile (Breccia and Alimena, 2015). Two groups showed the strength to consider potential cardiovascular risk factors, such as personal and previous history of cardiovascular disease, hypercholesterolemia, diabetes, smoking, hypertension, obesity and severe renal impairment as consequence of diabetes and hypertension, as stated by the European Cardiolology Association (ESC) (Breccia et al., 2015; Rea et al., 2015). In particular, our group retrospectively applied the SCORE chart in a series of 82 patients treated with nilotinib second or first-line: the results showed that none of the patients classified as low risk developed cardiovascular events, that were, indeed, observed only in patients with moderate and in particular high risk profile (Breccia et al., 2015). Same results were observed from the French group: 57 patients were retrospectively classified according to ESC criteria and as in the previous study, cardiovascular events were observed with a major incidence in very high/high risk profile (Rea et al., 2015). Therefore, it become of paramount importance identify from baseline clinical features that may predispose patients to serious adverse events during treatment and select the appropriate line of therapy according to an holistic approach (Breccia and Alimena, 2015). Aim of our paper is to propose a correct guide for placement of patients at baseline before treatment with nilotinib and for a subsequent monitoring in order to prevent and manage cardiac and vascular peripheral disorders.

2. Methods

We performed a systematic review of all published literature and recent abstracts reported at international meetings about safety reported during nilotinib treatment. We included in the research the following terms: nilotinib, cardiovascular, peripheral artery disorders, PAOD, cardiac ischemia, glucose, lipidic, cholesterol. This analysis allowed us to focus on some recurrent side effects and to discuss in a national not supported board, including cardiologist, how to prevent these events according to identification of baseline features and how to manage according to current international guidelines for the treatment of cardiovascular and metabolic complications. Therefore, we referred to European Society of Cardiology guidelines for the management of cardiac and peripheral disorders management and to American diabetes association (ADA) guidelines for the management of diabetes.

3. CV risk factors target: practical tips

3.1. Basal assessment

The baseline visit is a primary starting point necessary to establish the best follow-up for CML patients. Independently from TKI choice and risk profile, all CML patients have to be evaluated with physical examination (including blood pressure, heart rate, peripheral pulses), exhaustive blood test panel (blood count, glucose, urea, creatinine, LDL and HDL cholesterol, triglycerides, fibrinogen, VES, sodium, potassium, calcium, magnesium, TSH, uric acid, homocysteine, HbA_{1c}) (Box 1).

Electrocardiography with QT and QTcF evaluation and echocardiography should be performed, in particular for patients' candidate to second-generation TKIs. Echocardiography data should consider not only left ventricular function with ejection fraction, but also diastolic function, presence of valvular disease and arterial pulmonary pressure. In patients with previous myocardial infarction, without a recent stress test, a provocative cardiac stress test could be performed before the beginning of nilotinib therapy, according to general clinic conditions and cardiologist suggestion Box 1).

As for PAD risk, a vascular evaluation is recommended: the Edinburgh Claudication Questionnaire has a good sensibility for identification of symptomatic PAOD patients (Leng and Fowkes, 1992). Asymptomatic patients with peripheral pulses and no risk factors may be scheduled for 12 months follow up. Asymptomatic patients with risk factors or absence of a peripheral pulse should be evaluated by vascular specialist with ankle-brachial index (ABI) (Ferket et al., 2012). If ABI $\geq$0.9 a 12 months follow-up should be sufficient, while in patients with ABI <0.9 other tests are mandatory, such as lower limbs and carotid ultrasound and a 6 months follow-up. Anyway, measurement of carotid intima-media thickness and/or screening for atherosclerotic disease by carotid artery ultrasound should be considered in asymptomatic adults at moderate risk (Perk et al., 2012). Patient symptomatic for claudicatio intermittens should be evaluated by vascular specialist with ABI and their follow-up with echocolor-doppler can be scheduled on 3 or 6 months with ABI <0.7 for cut off (Box 1). ABI measurement in CML patients required confirmation by prospective studies (Kim et al., 2013; Aichberger et al., 2011).

These data should allow the physician to prepare a full cardiovascular risk assessment, and to schedule an appropriate follow-up program for the patient. Indeed, clinicians should gather data about presence of cardiovascular risk factors and their status, past medical history, with focus on comorbidities, screening on cardiovascular and respiratory diseases, ongoing medications (Box 1). These data should allow defining a stratification of global cardiovascular risk according to current guidelines, which is useful for patients independently from CML and that allow clinicians to establish a risk-benefit ratio for a given TKI according to the clinical goal the patient needs to achieve.

3.2. Risk stratification

In 2012, European Society of Cardiology (ESC), together with a task force of other scientific Societies, produced an extensive evidence-based document of guidelines with strategies on CVD prevention. The estimation of CV risk was based on the Systematic Coronary Risk Evaluation (SCORE) project, which was developed through years; special risk charts were thus produced based on the SCORE and were applied to low and high-risk countries obtaining consensus in all Europe. The SCORE system estimates the 10-year risk of a first fatal atherosclerotic event, comprehending myocardial infarction, stroke, aneurysm of the aorta and other, so it is quite useful for a larger population. The "chart" tool is an interesting