Management of Ponatinib in Patients with Chronic Myeloid Leukemia with Cardiovascular Risk Factors

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Keywords

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Abstract

Cardiovascular (CV) adverse events are considered common complications of ponatinib treatment. Recently, it has been demonstrated that ponatinib dose reductions in definite settings can obtain optimal responses and lower ponatinib-related CV events. In this study, we describe the management of 5 patients with chronic myeloid leukemia treated with ponatinib, from second to fourth line of tyrosine kinase inhibitor therapy, carrying high pre-ponatinib CV risk, who obtained optimal molecular response and developed no CV adverse event during follow-up. Among these 5 patients, 2 had diagnosis of ischemic heart disease and underwent percutaneous angioplasty, 2 had type 2 diabetes and arterial hypertension, and 1 had only arterial hypertension. Median follow-up for ponatinib therapy is 1,039 days (34.6 months). Median dosage administered is 30 mg a day. SCORE charts were used to estimate risk of CV death in 10 years and Charlson Comorbidity Index was applied to estimate age-adjusted risk of

death related to comorbidities. Strict cardiologic follow-up (complete evaluation every 3 to 6 months) and maximum effort in the control of CV modifiable risk factors are strongly recommended in the management of ponatinib treatment in patients at high risk for CV events and may allow the use of ponatinib in patients belonging to CV risk category.

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Background

Ponatinib is a third-generation tyrosine kinase inhibitor (TKI) indicated in adult patients with diagnosis of chronic myeloid leukemia (CML) who are resistant to dasatinib or nilotinib or who have the T315I mutation. Clinical studies have been conducted on a population of patients who had already underwent at least two other TKIs and demonstrated high efficacy and acceptable toxicity profile [1, 2].

Cardiovascular (CV) adverse events (AEs) are considered common complications of ponatinib treatment. Commonly, pre-existing CV risk factors or CV events in

Table 1. Age, CCI, SCORE pre-ponatinib (pre-Pona), and ponatinib (Pona) treatment data of the 5 patients presented in the text

No.	TKI line	Age at Pona	Median Pona dose, mg/day	CCI 10-year risk	SCORE pre-Pona	Best MR Pona	non-CV AE	Pona exp., months	Follow-up, months
1	3	53	30	21%	10%	MR3	abdominal cramps	4	17
2	2	72	20	21%	15%	MR3	high lipase levels	44	44
3	3	61	16.5	0%	5%	MR3		44	44
4	4	68	18	53%	7%	MR3		34	34
5	4	46	20	90%	2%	MR4	erectile deficit, high lipase levels	28	34

patients with CML usually prevent the clinicians in prescribing ponatinib, even when it would be the best choice in terms of expected efficacy. The phase II PACE trial highlighted the risk for arterial occlusive disease and CV AEs in general in patients treated with ponatinib. The drug was temporarily suspended from commerce by US FDA and reintroduced when analysis on CV risk factors in patients who developed CV complications was completed and demonstrated that those occurred mostly in patients with pre-ponatinib high CV risk [3]. Cardiovascular assessment, accurate control, and improvement of modifiable CV risk factors are recommended in patients eligible to ponatinib treatment [4]. The Systemic Coronary Risk Evaluation (SCORE) charts are a useful tool validated in estimating CV risk of death at 10 years and take into account these variables: age, gender, smoking status, systolic blood pressure (SBP), total cholesterol levels, high-/low-risk countries [5–7]. The SCORE charts have been used to predict the risk of developing a CV AE in patients undergoing ponatinib treatment [8]. Recently, international guidelines for CV disease prevention were published and the SCORE charts were judged easy-to-use for a rapid evaluation of the patients' risk, but not extensively applicable (age 40–65 years) and giving limited information (only estimation of fatal CV events). For patients with diagnosis of diabetes mellitus, renal failure, or CV diseases, the use of modified scores is recommended by the same guidelines [9].

Recently, it has been demonstrated that ponatinib dose reductions in definite settings can obtain optimal responses and lower ponatinib-related CV AEs. Pharmacokinetic analysis has indicated the possibility of reducing the starting dose of ponatinib to 15 mg/day and preliminary data showed advantages in terms of safety while maintaining its efficacy [10].

In this study, we describe the management of 5 patients with CML treated with ponatinib, from second to fourth line of TKI therapy and carrying pre-ponatinib

CV risk, who obtained optimal molecular response and developed no CV AEs during or after ponatinib treatment.

Patients and Methods

In our center, 5 patients with history of CV risk or CV disease were treated with ponatinib in at least second line of TKI therapy for CML, with first dose of ponatinib prescribed between May 2015 and April 2018. Among these 5 patients, 2 had diagnosis of ischemic heart disease and underwent percutaneous angioplasty, 2 had type 2 diabetes and arterial hypertension, and 1 had only arterial hypertension. Median follow-up for ponatinib therapy is 1,039 days (34.6 months). Median dosage administered is 30 mg a day. For all the 5 patients, stable or improved molecular response was registered during ponatinib treatment, with respect to the one they had before. Three of five patients are still in treatment with ponatinib.

Pre-ponatinib CV risk at 10 years was estimated applying the SCORE charts. The Charlson Comorbidity Index (CCI) was used to determine impact of comorbidities before ponatinib. CCI was applied in CML and demonstrated affordability in the estimation of prognosis [11–13].

Reports

We here report brief descriptions of the management of patients with pre-ponatinib CV risk. Median follow-up is 37 months starting from first ponatinib dose. Data exposed in the following descriptions are reported in Table 1 for better visualization.

Patient 1

Patient 1 is a 47-year-old male who started ponatinib when he was 53 as the third-line therapy of CP-CML, being dasatinib intolerant (relapsing pleural effusion). Dasatinib was the second-line TKI, after imatinib first line. Imatinib was stopped 3 months after the beginning of the therapy because of muscle cramps, diffuse edema, and increased amylase and lipase levels. At that time, partial cytogenetic response was achieved. Dasatinib second line was withdrawn in October 2016 because of relapsing pleural effusion. Dasatinib dose has been gradually decreased to 50 mg every other day, without benefit on toxicity, before deciding for drug with-

drawal. At the time of dasatinib withdrawal, molecular evaluation revealed MR2. Before ponatinib first dose, comorbidities were arterial hypertension, diabetes mellitus type 2, and chronic HCV infection, accounting for a CCI of 5 (21% 10-year estimated survival). CV risk SCORE accounted for a 10% risk, with SBP 150 mm Hg, total cholesterol 270 mg/dL, and smoke exposition positive. The patient was already taking low-dose aspirin (100 mg once a day). Initial dose was 45 mg a day and dose reduction to 30 mg and then to 15 mg was prescribed due to a non-CV AE (abdominal cramps). Computed tomography scan and normal amylase and lipase levels excluded pancreatitis. Ponatinib was stopped after 3.8 months for persisting abdominal cramps, with resolution some days after withdrawal. Response evaluation revealed MR2.

Patient 2

Patient 2 received diagnosis of accelerated-phase CML at 71 years and started ponatinib 1 year later as a second-line TKI, for intolerance to dasatinib first line: three episodes of pleural effusion. Response to dasatinib at the moment of suspension was MR3. Comorbidities at first ponatinib dose were chronic obstructive pulmonary disease, arterial hypertension, and chronic HBV infection, with 5 points at CCI, meaning 21% expected survival at 10 years. CV SCORE accounted for 15%, with SBP 120 mm Hg, total cholesterol 160mg/dL, and smoke exposition negative. Low-dose aspirin was prescribed in association with ponatinib. Initial ponatinib dose was 45 mg a day, and dose reduction was prescribed to 30 mg when MR3 was reached and then to 15 mg a day when high lipase values occurred at control exams. Dose reduction obtained normalization of lipase and amylase values. No CV AEs were registered. The patient was still taking ponatinib at the dose of 15 mg a day at checkpoint date.

Patient 3

Diagnosis of CP-CML occurred at 52 and third-line therapy with ponatinib was prescribed for resistance to second-line dasatinib therapy (no ABL domain mutations revealed) at 61 years of age, when molecular response was MR3. First-line TKI was imatinib, which was withdrawn because of resistance (confirmed loss of MR3), with no demonstration of ABL domain mutations. Pre-ponatinib comorbidities were arterial hypertension, type 2 diabetes mellitus, and active metastatic breast cancer receiving chemotherapy. CCI accounted to 9, with 0% expected survival at 10 years. The CV SCORE revealed 5% possibility of CV death in the next 10 years, with SBP 150 mm Hg, total cholesterol 200 mg/dL, and smoke exposition positive, but actual CV risk was surely higher considering active breast cancer and chemotherapy. Low-dose aspirin was prescribed in association with ponatinib, according to the high CV risk. During ponatinib treatment, atrial fibrillation was diagnosed and the patient started anticoagulant therapy with low-molecular-weight heparin. Aspirin prophylaxis was not withdrawn. Initial dose of ponatinib was 30 mg, which was reduced to 15 mg when MR3 was reached. The patient was still taking ponatinib at the dose of 15 mg a day at checkpoint.

Patient 4

Patient 4 was 59-year-old at CP-CML diagnosis and started ponatinib when he was 68, as the fifth-line therapy, being considered intolerant to all other TKIs. Comorbidities at ponatinib first dose were hypertensive-ischemic chronic heart disease with stable angina and abdominal aorta aneurysm. A CCI of 4 points revealed

a 53% probability of survival at 10 years. The SCORE accounted for 7% risk, with SBP 140 mm Hg, total cholesterol 190 mg/dL, and the absence of smoke exposition. The patient was already assuming antiplatelet therapy at the time of ponatinib first dose. In spite of the high CV risk, ponatinib was the only possible choice for this patient. Start dose was 30 mg and reduction to 15 mg a day was applied when MR3 was reached, 2 months after the first dose. The patient was still taking ponatinib at the dose of 15 mg a day at checkpoint. No CV AEs were registered during ponatinib treatment.

Patient 5

Patient 5 was diagnosed with CP-CML when he was 39 years old and switched from third-line dasatinib to ponatinib because of dasatinib intolerance (persistent elevated lipase and amylase levels also after dose reductions). CCI at ponatinib first dose was 2, with a 90% probability of survival at 10 years. Pre-ponatinib SCORE was 1%, but it was considered not affordable, due to preexistent diagnosis of chronic heart disease (STEMI during nilotinib). The patient was already assuming low-dose aspirin at first dose. Start dose was 30 mg a day, reduced to 15 mg a day for non-CV AEs (erectile deficit and high lipase levels). Doppler evaluation excluded a vascular cause for erectile deficit and the patient was addressed to endocrine evaluation. The patient stopped ponatinib treatment for persistence of high lipase levels after 28.5 months of treatment, having reached MR4, and started off-therapy monthly follow-up.

Discussion

No CV AE was reported for any of these 5 patients recently treated in our center and bearing pre-ponatinib CV risk factors. Strict cardiologic control was operated during ponatinib therapy. For this purpose, these patients have been followed by cardio-oncologic specialists, who are confident with hematological medications and sensible to evaluate TKIs adjunctive CV risk in modulating cardiologic treatments. All the patients had been evaluated every 6 months at cardio-oncology unit with visit, electrocardiogram, and echocardiography, and the risk-benefit of TKI therapy was collegially debated. CV therapies were optimized and maximum effort was put into counselling for lifestyle adjustments to reduce the weight of modifiable CV factors on global risk.

The median SCORE accounted for 7% among these 5 patients, but this value has to be considered as underestimated because it does not consider history of chronic heart disease (2 patients) and age over 65 years (2 other patient). The use of the SCORE can be useful and quick to assess when evaluating the CV global risk of a patient who has to be treated with drugs that can have an impact on the risk itself, but it is only validated for primary prevention. Moreover, it was not validated in large cohorts of patients with diagnosis of CML assuming TKIs with

known associated CV risk. Median CCI score was 5, meaning a 21% probability of survival at 10 years. Taking into account chronic and acute heart diseases and other CV disease history, we think that CCI has to be used in association with the SCORE charts to better estimate CV and overall prognosis in this kind of patients.

Median ponatinib duration of therapy was 34.6 months between the 5 patients described, of which 3/5 were still taking ponatinib at checkpoint. Ponatinib dose was reduced in all of the 5 patients with CV risk at our center and lower affordable dose was prescribed and maintained with target molecular response at least MR3. None of the 5 patients lost molecular response during ponatinib, in spite of dose reduction.

Exception made for patient 1, who stopped ponatinib due to a non-CV AE (abdominal cramps), the drug was well tolerated and dose reduction allowed long duration of treatment, with a median ponatinib treatment length of 34.6 months. Ponatinib withdrawal occurred in patient 5 too, due to high lipase and amylase levels after 28 months of treatment, and he is now in off-therapy follow-up.

Conclusions

Cardiovascular comorbidities are often present at diagnosis in CML, due to the similar median age of onset of both diseases and of global frequency of CV diseases. CV risk factors in absence of overt disease are even more prevalent in the general population.

The SCORE charts can be used, but they are probably not affordable enough to estimate CV risk in CML patients who have to assume TKIs that carry adjunctive CV risk. Other scores have to be validated in a large cohort of CML patients assuming TKIs. Using CCI in association with SCORE charts and/or with other risk scores may help in better define CV and overall risk of death and of CV non-fatal events in patients eligible to ponatinib and other TKIs.

The presence of a moderate to high CV risk is commonly considered a contraindication to prescribe ponatinib as a therapy of choice in CML even in cases in which other TKIs available do not seem to assure the same efficacy. In the cases we described, 5 patients with CV risk factors and/or chronic heart disease, no CV AEs was registered with a median follow-up of 37 months. All of the 5 patients started with a dose between 45 and 30 mg a day and then passed to the lower dose of 15 mg a day. Dose reduction probably reduced TKI-related CV risk and maintained efficacy on molecular response, though.

Strict cardiologic follow-up (complete evaluation every 3 to 6 months) and maximum effort in the control of CV modifiable risk factors are strongly recommended in the management of ponatinib treatment in patients at high risk for CV events.

Statement of Ethics

This study was approved by our local ethics committee and consent for data collection and publication was obtained from the patients involved in the study.

Disclosure Statement

The authors declare that they have no competing interests.

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Availability of Data and Material

The datasets generated and/or analyzed during the current study are not publicly available due to privacy laws but are available from the corresponding author on reasonable request.

Author Contributions

M.S.: data collection, writing, and editing; V.A.: data collection and elaboration; A.D.C.: data collection; M.S.: data collection; G.N.: data collection and elaboration; F.D.P.: data collection and revision; A.P.: data collection; A.R.: revision; S.S.: revision and editing.

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