

Insights into the optimal use of ponatinib in patients with chronic phase chronic myeloid leukaemia

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Abstract: There are five tyrosine kinase inhibitors (TKIs) that are currently approved (in the European Union and the United States) for the treatment of chronic myeloid leukaemia (CML) in the chronic phase (CP) and each of them has its own efficacy and toxicity profile. Oral ponatinib (Iclusig®) is a third-generation TKI structurally designed to inhibit native *BCR-ABL1* tyrosine kinase and several *BCR-ABL1* mutants, including T315I. Ponatinib is now approved for patients with CML who are resistant or intolerant to prior TKI therapy (European Union) or for whom no other TKI therapy is indicated (United States). Despite achieving results in heavily treated patients, which led to its approval, the drug may induce cardiovascular events, requiring a careful baseline assessment of predisposing risk factors and specific management during treatment. 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 maintained its efficacy. This review summarizes the results achieved and drug-related side effects reported in all clinical trials and real-life experiences, testing ponatinib in patients with CP-CML. In addition, we focus on the appropriate use of ponatinib in clinical practice suggesting some useful recommendations on the proper management of this drug.

Keywords: chronic myeloid leukaemia, dose reduction, ponatinib, safety

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Introduction

The therapeutic scenario of chronic myeloid leukaemia (CML) has drastically changed after the introduction of highly selective target therapies for *BCR/ABL1* kinase, which have greatly improved the outcome of patients affected by this malignant disease. Imatinib, which became available in the early 2000s, was the first tyrosine kinase inhibitor (TKI) able to induce a high rate of complete cytogenetic response (CCyR) compared with interferon in the IRIS trial.¹ Although the results observed with imatinib were impressive, about 25% of patients showed primary and secondary resistance that is still considered a therapeutic challenge in patients with CML. Primary resistance consists of the failure of achieving a landmark response, while secondary resistance is defined as the achievement of a haematological or cytogenetic response subsequently lost.^{2,3} Resistance

is often related to the occurrence of point mutations of the *ABL* kinase domain that, by inducing a conformational change in the adenosine triphosphate (ATP)-binding pocket, suppress the inhibitory activity of TKIs on the *BCR/ABL1* fusion protein, causing a reactivation of CML cells' proliferative ability.^{4,5} The T315I mutation, or gatekeeper mutation, is characterized by the replacement of a wildtype threonine with a hydrophobic isoleucine in the ATP-binding pocket, causing steric hindrance.^{6,7} The onset of the T315I mutation occurs in up to 20% of resistant patients with CML⁸ and confers resistance to all available TKIs (imatinib, nilotinib, dasatinib and bosutinib). Therefore, to date, in patients with CML harbouring the T315I mutation, therapeutic approaches are greatly limited. Ponatinib is a third-generation TKI with a carbon-carbon triple bond that extends from the purine

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scaffold. Through its structure, it is able to overcome the T315I resistance, escaping the steric hindrance caused by the amino-acidic substitution.^{9,10} Ponatinib is 500 times more potent than imatinib in the inhibition of *BCR-ABL1* and suppresses also the activity of the fibroblastic growth factor receptor, the platelet-derived growth factor receptor, the vascular endothelial growth factor (VEGF) receptor (VEGFR), the *fms*-like tyrosine kinase 3 (FLT3), the sarcoma kinase (SRC) and the stem growth factor receptor (KIT).¹¹ The use of ponatinib for the treatment of heavily pretreated patients with CML due to resistance or intolerance, was approved in 2012 by the United States Food and Drug Administration (US FDA) according to the efficacy results of the PACE trial¹² that demonstrated major cytogenetic response (MCyR) rates of over 70%. However, in 2013 the drug was removed by the market because of the increased incidence of cardiovascular events, and the EPIC trial,¹³ which tested ponatinib compared with imatinib as frontline therapy in patients with CML, was immediately closed. After a retrospective analysis of phase I and II trials,¹⁴ which identified pre-existing risk factors in patients who had developed cardiovascular events, 1 year later, the drug was reintroduced in the market. Although dose adjustment is now recommended, ponatinib seems to induce deep and durable responses in patients with CML, regardless of their mutational status. The aim of this review is to report all the clinical experiences (phase I, II and III trials and real-life experiences) that detail the use of ponatinib in literature, focusing on patients affected by chronic phase (CP)-CML with recommendations for the appropriate use in this subset of patients.

Mechanism of action and metabolism

Ponatinib is a third-generation TKI, 520 times more potent than imatinib, that inhibits both wildtype and mutant *BCR-ABL1*, including the T315I mutation, which results from a threonine to isoleucine substitution at position 315 of the *ABL* gene. Ponatinib's structure, according to the interactions with the target oncoprotein, can be subdivided into five main chemical units. The hinge region is made up of fused aromatic rings (imidazol-1,2-pyridazine), able to obtain hydrogen bonds with the enzyme pocket and hydrophobic interaction with the aspartate-phenylalanine-glycine (DFG) motif of the enzyme.¹⁵ The second domain of ponatinib represents the main difference of

ponatinib from other TKIs. In addition to the inability of the first- and second-generation TKIs to create a hydrogen bond in case of threonine replacement with isoleucine in T315I mutant leukemic cells, the isoleucine determines steric clash, blocking the access of the TKI into the hydrophobic pocket but still allowing ATP to bind.¹⁶ Since dasatinib, bosutinib and nilotinib need this hydrogen bonding to be able to induce an antileukemic effect, ponatinib has a triple bond ethynyl linker that allows it to span the bulky isoleucine side chain. Furthermore, the triple bond allows a 10-fold increase in the potency compared with previous single or double-bonded molecules.¹⁷ Considering the pharmacokinetics of ponatinib, doses ranging from 15 to 60 mg induce proportional increases of peak plasma levels (C_{max}) and the area under the concentration–time curve, but the absolute bioavailability of the drug is still unknown. Ponatinib plasma concentrations after a high-fat or low-fat meal do not appear different if compared with fasting administration.

There is a proportional relationship between the dosage of ponatinib and peak blood concentration. A half-life of 22 h with a trough of 40 nM in blood concentration is associated with 30 mg a day of ponatinib, and this dose seems adequate for suppressing *BCR-ABL* mutation emergence.¹⁸ However, in the case of the T315I mutation, resistant clones may be recovered even at concentrations as high as 320 nM.¹⁶ Ponatinib is metabolized mainly by the hepatic system through CYP3A4, CYP2C8, CYP2D6, and CYP3A5 to a N-desmethyl metabolite that is four times less active than its parent drug, and by esterases or amidases to an inactive carboxylic acid. After a single oral dose of radiolabelled ponatinib, 5% of the drug was detected in the urine, while 87% was found in the faeces.¹⁹ The concomitant administration of ponatinib and strong CYP3A4 inhibitors such as protease inhibitors (indinavir, ritonavir, telaprevir), selective serotonin reuptake inhibitors (nefazodone), macrolide antibiotics (clarithromycin, telithromycin), vasopressin antagonists (conivaptan), azoles (itraconazole, voriconazole) and others, requires a reduction of the starting dose of the third-generation TKI. The US FDA recommended a dose reduction to 30 mg daily in patients with hepatic impairment; other recommendations provide caution in cases of ponatinib administration in patients with poor renal function, while its use is forbidden during pregnancy or breastfeeding.²⁰

Phase I trial

The MD Anderson Cancer Center (MDACC) group coordinated a sponsored phase I dose-escalation trial in which 81 patients with resistant haematologic cancers were enrolled, including 60 patients with CML in all phases of disease [43 with CP-CML, 9 with accelerated phase (AP)-CML, 8 with blast phase (BP)-CML] and 5 with Ph-positive acute lymphoblastic leukaemia (ALL). Ponatinib was given once daily at doses ranging from 2 to 60 mg. The primary endpoint of this trial was to define the maximum tolerated dose or a recommended dose of oral ponatinib administered once daily. In the 60 mg daily cohort, 6 out of 19 patients reported dose-limiting toxicities (DLTs), at 45 mg/day, DLT was reported in a patient, while no DLT effects were observed in cohorts receiving up to 30 mg. All the adverse events were clearly dose-related. The most common nonhaematologic toxicities were skin disorders (rash, acneiform dermatitis and dry skin), constitutional symptoms (arthralgia, fatigue and nausea), pancreatitis and increased pancreatic enzymes without pancreatitis. As regards haematological toxicity, in the 43 patients with CP-CML grade 3–4 thrombocytopenia occurred in 12 patients (28%), neutropenia in 6 patients (14%), and anaemia only in 1 patient (2%). Pharmacodynamics results showed, at doses of 15 mg or more, 32 of 34 patients (94%) were characterized by a decreasing of 50% or more in *CRKL* phosphorylation (a surrogate of *BCR/ABL1* activity), including 8 of 10 patients (80%) with the T315I mutation. Considering the 43 patients with CP-CML, after a median follow up of 73 weeks, 42 (98%) had a complete haematologic response (CHR), 31 (72%) had a MCyR, and 27 (63%) had a CCyR, achieved after a median time of 12 weeks. Furthermore, 19 (44%) achieved a major molecular response (MMR), including 9 (21%) who had a deeper molecular response. The median time to reach a molecular response was 16 weeks (range 8–97 weeks). All 12 patients with CP-CML who carried the T315I mutation had a CHR (100%), 11 (92%) had a MCyR, 9 (75%) had a CCyR, and 8 (67%) had a MMR. Overall, 15 patients with CP-CML carried a non-T315I mutation at baseline; among them, 14 (93%) achieved a CHR, 10 (67%) achieved a CCyR and 8 (53%) had an MMR.¹⁸ Subsequently, these results were updated with a median follow up of 53.1 months. Among the patients with CP-CML, 72%, 65%, 56%, 42%

and 28% achieved MCyR, CCyR, MMR, MR⁴ and MR^{4.5}, respectively.²¹ According to the evidence of this phase I trial, the standard oral daily dosage of ponatinib chosen in the subsequent studies was 45 mg.

Phase II trials

PACE trial

The phase II PACE trial allowed the approval of this drug for the treatment of patients with CML in December 2012 by the US FDA. This trial assessed the safety and efficacy of ponatinib, at a starting dose of 45 mg/day, in a selected subset of patients with CML and Ph+ ALL who were intolerant (12%) or resistant (88%) to nilotinib or dasatinib or who had developed the *BCR-ABL1* T315I mutation. Of 449 patients enrolled in the PACE study, 270 (60%) were in CP; 203 (75%) patients had developed unacceptable side effects or primary or secondary resistance to nilotinib or dasatinib and 67 (25%) had the T315I mutation at the time of starting ponatinib. Among this group of patients, 19 (7%) had received only one prior TKI, while 97 (36%), 142 (53%) and 12 (4%) were previously treated with two, three and four prior TKIs, respectively. After a median follow up of 15 months, CCyR was observed in 46% of patients (66% with T315I mutation), MMR in 34% (56% with T315I mutation) and MR^{4.5} in 15% (23% with T315I mutation); only three (1%) patients had progression to AP-CML or BP-CML. The median time of achieving a MCyR was 2.8 months (range 1.6–11.3 months); at 12 months, overall survival (OS) and progression-free survival (PFS) were 94% and 80% respectively. The number of mutations at baseline did not affect the survival and response rates.¹² An update of PACE at 5-years of follow up showed in 267 patients with CP-CML, the cumulative rates of MCyR was 60% and CCyR 54%, while the cumulative rates of MMR was 40% and MR^{4.5} 24%. At 5 years, OS and PFS were 77% and 49% respectively, confirming a long-term clinical benefit, regardless of the dose reduction for specific toxicities. Serious nonhaematological adverse events were characterized by lipase increases (10%), abdominal pain associated with pancreatitis (5%), grade 3–4 neutropenia (18%), thrombocytopenia (29%) and anaemia (9%) predominantly reported during the initial phase of treatment. Only five deaths were considered to be associated with ponatinib. The emergent issue was the occurrence

of arterial occlusive events (AOEs): the US FDA temporarily removed ponatinib from the market. After a median follow up of 24 months, approximately 20% of patients developed AOEs: 3.6% experienced a peripheral vascular event, 4% a cerebrovascular event and 6.2% a cardiovascular event (Table 1).²² Analysing the 21 patients with myocardial ischemic event, 95% presented at least one cardiovascular risk factor, while 81% had at least two risk factors at baseline. Among them (14 myocardial infarction, 5 coronary artery disease, 2 angina), 10 had a cardiac disease at baseline, while among the 6 patients who had developed a myocardial infarction with no previous documented cardiac disease, 5 presented one risk for AOEs at the time of enrolment.¹⁴ According to these retrospective safety data, in January 2014, the US FDA established the reintroduction of ponatinib in the market, but only after having included a specific warning box which recommended an in depth assessment of cardiovascular risks at baseline in order to prevent as much as possible the occurrence of AOEs. Another recent retrospective analysis showed the better survival outcomes induced by ponatinib in heavily pretreated patients with CP-CML (included in PACE trial) who presented the T315I mutation compared with the allogeneic transplantation (alloSCT). In total 184 patients (128 in the ponatinib group and 56 in the alloSCT group) were analysed. Overall, 90 patients were in CP-CML (64 in the ponatinib group, 26 in the alloSCT group), 26 in AP-CML (18 in the ponatinib group, 8 in the alloSCT group), 41 in BP-CML (24 in the ponatinib group, 17 in the alloSCT group), and 27 with Ph+ ALL (22 in the ponatinib group, 5 in the alloSCT group). The 24-month and 48-month OS rates were significantly lower in CP-CML patients who underwent alloSCT compared with those who received ponatinib (24 months: 60.5% *versus* 84%, respectively; $p = 0.004$; 48 months: 55.8% *versus* 72.7%, respectively; $p = 0.013$). Median OS was longer for the ponatinib group (not reached *versus* 103.3 months; $p = 0.017$).²³

MDACC experiences

The MDACC group designed a phase II trial investigating the efficacy of ponatinib in patients with CML-CP resistance or intolerance to only one TKI (imatinib, nilotinib or dasatinib). The primary endpoint of the study was to assess the rate of MCyR (CCyR + PCyR) at 6 months. As in

the PACE trial, the initial dose of drug was 45 mg/day, decreased to 30 mg/day subsequent to the safety warning from the US FDA in October 2013, followed by an early closure of the study. Only five patients were enrolled before the study was closed, all of them resistant to a prior TKI (three patients to imatinib and two patients to nilotinib). According to the cytogenetic response, only one patient did not achieve a CCyR at 3 and 6 months. After a median follow up of 22 months (range 18–26 months), four patients were in MR^{4.5}. Considering the toxicity profile of the drug, four patients developed hypertension (grade 2–3), but no venous or arterial thrombotic events were observed. In all patients, the starting dose of ponatinib was reduced according to its toxicity and the median time to first dose reduction was 3 months (range 1–8 months); at the last follow up two patients continue on 30 mg/day and three patients on 15 mg/day.²⁴ The MDACC group also tested ponatinib as a frontline therapy in patients with CP-CML in a phase II trial. A total of 51 patients were enrolled in the study. Overall, 43 patients started at the daily dose of 45 mg, which was subsequently reduced to 30 mg/day associated with primary prophylaxis with aspirin after the October 2013 US FDA recommendations, while 8 patients were given a starting dose of 30 mg per day. After a median follow up of 20.9 months, the cumulative rates of CCyR, MMR and MR^{4.5} were 96%, 80% and 55% respectively. None of the patients progressed to the AP or BP; estimated event-free survival, transformation-free survival, and the OS rate at 24 months were all 100%. Despite the excellent results in terms of effectiveness, ponatinib, especially in patients who started with the initial dose of 45 mg daily, induced several adverse events. The most frequent were rash (69%), dry skin (43%), alopecia (28%), elevated serum lipase (63%), constipation (51%) and abdominal pain (41%). Cardiovascular events were documented in 49% of patients, such as hypertension (29% and 14% with grade 3 and 4), cerebrovascular events (4%), acute coronary syndrome (2%) and myocardial infarction (1%). This trial clearly documented as ponatinib has a high clinical activity in the firstline treatment of patients with CP-CML inducing very rapid and deep cytogenetic and molecular responses. However, at high doses, ponatinib caused treatment interruptions in more than 80% of patients and dose reductions in almost two-thirds, showing a critical safety profile.²⁵

Table 1. PACE trial updated at several time points.

PACE trial update time	Number of patients in CP-CML	Number of previous TKIs administered	Reason for starting ponatinib	CCyR (%)	MMR (%)	DMR (%)	AOEs (%)	SAOEs (%)	OS (%)	PFS (%)
1 year	270	19 pts = 1 TKI 98 pts = 2 TKIs 153 pts ≥ 3 TKIs	214 pts = resistant 40 pts = intolerant 2 pts = missing	46	34	15	Cardiovascular = 15 Cerebrovascular = 3.6 Peripheral vascular events = 4.9	Cardiovascular = 5.1 Cerebrovascular = 2.4 Peripheral vascular events = 2	94	80
3 years				/	39	22	Cardiovascular = 12 Cerebrovascular = 8 Peripheral vascular events = 8	Cardiovascular = 8 Cerebrovascular = 6 Peripheral vascular events = 6	82	61
4 years				/	/	/	Total AOE = 29%	/	77	56
5 years				54	40	24	Cardiovascular = 16 Cerebrovascular = 8 Peripheral vascular events = 14	Cardiovascular = 12 Cerebrovascular = 10 Peripheral vascular events = 11	77	49

AOE, arterial occlusive event; CCyR, complete cytogenetic response; CP-CML, chronic phase chronic myeloid leukaemia; DMR, deep molecular response; MMR, major molecular response; OS, overall survival; PFS, progression-free survival; pts, patients; SAEs, serious adverse events; TKI, tyrosine kinase inhibitor.

Phase III trial

EPIC trial

The EPIC trial was a randomized phase III trial that evaluated the safety and the efficacy of ponatinib (45 mg/day) compared with imatinib (400 mg/day) as frontline treatment in patients with CP-CML; the primary endpoint of the study was to assess the rate of MMR at 12 months. A total of 307 patients were enrolled (155 assigned to ponatinib arm and 152 to imatinib arm), but the trial was closed on October 2013 after the US FDA warning for vascular adverse events, with a consequent short median follow up of 5.1 months reported. After 12 months of treatment 80% of patients receiving ponatinib achieved a MMR, against 38% of patients in imatinib arm. Cumulative rates for CCyR, MMR, MR⁴ and MR^{4.5} were 74%, 41%, 21% and 15% in the ponatinib group against 53%, 18%, 1% and 0% in imatinib group. Serious AOEes occurred in 10 (6%) patients treated with ponatinib and in 1 (1%) treated with imatinib.¹³

Ongoing trials

OPTIC trial

The OPTIC trial is a randomized phase II trial (ClinicalTrials.gov identifier: NCT02467270) designed to evaluate three different starting doses of ponatinib (45 mg, 30 mg, 15 mg) in patients with CP-CML resistant to at least two prior TKIs. The trial started in July 2015 and expected to enrol 450 patients (150 per arm) across 90 different sites. The primary endpoint is to assess the MCyR at 12 months, while secondary endpoints include the evaluation of vascular occlusive events, adverse events and serious adverse events rates. Patients who start with 45 or 30 mg daily, will receive a dose reduction to 15 mg once daily if they achieve a MCyR or a *BCR-ABL1* international scale (IS) < 1% by 12 months; a further dose reduction to 10 mg daily is provided to manage adverse events. Patients affected by uncontrolled cardiovascular disease, hypertension and diabetes are excluded from the trial.

Opus trial

Opus is a phase II trial (ClinicalTrials.gov identifier: NCT02398825) coordinated by

GIMEMA, aimed to assess the efficacy and the safety profile of ponatinib given to patients with CP-CML, resistant to imatinib at a daily dose of 30 mg. A dose reduction to 15 mg daily is recommended once patients achieve and confirm by a second test after 4 weeks a *BCR-ABL1* IS \leq 0.1%; if patients subsequently lost MMR, the dose may be increased again to 30 mg daily. Dose reduction is also recommended in the case of adverse event occurrence. The primary endpoint of the trial is to evaluate the rate of MCyR after 52 weeks of ponatinib treatment. Second endpoints include the evaluation of adverse events, CCyR and MMR rates at 52 weeks of ponatinib treatment.

Real-life experiences

A French group reported a series of 48 patients with CP-CML (71% resistant, 23% intolerant and 6% both) treated with ponatinib outside clinical trials. A total of 11 patients (23%) had a T315I mutation and the median starting dose of ponatinib was 45 mg/day. OS at 36 months was 81.5% and the cumulative incidence of MMR was 55% at 18 months. Overall, 29 patients (60%) experienced AOEes after a median time of 5.8 months; among them, 11 patients did not have any cardiovascular risk factors at the time of starting ponatinib (Table 2).²⁶

An Israeli experience reported that about 37 patients with CML received ponatinib outside of clinical trials. Features of the patients at baseline included a previous treatment with at least one TKI in all patients, with a CP, AP or BP phase in 57%, 16% and 27% of patients respectively. T315I mutation was detected in 24% of patients. A total of 22 patients (43%) received ponatinib at the starting dose of 45 mg/day (16 patients maintained this dose during the treatment), 10 patients (27%) received 30 mg/day and 11 (30%) patients received 15 mg/day. After a median follow up of 14 months (range 1–51 months), 21 patients (57%) achieved a CCyR, while 16 patients (43%) experienced at least a MMR or deeper responses. AOEes were seen only in two (5.4%) patients, causing a discontinuation of ponatinib (Table 2).²⁷ The Italian group collected data on 29 patients with CP-CML resistance or intolerance to only one prior TKI. Specifically, the causes of starting ponatinib were: primary resistance (38%), secondary resistance (45%), severe

Table 2. Real-life clinical experiences with ponatinib.

Authors	Number of patients/CML phase (%)	Number of previous TKIs administered	Reason to start ponatinib	Ponatinib dose/day	Median follow up (months)	MMR (%)	DMR (%)	AOEs (%)
Nicolini and colleagues ²⁶	48/ CP (100)	14 pts = 1 TKI 5 pts = 2 TKIs 29 pts = 3 TKIs	34 pts = resistant 11 pts = intolerant 3 pts = resistant and intolerant	45 mg (median dose)	26.5	55	NA	60
Shacham-Abulafia and colleagues ²⁷	37/ CP (56.7) AP (16.2) BP (37.1)	8 pts = 1 TKI 10 pts = 2 TKIs 19 pts ≥ 3 TKIs	33 pts = resistant 1 pt = intolerant 3 pts = missing	22 pts = 45 mg 12 pts = 30 mg 3 pts = 15 mg	14	47	24	2.7
Breccia and colleagues ²⁸	29/ CP (100)	1 pt = 3 TKIs	26 pts = resistant 1 pt = intolerant 3 pts = resistant and intolerant	17 pts = 45 mg 11 pts = 30 mg 1 pt = 15 mg	12	37.9	34.4	0

Shacham-Abulafia A, Raanani P, Lavie D, *et al.* Real-life experience with ponatinib in chronic myeloid leukemia: a multicenter observational study. *Blood* 2017; 130: 5249.²⁷
 AOE, arterial occlusive event; AP, accelerated phase; BP, blast phase; CP, chronic phase; DMR, deep molecular response; MMR, major molecular response; NA, not applicable; pts, patient; TKI, tyrosine kinase inhibitor.

Table 3. Real-life clinical experiences with low doses of ponatinib.

Authors	Number of patients/ CML phase (%)	Number of previous TKIs administered	Reason to start ponatinib	Ponatinib dose/day	Median follow up (months)	MMR (%)	DMR (%)	AOEs (%)
Iurlo and colleagues ³⁰	7/ CP (100)	5 pts = 1 TKI 2 pts = 2 TKIs	7 pts = intolerant	15 mg	9.9	71.4	28.6	0
Mauro and colleagues ²⁹	15/ CP (86.6) AP/BP (6.7) Unknown (6.7)	1 pt = missing 2 pts = 1 TKI 6 pts = 2 TKIs 6 pts ≥ 3 TKIs	15 pts = resistant	22.4 mg (median dose)	11	40	NA	NA

AEO, arterial occlusive event; AP, accelerated phase; BP, blast phase; CP, chronic phase; DMR, deep molecular response; MMR, major molecular response; pts, patients; TKI, tyrosine kinase inhibitor.

intolerance (3%), severe intolerance associated with molecular warning (7%) and the presence of a T315I mutation (7%). The ponatinib initial daily dose was 45 mg in 60% of patients, 30 mg in 38% and 15 mg in 2% of patients. After a median time of 12 months, 85% of patients achieved a better molecular response compared with the baseline. Among them, 10 (40%) patients achieved a deep molecular response. No AOE were observed (Table 2).²⁸

Low-dose ponatinib experiences

The Memorial Sloan Kettering Cancer Center group compared the efficacy and the safety of ponatinib in pretreated patients with CP-CML who received a low median average daily dose (22.4 mg/day in 15 patients) and those who were treated with a high median average daily dose (43.2 mg/day in 20 patients). Between the two groups no difference was found in the rate of MMR ($p = 0.344$) and MCyR ($p = 0.625$). Also, in terms of toxicity, no difference was observed considering adverse events of special interest (AESIs; Table 3).²⁹ Italian physicians reported a small series of seven patients with CP-CML: all intolerant to previous TKIs, treated with a low dose of 15 mg/day. All patients achieved at least an MMR starting ponatinib (four patients had a MMR, three patients had a molecular response⁴). After a median follow up of 9.9 months (range 4.9–24.0 months) all patients maintained molecular responses previously achieved and two reached an MR⁴. Overall, three patients developed hypertension during the course of treatment, but no other AOE were observed (Table 3).³⁰

Optimal use of ponatinib in clinical practice

Ponatinib dose recommendations in patients with CP-CML

Ponatinib was approved in December 2012 by the US FDA and is indicated in adult patients with CP, AP, or BP-CML who are resistant or intolerant to dasatinib or nilotinib and for whom subsequent treatment with imatinib is not clinically appropriate or who have the T315I mutation.^{31,32} The toxicity profile of ponatinib is well known: the US FDA created a specific warning box including the risk of cardiovascular events and liver toxicity related to this drug. For this reason, the starting recommended dose has now been suggested at lower than 45 mg/day. However, to date, there are no standardized guidelines recommending the initial dose of ponatinib in such particular CML cases or dose modifications during the treatment, and it is difficult to define a common therapeutic strategy for all patients with CML. Each patient needs a personalized treatment according to resistance or intolerance previously developed to other TKIs, considering comorbidities, cardiovascular risk assessment, the response to the initial dose of ponatinib and side effects during treatment. Recent results of sponsored clinical trials^{12,18,22} and real-life experiences^{29,30} documented in patients with CP-CML, even if given at low dose (30 mg or 15 mg), ponatinib induced or maintained an MMR or deep molecular response with a potential decreased incidence of cardiovascular events. Especially in patients who developed an important intolerance to previous TKIs, but had already achieved at least an MMR, the initial ponatinib dose of 30 or 15 mg daily should be always considered in order to reduce potential

drug-related risks. A particular consideration should be reserved to patients who developed a thrombotic event with other previous TKIs: in these cases, ponatinib should be given at a low dose only if patients have been already treated with all other available TKIs. A sub-analysis of the PACE study described a direct connection between the dose and the occurrence of AOE: each 15 mg dose reduction in the daily dose of ponatinib was associated with a 33% reduction in the risk of thrombotic events. The same sub-analysis showed that despite the majority of patients (86%) requiring a dose reduction within the first 12 months of therapy, the responses in patients with and without modification were comparable, and most patients who had a dose reduction after achieving a response, maintained that response.²² Furthermore, a subsequent analysis in which 671 patients were enrolled in three different trials, showed, through a logistic regression, that ponatinib dose intensity was related not only to the onset of cardiovascular events, but also to the occurrence of other common side effects. Rash, cardiac failure and pancreatitis were strongly associated with dose intensity (odds ratio >2). An odds ratio of >1.5 was associated with thrombocytopenia, AOE, cardiovascular events, increased lipase and transaminases, while no significant association was found between ponatinib dose intensity and venous thromboembolic, cerebrovascular or peripheral occlusive events and hypertriglyceridemia.³³

Use of ponatinib in patients with cardiovascular disease

The mechanisms associated with the onset of vascular occlusive events observed in ponatinib-based trials, are currently unknown. In murine models, *ABL1* seemed to control the endothelial function and the regulation of the angiogenic factor pathways, important for vascular homeostasis. Loss of *ABL* kinases leads to increased endothelial cell apoptosis both *in vitro* and *in vivo*, contributing to vascular dysfunction, infarction, and tissue damage and causing a higher risk of myocardial injury (based on cardiac enlargement and scarring), interstitial lung fibrosis, fibrin deposition in the airways and increased embryonic mortality.³⁴ According to these findings the increased rate of thrombotic events in ponatinib patients could be explained by its powerful anti-*ABL1* activity. Furthermore, ponatinib is also a potent

inhibitor of the VEGF acting on its intracellular domain and preventing its initial phosphorylation and downstream signalling. VEGF binding with VEGFR2 activates several intracellular signalling pathways including the phosphatidylinositol-3-kinase (PI3K) and the mitogen-activated protein kinase pathways, which upregulate the expression of endothelial nitric oxide synthase (eNOS), leading to vasodilation. Ponatinib inhibiting VEGF, decreases the production of nitric oxide (NO) leading to vasoconstriction, elevated peripheral vascular resistance, and hypertension.³⁵ An appropriate assessment of the cardiovascular status of patients before starting ponatinib and an adequate monitoring of all the cardiovascular risks from baseline is strongly recommended. Cardiovascular risk should be evaluated through the SCORE chart developed by the European Society of Cardiology,³⁶ this score provides probabilistic information and stratifies patients in four risk categories (low, intermediate, high and very high risk) according to sex, age, smoking habits, systolic pressure and total cholesterol level. Probably, in patients who presented a moderate cardiovascular risk, ponatinib should be started at a dose of 30 mg daily and reduced to 15 mg after achievement of CCyR and MMR. However, if these groups of patients had already achieved at least an MMR with previous TKIs, the initial dose could be 15 mg daily with a potential escalation if the molecular response worsens. Starting ponatinib in patients with a high cardiovascular risk at baseline is still a controversial issue. Patients who suffered from uncontrolled hypertension or hypercholesterolaemia are not perfect candidates for ponatinib, even if given at low doses. Indeed, in young patients with a previous therapeutic control of these risk factors, ponatinib may be taken into account, but only if administered at low doses. The therapeutic approach could be different for patients with low cardiovascular risk at the time of starting ponatinib: an initial dose of 45 mg/day should be contemplated and then reduced after achievement of *BCR-ABL1* IS \leq 1%. The management of cardiovascular adverse events during ponatinib treatment is still a strongly debated topic. Results from a 4-year update of a phase I trial³⁷ showed as the exposure-adjusted yearly incidence rate of AOE (number of patients with events per 100 patient-years) was 10.8 or 8.3 for adverse events or serious adverse events, respectively and the median time of developing occlusive arterial events was

13.8 months. Also, data from the PACE 4-year follow up³⁸ documented that the incidence of AOE in patients with CP-CML was 29% (14% cardiovascular, 12% cerebrovascular, 11% peripheral vascular), highlighting that AOE need careful management. According to these data, primary prophylaxis with aspirin (75–100 mg/day) or clopidogrel (75 mg/day) should be always considered, even for low-risk patients and for patients who receive low doses of ponatinib.³⁹ There is no evidence that supports this therapeutic decision; however, haematologists and cardiologists should jointly assess patient risk and the added risk introduced by ponatinib in order to eventually start antiplatelet drugs and prevent cardiovascular events. In addition, the role of ponatinib in elderly patients with CML should be more deeply clarified. As age represents a single independent prognostic factor in development of cardiovascular events, ponatinib administration should be managed very carefully in this subset of patients. In patients with Ph+ ALL, ponatinib as a single agent is being widely testing as a valid therapeutic alternative for elderly patients not eligible for intensive chemotherapy; an Italian study, which is ongoing, is assessing the safety and efficacy of ponatinib frontline in elderly patients as well as young patients who are not candidate for more intensive treatment.⁴⁰

Role of ponatinib for TKI-resistant/intolerant or T315I-mutated CML

The detection of T315I mutation in resistant patients with CP-CML, requires treatment with ponatinib. Ponatinib is characterized by a wide spectrum of activity against the majority of *BCR/ABL* mutations related to imatinib and second-generation TKI resistance and is an approved TKI that has activity against T315I mutation. Patients who carried this type of mutation should start ponatinib at full dose, modulating the initial dose according to the baseline cardiovascular risk assessment and the level of response achieved. However, the emerging concerns over arterial thrombosis are likely to limit the use of ponatinib in patients with the T315I mutation and a high cardiovascular risk at baseline. Furthermore, there will be a growing number of patients, with T315I mutations, who will have to stop ponatinib due to serious arterial complications and who are not transplant candidates. In this subset of patients, omacetaxine mepesuccinate, approved

by the US FDA in October 2012 for patients with CP and AP-CML failing two prior TKI agents,⁴¹ could represent a valid therapeutic option. Indeed, omacetaxine mepesuccinate has shown encouraging results in patients with T315I mutations previously treated with two or more TKIs and it is characterized by an acceptable tolerability without cardiovascular toxicity.^{42,43}

Future perspectives

The real benefits of ponatinib in clinical practice should be assessed in depth and more studies are required to establish whether low doses of ponatinib are effective on the outcome of heavily pretreated patients with CML. The OPTIC trial (ClinicalTrials.gov identifier: NCT02467270), which is ongoing, randomizes refractory patients with CP-CML to three different starting doses of ponatinib with the goal to establish the optimal dose of ponatinib in these patients. Furthermore, a new randomized phase III study (OPTIC-2L trial, ClinicalTrials.gov identifier: NCT02627677) has recently been launched, comparing ponatinib at two different starting doses *versus* nilotinib in patients who have failed imatinib. Possible mechanisms that could predict the occurrence of resistance to ponatinib are not still documented in detail. An Australian group demonstrated the prognostic significance of low-level *BCR/ABL1* mutations detected by sensitive mass spectrometry before starting ponatinib in 363 TKI-resistant patients. Indeed, the study showed that patients who harboured T315I plus multiple low-level mutations (20, 9%) had substantially inferior responses compared with those with T315I as the sole mutation detected (43, 19%). The cumulative incidence of MCyR at 12 months and CCyR and MMR at 18 months for CP-CML patients with T315I only was 79%, 74%, and 63%, respectively, whereas it was 50%, 45%, and 35%, for those with T315I plus additional mutations, respectively. However, the study also reported that the patients without T315I, but with multiple low-level mutations had better rates of response to ponatinib compared with those responses observed in imatinib-resistant patients who harboured multiple mutations treated with nilotinib/dasatinib.⁴⁴ These data suggest that ponatinib may be very effective in resistant patients with multiple low-level *BCR/ABL* mutations compared with other second-generation TKIs, and that detecting these mutations through

next generation sequencing techniques before starting any treatment, may steer towards a ponatinib therapeutic approach. New trials are needed to assess whether the potential combination of ponatinib with other new drugs could induce better responses acting on different pan-leukaemic pathways and could lead to an earlier dose reduction, preventing serious side effects. Novel agents with different mechanisms of action are now being investigated in several trials in patients with CML. Among them, we can find ABL-001, an allosteric potent inhibitor of *BCR/ABL1*, which is now being tested in a phase I trial as single agent or in combination with first and second-generation TKIs, and rebastinib, a small molecule able to inhibit *BCR/ABL1* by changing the conformation of the folded protein and by disallowing ligand-dependent and ligand-independent activation, which is being evaluated in a phase I trial in resistant or refractory patients with CML and acute myeloid leukaemia (AML).^{45,46} Furthermore, vismodegib is a selective hedgehog pathway inhibitor, which was tested *in vitro* and in murine model in combination with ponatinib. A Japanese group showed that the overall tumour burden, assessed by *BCR-ABL1* m-RNA from bone marrow cells, was significantly lower in vismodegib plus ponatinib-treated resistant mice with CML compared with ponatinib alone.⁴⁷ Venetoclax is a potent and highly selective B-cell lymphoma (BCL)-2 inhibitor with strong antitumor activity and was recently approved by the US FDA for chronic lymphocytic leukaemia and has entered clinical testing for AML, lymphoma, and multiple myeloma. An *in vitro* study indicated that the BCL-2 inhibitor, venetoclax, may be a powerful strategy against *ABL* TKI-resistant cells, including T315I mutation by enhancing the cytotoxic effects of *ABL* TKI against those Ph+ leukaemia cells.⁴⁸ PF-114 mesylate is a novel third-generation TKI developed to target T315I and other resistant *ABL* mutations. Preliminary results of a phase I clinical trial which assessed the efficacy of PF-114 mesylate in patients with CP or AP-CML who were resistant to at least one of the second-generation TKIs or intolerant to previous treatment with TKIs or who have T315I mutation in the *BCR-ABL* gene, seems to be promising. Pharmacokinetic analysis showed a half-life of 19 h, supporting a once-daily regimen. Most of the responses were observed with the dose of 200–300 mg/day. No vascular occlusive events were reported, and the most common side

effect was skin toxicity.⁴⁹ Another *in vitro* study demonstrated the specific anti-T315I activity of an aurora inhibitor called AKI603.⁵⁰

Conclusion

Ponatinib has efficacy in resistant or intolerant patients with CP-CML to previous lines of therapy in terms of cytogenetic and molecular responses, but a risk–benefit assessment should be always taken into account in each patient. Baseline factors such as age, comorbidities, disease status, mutational status, reason for change of therapy (intolerance or resistance), cardiovascular risk and lines of previous treatment, must be necessarily considered before starting ponatinib in order to establish the safer initial dose. According to the results achieved and the safety profile, low doses of ponatinib must be always considered in specific subsets of patients. The results of ongoing clinical trials testing ponatinib in different doses (ClinicalTrials.gov identifiers: NCT02467270, NCT02398825), are expected to provide further information regarding the benefit–risk balance in ponatinib-treated patients.

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Conflict of interest statement

MB declare honoraria from Novartis, BMS, Pfizer, Incyte; all the other authors declare that they have no conflict of interests.

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