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Life after ponatinib failure: outcomes of chronic and accelerated phase CML patients who discontinued ponatinib in the salvage setting

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Abstract

BACKGROUND: Ponatinib is a pan-tyrosine kinase inhibitor (TKI) with efficacy in multi-refractory CML patients who have failed other TKIs. Despite excellent response rates, resistance or intolerance may develop.

METHODS: We conducted a retrospective review of the outcome of patients with chronic (CP) and accelerated (AP) phase CML refractory to prior TKI who discontinued ponatinib for resistance or intolerance.

RESULTS: Nineteen CP patients, discontinued due to resistance (n=13), toxicity (n=5), and to pursue stem cell transplantation (n=1). At discontinuation, 14 were still in CP, 3 had progressed to AP, and 2 to blast phase (BP). Three CP patients improved their cytogenetic response (CyR) to complete CyR (CCyR), 2 after SCT and one on omacetaxine. None of the twelve patients, without a major cytogenetic response at ponatinib discontinuation, including all patients treated with subsequent TKIs, responded to therapy. Seventeen AP patients, stopped ponatinib due to resistance (n=15) or intolerance (n=2). At discontinuation, 14 were still in AP and 3 had progressed to BP. Four patients were treated with SCT and one achieved major molecular response. None of the twelve patients treated with non-SCT approaches responded to subsequent therapy. Median survival for all patients was 16.6 months after ponatinib discontinuation (31, 9, and 13 months for patients in CP, AP, and BP, respectively). Median survival was 60 months for patients who discontinued ponatinib for toxicity and 11 months for those who discontinued for resistance.

CONCLUSIONS: Long term outcome of patients with ponatinib failure are poor with estimated 1-year OS and EFS rates of 54% and 40%, respectively. New treatment options are required for this subset of patients.

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Keywords

ponatinib; chronic myelogenous leukemia; salvage; chronic phase; accelerated phase; outcomes

INTRODUCTION:

Tyrosine kinase inhibitors (TKI) have transformed the outcome of patients with chronic myeloid leukemia (CML) and are the current mainstay of therapy. Most patients with CML derive durable cytogenetic and molecular responses with first or second-line TKIs [1–6]. However, resistance or intolerance eventually develops in 38 to 50% [3, 7] of patients after first line TKI therapy (imatinib, dasatinib, nilotinib), requiring a switch to second line therapy. Second line options include bosutinib, ponatinib or another second generation TKI that the patient had not failed before [8–10]. The efficacy of next-in-line TKI is heavily dependent upon responses achieved to prior TKIs [11, 12]. Acquisition of mutations in the BCR-ABL kinase domain is the best characterized mechanism behind TKI drug-resistance, and selection of subsequent therapy based on predicted sensitivity contributes significantly to outcomes on subsequent TKIs [13, 14].

Ponatinib is a potent multi-targeted TKI [15] with proven efficacy in multi-refractory CML patients who have failed at least 2 other TKIs. Initial trials demonstrated high response rates to ponatinib among patients with refractory Philadelphia positive leukemia who had failed other TKIs or those with T315I, a mutation that has been refractory to all other currently available TKIs [16, 17]. Although responses to ponatinib are durable with 82% of patients projected to maintain major cytogenetic response (MCyR) at 4 years, a significant number of patients discontinue ponatinib because of resistance or intolerance [18]. The outcome of these patients has not previously been reported. We thus analyzed the long-term outcomes of patients treated with ponatinib for CML in chronic or accelerated phase who discontinued ponatinib for resistance or toxicity.

METHODS:

PATIENT POPULATION:

We conducted a retrospective analysis of all patients treated with ponatinib at our institution in prospective clinical trials and who discontinued ponatinib for any reason. Eighty two patients were screened for enrolment into two clinical trials evaluating ponatinib in relapsed refractory leukemias (CML, acute myeloid leukemia, Philadephia+ acute lymphoblastic leukemia). These trials included a phase 1 study and the pivotal phase 2 study (PACE). Among them, 8 were considered ineligible for or withdrew consent before initiating therapy and 19 were excluded from this analysis because their diagnosis was other than CML (AML, n = 9; Ph+ ALL, n = 5; CML-BP, n = 5). The remaining 55 patients with a diagnosis of CML in chronic (CP) or accelerated (AP) phase who received ponatinib therapy from January 1, 2008 to July 31, 2016 after resistance or intolerance to at least 2 prior TKIs were all included in this analysis. Patient who were in blast phase (BP) when they started ponatinib were not included. Patients who either died while on ponatinib therapy or were lost to follow up while on ponatinib were also excluded from the analysis. Variables

collected included the following: age, gender, number of prior therapies, duration of ponatinib therapy, BCR-ABL mutational status (by Sanger sequencing) before starting ponatinib and at ponatinib discontinuation, hematological parameters including WBC, platelets, hemoglobin, lactate dehydrogenase (LDH), splenomegaly, other chromosomal abnormalities (clonal evolution (CE)) at ponatinib start and at discontinuation, and cytogenetic (CyR) and molecular (MolR) response to ponatinib. Patients were also assessed for the disease phase at the time of ponatinib discontinuation, reasons for discontinuation, disease characteristics at the time of ponatinib discontinuation, treatments received after ponatinib, and the CyR and MolR to such therapy, adverse vascular events after discontinuing ponatinib, and survival post ponatinib discontinuation. Subsequent therapies were coded into four groups based on the therapy received immediately after ponatinib discontinuation: 1) a TKI with or without other therapies, 2) allogeneic stem-cell transplantation (SCT), 3) supportive care/cytoreduction only, and 4) other non-TKI therapies.

DEFINITIONS:

Definitions of CP, AP and BP were per standard definitions used in ponatinib trials [17]. Responses were defined as previously described [19]. Patients who developed a persistent chromosomal cytogenetic abnormality (CCA) in their Philadelphia chromosome-negative metaphases were classified under the ‘warning’ response, as per ELN criteria.

STUDY ENDPOINTS:

Study endpoints included overall survival (OS), event free survival (EFS), failure free survival (FFS) and transformation free survival (TFS). EFS, FFS and TFS were calculated from the time of ponatinib discontinuation to the time of event, failure or transformation on the first treatment after ponatinib discontinuation, respectively. An event was defined by the loss of complete hematologic response (CHR), loss of MCyR, transformation to AP/BP, or death while on therapy. Failure was defined by any event, lack of complete CyR (CCyR) by 18 months or partial CyR (PCyR) by 12 months, transformation, treatment discontinuation for any reason, or death. Transformation-free survival was defined as the progression to AP or BP, or death from any cause while on therapy. Overall survival was calculated from the time of ponatinib discontinuation to time of death at any time.

STATISTICAL ANALYSIS:

Data was summarized by medians and ranges for continuous variables, and by numbers and percentages for categorical variables. Survival estimates were developed by the Kaplan-Meier method of analysis. Survival comparisons were made using the log-rank test. A p-value of <0.05 was considered statistically significant.

RESULTS:

A total of 55 CML patients received treatment with ponatinib at MDACC during the study period, 32 in CP and 23 in AP [Figure 1]. Of them, 19 patients were excluded from further analysis for the following reasons: 4 died while on ponatinib, 13 were lost to follow up while on ponatinib or immediately after discontinuation of ponatinib, and 2 came off study drug

due to study termination but continued therapy with commercially available ponatinib. The remaining 36 patients, 19 treated with ponatinib in CP and 17 in AP, were included in the analysis. Patient and disease characteristics are summarized in Tables 1a & 1b. Patients had received a median of 4 (range, 2 – 6) prior therapies, including a median of 3 (range, 2 to 4) TKI prior to ponatinib. Median duration of ponatinib therapy was 17 months (range, 0.1 – 61 months). Median age at discontinuation was 67 years (range, 22 – 94 years).

OUTCOMES AFTER PONATINIB DISCONTINUATION:

Of 19 patients treated in CP, 13 discontinued ponatinib due to lack of efficacy defined as follows: progression to AP or BP, n = 5 (3 AP, 2 BP); loss of hematologic response, n = 4; no hematologic response, n = 2; loss of MCyR, n = 1; and stem cell transplantation (due to 7q- chromosomal abnormality in Ph negative metaphases, while in CCyR), n = 1. Five patients discontinued ponatinib due to toxicity: 2 with pancreatitis and 1 each for stroke, headache, and thrombocytopenia [Table 2]. One additional patient elected to discontinue ponatinib and pursue a stem cell transplant (CCyR at the time of ponatinib discontinuation, 10 months after start of ponatinib). At the time of ponatinib discontinuation, 14 were still in CP with the following response status: major molecular response (MMR), n = 1; CCyR, n = 3; no CyR (n = 9) or minor CyR (n = 1) (NR/mCyR). Subsequent therapy for patients still in CP included stem cell transplant (SCT), n = 4; supportive care/cytoreduction only (SC), n = 3; dasatinib, n = 2; omacetaxine, n = 2; bosutinib + decitabine (DAC), nilotinib, and imatinib, n = 1 each. The 3 patients who progressed to AP received dasatinib + DAC, low-dose cytarabine (LDAC), and SC, 1 each; the 2 patients in BP received HyperCVAD + dasatinib followed by SCT, and ponatinib + LDAC, respectively. Of the 3 CP patients in CCyR at discontinuation, 1 died from sepsis in nursing home a month after discontinuing ponatinib (stopped due to thrombocytopenia); 1 patient received SCT (7q- CCA/Ph-) and died in MMR 11 months post SCT; 1 patient is in MMR 47 months after SCT. The only CP patient in MMR at discontinuation had discontinued therapy because of a stroke and maintains MMR, off all treatment, 29 months after ponatinib discontinuation. Three CP patients improved their cytogenetic responses from NR/mCyR to CCyR with subsequent therapy: 2 after SCT (1 died 8 months after SCT of unknown cause and 1 still in MMR after 25 months), and one after receiving omacetaxine (alive and in MMR after 12 months). None of the remaining 12 patients (CP 8, AP 3, BP 2) improved their responses after ponatinib discontinuation (i.e., all remained in NR/mCyR). The median survival (OS) after ponatinib discontinuation of the 19 patients that had received ponatinib in CP was 26 months [Fig 2]. Twelve patients have died: 5 deaths were attributed to disease (CP, n = 2; BP, n = 2; and AP, n = 1); 4 due to unknown causes (CP, n = 3; AP, n = 1); and 3 from sepsis (CP, n = 2; AP, n = 1).

Of 17 patients treated in AP who eventually discontinued ponatinib, 15 stopped due to resistance (no response, n = 9; progression to BP, n = 3; loss of hematological response, n = 2; persistence of accelerated phase with new clonal evolution, n = 1) and 2 for toxicity (stroke, n = 1; nausea, n = 1). At the time of discontinuation, of the 14 patients still in AP, 13 had NR or mCyR and 1 PCyR. Subsequent therapy for patients still in AP was supportive care only, n = 5; dasatinib, n = 3; SCT, n = 3; dasatinib + DAC, n = 2; and hydroxyurea, n = 1. The 3 patients that had transformed to BP were treated one each with SCT, combination

chemotherapy with fludarabine and cytarabine (BIDFA), and combination chemotherapy with mitoxantrone + etoposide (VP-16) + ponatinib, respectively. The patient with PCyR at discontinuation (discontinued due to nausea, still in AP) died 3 months later from heart failure. Four patients (AP, n = 3; BP, n = 1) received SCT. The one patient who had transformed to BP achieved MMR but died of undetermined cause 12 months after SCT. Of the 3 patients still in AP at the time of SCT, one maintains MMR 63 months after SCT, one died from sepsis 4 months after receiving SCT, and one did not respond, then received treatment with dasatinib + DAC and died of progressive disease 5 months later. The remaining 12 patients (AP 10, BP 2; all non-SCT) did not respond to subsequent therapy after ponatinib (i.e., all remained in NR/mCyR) [Table 3]. The median survival after ponatinib discontinuation was 9 months [Figure 2]. Twelve patients have died of the following causes (stage of disease at ponatinib discontinuation in parenthesis): sepsis, n = 3 (AP, n = 3); progression, n = 4 (AP, n = 3; BP, n = 1); undetermined, n = 5 (BP, n = 1; AP, n = 4); major hemorrhage, (BP, n = 1).

Among patients who received non-SCT therapies after ponatinib discontinuation, reasons for not opting for SCT included lack of suitable donor (n = 5); poor performance status (n = 5); patient's and/or physician's choice (n=5); early death soon after discontinuation (n = 4); comorbidities (n = 4); previous SCT (n = 1); SCT not considered at the time of last follow up (n = 1); sustained MMR off therapy (n = 1); transplant workup in progress (n = 1).

OUTCOMES POST-PONATINIB FAILURE:

The median OS for all 36 patients was 16 months (range, 0.2–70) [Figure 3], with projected 1-year OS and EFS rates of 54% and 40%, respectively. Median survival by phase at the time of discontinuation was 31.3 months in CP, 8.9 months in AP, 13 months in BP [Figure 4; p = 0.15]. The 12-month survival probabilities by first treatment used after ponatinib discontinuation were 74% with TKI 74%, 56% with SCT, 30% with supportive care, and 50% with other treatments (Figure 5). There was a trend for better OS for patients who discontinued ponatinib because of toxicity compared to those who discontinued because of lack of response or resistance (Figure 6; 60 months vs 11 months, p = 0.25).

MUTATIONS BEFORE PONATINIB INITIATION AND AT PONATINIB DISCONTINUATION:

Among patients treated in CP, the following mutations were detected before starting ponatinib: T315I alone in 2, E255K/T315I in 2, M315T/F359V in 1, and F359I, V299L, G250E, E453K, and F317L in 1 each. All of them maintained the same mutation at the time of ponatinib discontinuation except for the patient with M315T/F359V, in whom these mutations were no longer detectable but three new mutations were identified (F317L/E450G/I347F), and the patient with E453K who had no detectable mutations at the end of therapy.

In the CML-AP category, the following mutations were noted at the start of ponatinib therapy: T315I alone in 2, T315I with one additional mutation in 2 (L298V and Y253H, respectively), and Y253H, G250E, and F317/F35V 1 each. All of them retained the same mutation upon ponatinib discontinuation except for the patient with T315I/L298V who had only L298V detected at the time of discontinuation.

VASCULAR ADVERSE EVENTS:

Four patients developed or continued with grade 3–4 vascular adverse events after ponatinib discontinuation. One patient developed severe peripheral vascular disease while on ponatinib and received a stent at the time of ponatinib discontinuation, and 18 months later a vascular bypass; no further signs of arterial insufficiency have occurred after 25 months of follow-up since discontinuation. One patient developed headaches within a few days of starting ponatinib leading to treatment discontinuation. A temporal artery biopsy was consistent with giant cell arteritis. Another patient was diagnosed with pulmonary hypertension during ponatinib therapy; pulmonary pressures gradually normalized over six months after discontinuation. This patient also had Raynaud's phenomenon while on ponatinib which was controlled on amlodipine. Another patient presented with ocular ischemic syndrome soon after starting ponatinib. Fifteen days after discontinuation, she suffered a cerebrovascular accident. No recurrence of any such event has occurred after 2 months of follow-up from discontinuation of ponatinib. Finally, one patient had an acute myocardial infarction just before she discontinued ponatinib and had not experienced additional cardiovascular events after discontinuation (22 months of follow-up).

DISCUSSION:

Ponatinib was fast tracked for approval in December 2012 for use in patients with CML in whom other TKIs had failed, based on the results of a pivotal, phase II, single arm study (PACE trial). This study showed clinical benefit for patients with CML-CP, more than 90% of whom had received at least 2 prior TKI, with MCyR, CCyR, and MMR rates of 56 %, 46%, and 34%, respectively reported after a median follow up of 15 months [17]. The majority of these patients (91%) were estimated to maintain their MCyR at 1 year. The MaHR (major hematologic response) rates among patients with AP or BP were 58% and 32%, respectively, suggesting a clinical benefit in this setting as well [20]. Response rates were even higher (72%) among patients with CML-CP with T315I, a 'gatekeeper' mutation, conferring resistance to all other available TKIs [17]. T315I mutation develops in up to 20% of patients with TKI-resistant disease [21]. A recently reported 4-year update of the PACE trial reported upon 41% of the CML-CP patients who remained on study therapy. Of them, 87% and 74% maintained their MCyR and MMR. Estimated 4-year overall survival and progression free survival rates in CML-CP and CML-AP were 77% and 56%, respectively [18].

Despite these excellent results with ponatinib, some patients are primarily unresponsive while others may eventually lose their response and develop secondary resistance. Ponatinib may also be associated with adverse events, most notably arterio-thrombotic events that may make therapy unsustainable for some patients, occasionally even in the setting of an adequate response. Treatment options for patients with resistance or intolerance to ponatinib are limited in the context of previous exposure to 2 or more prior TKI or with T315I mutation. The outcome of patients who experience failure to ponatinib, although predicted to be poor, has to our knowledge, not been previously thoroughly described. In this report, we present the outcome after ponatinib discontinuation in a cohort of patients treated with ponatinib in CP or AP who experienced failure to ponatinib therapy. As expected, the

outcome is poor. Few patients experienced a favorable response, mostly with SCT, but the overall survival was short, with a median of 16 months. Although patients still in CP at the time of treatment discontinuation had a somewhat longer expected median survival, this was still less than 3 years. For those in AP, the median survival was a mere 8.9 months. To put these outcomes in context, survival after imatinib failure (i.e., after 1 TKI failure) was reported to be 72% at 3 years for patients still in CP and 30% for those in AP after failure [22]. For patients who discontinued dasatinib or nilotinib used as frontline therapy, the projected 3-year survival is 75%. There is less published data for patients who have received two prior TKIs. In one series, patients who received two prior TKI (imatinib and either dasatinib or nilotinib) and, upon failure, received a third TKI (i.e., the alternative 2nd generation TKI, dasatinib or nilotinib) had a projected median survival of 20 months [23]. Since there are currently 5 available TKIs (imatinib, dasatinib, nilotinib, bosutinib and ponatinib), a natural path is to attempt the use of a TKI that has not been previously used for a given patient. However, notably in our series, none of the patients who received another TKI after ponatinib discontinuation showed even a transient response, even when T315I was not detectable. This is perhaps not unexpected. None of the other TKIs are predicted to induce any response among patients who have a T315I mutation, although this represented a small subset of our patients. In other settings, ponatinib may also be superior to other agents. In second line therapy after imatinib resistance, dasatinib, bosutinib and nilotinib all induce CCyR in less than 50% of patients [22]. Among patients who have received imatinib and either dasatinib or nilotinib, case-report series using the alternative TKIs have reported a MCyR rate of 32% [23]. In a prospective series using bosutinib after imatinib and either dasatinib or nilotinib, the cumulative rate of MCyR was 40% [24]. The response rate with ponatinib in a population of patients of whom 92% had received at least 2 prior TKIs and 56% at least 3 prior TKIs, 56% had a MCyR (including 46% with CCyR) [17]. Thus, the lack of response to TKIs that have given response rates that are lower in less heavily treated patients than what ponatinib induces after multiple TKI failures, is perhaps not unexpected. The collective experience thus suggests that with failure to progressively more TKIs, the outcome worsens and the expected probability of survival shortens.

Only three CML-CP patients achieved durable molecular responses after experiencing failure to ponatinib: two after SCT and one after omacetaxine. SCT should be considered in all patients after ponatinib failure, and likely even earlier. Although SCT has generally fallen out of favor as an initial therapy, and little of it is performed after failure to one TKI, patients who need a third TKI should initiate considerations of TKI at that time if not already discussed earlier. The ELN recommends HLA typing of all patients upon start of second line therapy (and upon diagnosis if warning signs present), and performing SCT as third line therapy. We should acknowledge that although this strategy seems reasonable, there is a paucity of data on the outcome for these patients after SCT. Recently, Olavarria et al. reported on a series from the European Group for Blood and Marrow Transplant (EBMT) including 437 patients who had received second generation TKI including 164 who had received dasatinib and nilotinib sequentially. The projected survival for patients transplanted in CP was 67% [25]. Additional data is required to better understand the risks and benefits of SCT in this setting, and the outcome after ponatinib failure, but the ELN recommendation of considering SCT after failure to two TKI is reasonable.

Omacetaxine is currently available for patients who have received prior therapy with at least 2 TKI or who have the T315I. Omacetaxine (and homoharringtonine) have been used for many years to manage patients with CML with some success. The response rate for patients in CP is a modest 18% [26]. Still, considering it has received regulatory approval for this indication in some countries, this could be an option for patients who have resistance or intolerance to ponatinib that are not eligible for SCT.

A promising approach for patients with resistance to ponatinib is ABL001, a novel allosteric inhibitor of BCR-ABL1 kinase activity. Preliminary results of an ongoing phase 1 study have been presented reporting a 75% rate of CCyR and MMR of 42% among patients with CP, 95% of whom had received at least 2 prior TKIs [27]. How these results compare to what is expected with ponatinib, both in terms of efficacy (response rate, durability, etc) and safety, cannot be assessed at this time, but the prospects of having a new alternative for these few but treatment option-deprived patients are very welcome.

One important reason why some patients discontinue ponatinib is intolerance. Adverse events were the reason for discontinuation in 19% of patients in our study cohort. Among them, arterio-thrombotic events have emerged as a salient tolerability concern for TKIs. A change of therapy is frequently considered and often necessary when a patient experiences one such event. Although the risk of these events is perhaps most significant with ponatinib, this seems to be a class effect with other TKIs sharing a significant risk [28, 29]. The risk of one agent compared to the other is difficult to assess because 2nd and 3rd generation agents have not been directly compared. Dasatinib and nilotinib share an approximately two-fold higher risk of cardiovascular events and a higher risk of cerebrovascular events compared to imatinib, at least in the frontline setting where they have been compared in randomized trials [3, 7]. Nilotinib also has an increased risk of peripheral arterial disease in that setting. This suggests that a change to any of these agents after an arterio-thrombotic event with ponatinib may still put the patient at risk. The incidence of these events with bosutinib appears to be more similar to that with imatinib [30]. With the limitations of these analyses and the risks of over-interpreting such extrapolations, imatinib and possibly bosutinib might be better alternatives in such instances, if the only reason for discontinuation is intolerance. However, other patients in our series changed therapy for adverse events such as pancreatitis and thrombocytopenia. Although there is relatively little cross intolerance between different TKI, myelosuppression is shared by all TKI and recurrent thrombocytopenia is not uncommon after change to alternative TKI. Pancreatitis has been reported with nilotinib, but also with other TKI albeit at a relatively lower rate. Still, with the limitations of a small sample size, patients who discontinued ponatinib for toxicity had a relatively better outcome in our series (median survival 60 months) perhaps reflecting a wider menu of treatment options and better probability of responding if the next TKI is tolerated.

Factors affecting variability in responses to ponatinib are beginning to be understood. Gene expression studies have demonstrated that patients who fail TKIs harbor characteristic genetic signatures, distinct from TKI responders, involving dysexpression of various key molecular pathway mediators even before any morphological evidence of progression [31]. The number of mutations at baseline have been associated with responses to ponatinib treatment. Patients who harbor mutations in addition to T315I fare poorly compared to those

with T315I alone [32]. Of interest, in-vitro studies have demonstrated that development of T315I-inclusive compound mutations, involving key positions in the binding domain, confer a high degree of resistance to ponatinib [32]. Compound mutations constitute about 70% of double BCR-ABL kinase mutations and increase in frequency with the number of prior TKIs [33]. Results from in-vitro studies suggest that lower plasma concentrations of ponatinib might prove sub-therapeutic against certain high risk T315I compound (G250E/T315I, E255K/T315I, and E255V/T315I) [33] and non-T315I single and compound (e.g. E255V, Y253H/E255V, E255V/V299L, and F317L/F359V) mutants, a concern that warrants investigation in alternate dose schedule studies [34] [35, 36]. Importantly, none of the three patients in our series with known high-risk double mutations (F317L/F359V 1, E255K/T315I 2) responded to ponatinib. However, we did not undertake testing to determine if these double mutations were compound as opposed to polyclonal in nature. Resistance may also develop secondary to activation of mechanisms involving BCR-ABL1 kinase independent pathways [37]. One might conjecture if these are, most likely, the operational mechanisms of resistance in patients who lack a BCR-ABL mutation both before initiating ponatinib and the time of ponatinib failure or in those with mutations with in vitro sensitivity to ponatinib. Better defining these mechanisms of resistance is of paramount relevance to developing better strategies to manage such patients.

In conclusion, patients who experience resistance or intolerance to ponatinib have a bleak prognosis, with minimal probability of response to subsequent therapy and short survival expectations. Within this, there is perhaps a trend for better outcome for patients with intolerance to ponatinib compared to those with resistance. New treatment options are required for this small but significant subset of patients.

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JC provided conception and design of the study, collection, analysis, and interpretation of data, provided patient data for study, writing and revising the manuscript, and final review and approval of the manuscript. PB and ARS have contributed equally towards this manuscript and are first co-authors for this article; they contributed equally to data collection and analysis, and writing, reviewing and approving the manuscript. SP, SD provided collection and analysis of data. HK, FR, GB provided patient data for study, revision of the manuscript, and final review and approval of the manuscript. AA provided review of the manuscript. GGM, SV, TK, NJ, AA, JB, KB, SK, EJ provided data for the study, and review and approval of the manuscript.

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Key message: Lack of response to ponatinib, after failing other tyrosine kinase inhibitors, predicts a considerable risk for subsequent treatment failure. Long term outcomes after ponatinib discontinuation are dismal with estimated 1-year overall survival and event free survival rates of 54% and 40%. New treatment options are required for this small, but significant, subset of patients.

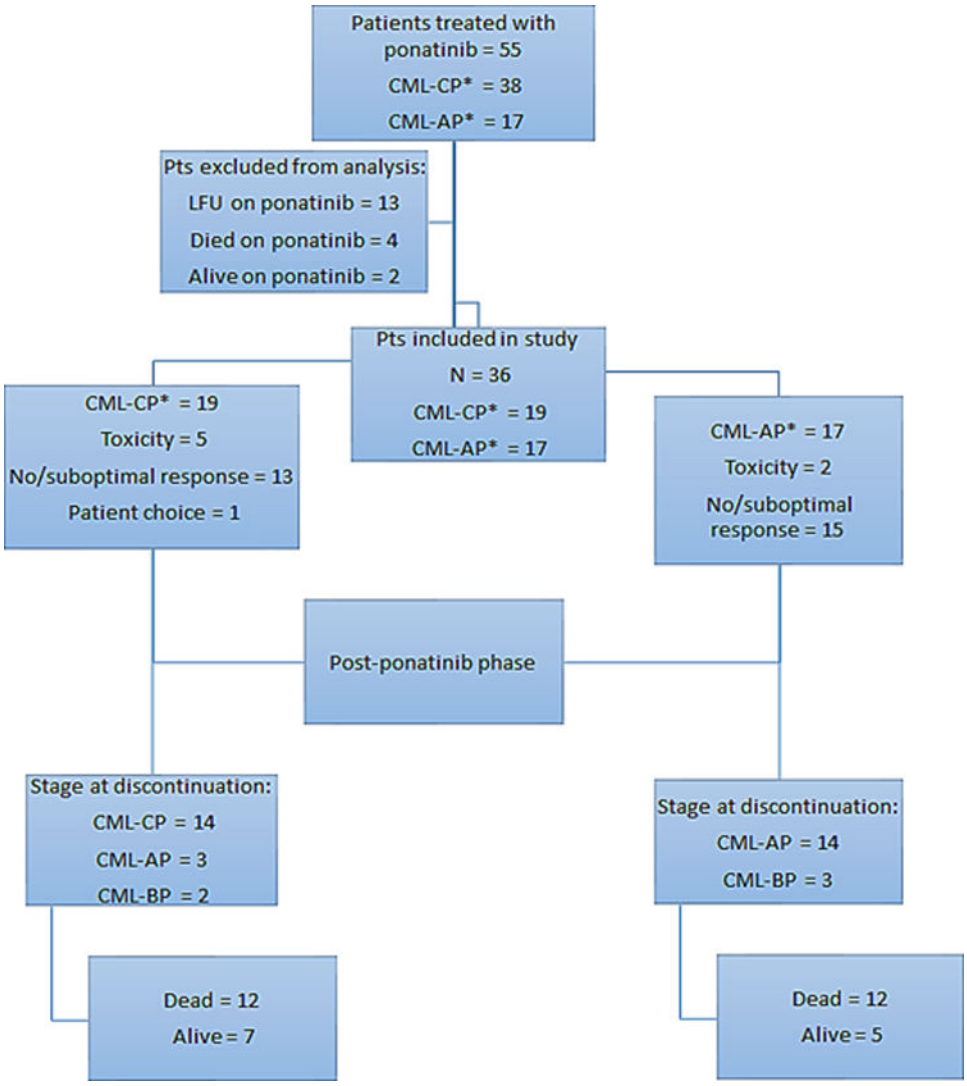

Figure 1:

Study plan for evaluating outcomes on CML pts after ponatinib resistance or intolerance. CML-CP*, CML-AP* - Phases at starting ponatinib; CML-CP, CML-AP, CML-BP - phases at discontinuation of ponatinib

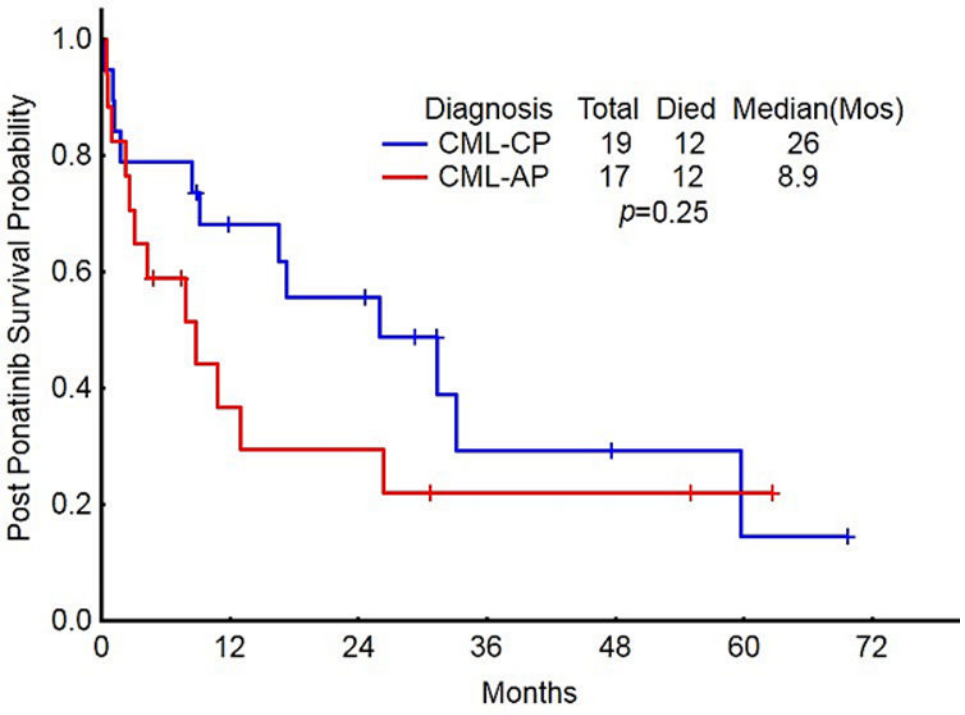

Figure 2:
Overall survival for patients who discontinued ponatinib by stage at disease at start of ponatinib treatment.

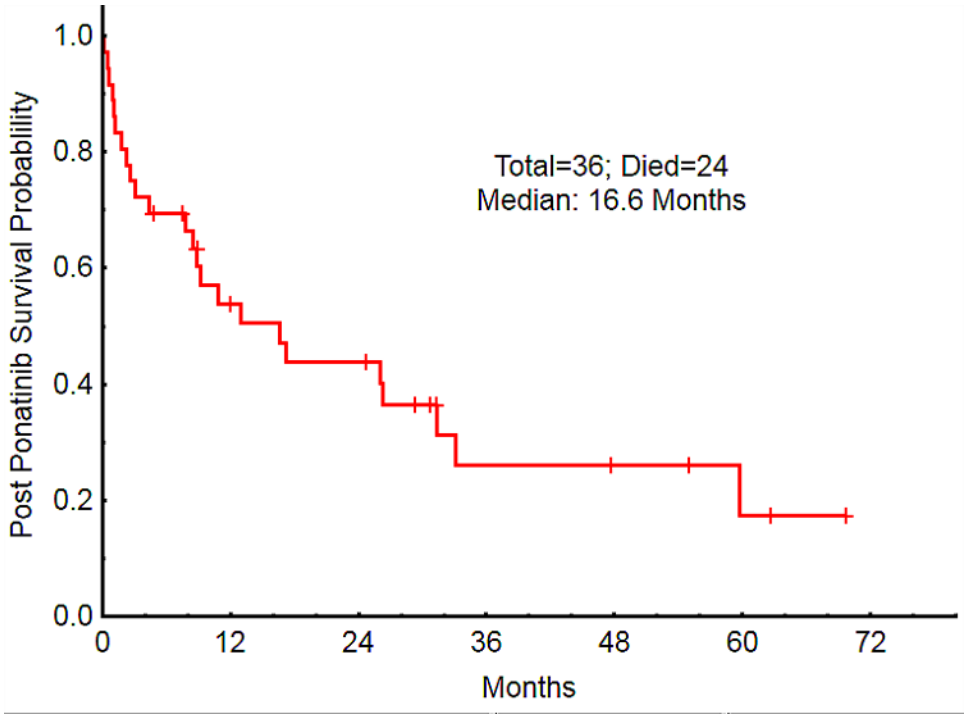

Figure 3:
Overall survival (OS) after failure to ponatinib for patients treated in CP or AP.

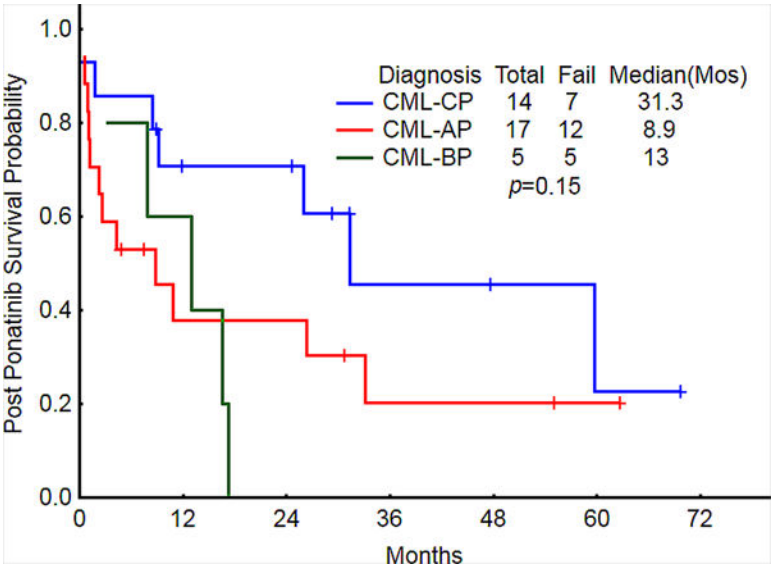

Figure 4:

Overall survival for patients who discontinued ponatinib by stage at the time of treatment discontinuation

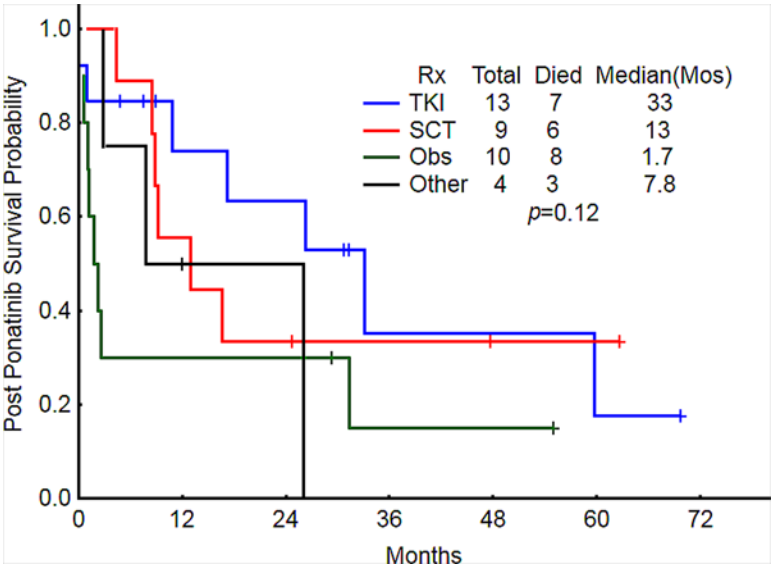

Figure 5:

Overall survival for patients who discontinued ponatinib by treatment received post ponatinib

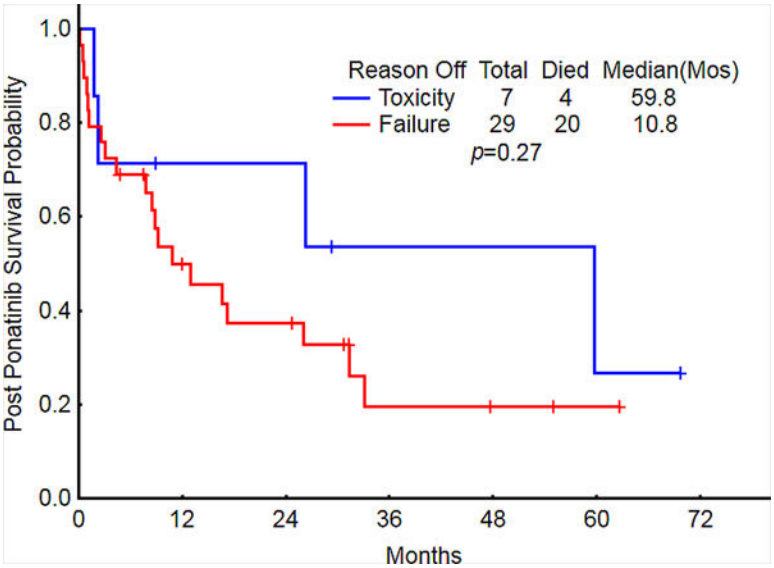

Figure 6:

Overall survival of pts who discontinued ponatinib by whether they discontinued because of resistance or toxicity.

Table 1A:

Baseline patient characteristics at start of ponatinib therapy:

Characteristics	No. (%), or Median [range]	
	CML-CP N = 19	CML-AP N = 17
Age (years)	59 [20–87]	53 [24–67]
Male (%)	11 (58)	8 (47)
Duration of CML before ponatinib (years)	9 [1–14]	6 [1–23]
No. of prior therapies	4 [2–6]	3 [2–6]
Mutation status *		
T315I^ (%)	4 (22)	4 (24)
Other mutations^ (%)	9 (47)	6 (35)
No mutations (%)	9 (47)	10 (59)
Weeks of ponatinib therapy	136 [0.6–232]	52 [1.1–266]
Clonal evolution (%)	0 (0)	9 (53)

Table 1b:

Patient characteristics at ponatinib discontinuation

Characteristics	No. (%), or Median [range]		
	CML-CP N = 14	CML-AP N = 17	CML-BP N = 5
Age (years)	59 [23–68]	50 [42–73]	51 [26–87]
WBC count (x 10^9/L)	3.7 [0.1–9.4]	2.5 [1.7–5.3]	2.8 [0.1–30.8]
Hgb (g/dL)	12 [8.5–13]	10.3 [7.9–13]	11.6 [8.1–13.6]
Plt (x 10^9/L)	60 [13–436]	45 [2–309]	45 [7–260]
Serum LDH (IU/L)	400 [163–541]	450 [172–740]	226 [771–4082]
Splenomegaly (%)	1 (7)	2 (12)	2 (40)
Mutation status *			
T315I (%)	1 (7)	4 (24)	2 (40)
Other mutations ^ (%)	4 (29)	9 (53)	1 (20)
No mutations (%)	10 (70)	8 (47)	3 (60)
Additional clonal evolution ^^ (%)	0 (0)	7 (41)	3 (60)
CyR status			
CCyR (%)	4 (28)	0 (0)	0 (0)
PCyR (%)	0 (0)	1 (6)	0 (0)
Minor CyR (%)	1 (7)	0 (0)	0 (0)
No CyR (%)	9 (65)	16 (94)	5 (100)
MR status			
MMR (%)	0 (0)	0 (0)	0 (0)
MR4.5 (%)	1 (7)	0 (0)	0 (0)
Reason for ponatinib discontinuation			
Therapy failure (%)	9 (63)	15 (90)	5 (100)
Toxicity (%)	5 (37)	2 (10)	0 (0)

* Patients may have had more than one mutation

^ -In the CML-CP cohort, the following mutations were detected before starting ponatinib: T315I (n = 2), E255K/T315I (n = 2), M315T/F359V, F359I, V299L, G250E, E453K, F317L (n = 1, each). All of them retained the same mutation at discontinuation, except for: 1) patient with M315T/F359V, this clone was replaced by one with F317L/E450G/I347F); 2) the patient with E453K had no detectable mutation at discontinuation. In the CML-AP cohort, the following mutations were detected: T315I (n = 2), T315I/L298V (n = 1), T315I//Y253H (n = 1), Y253H, G250E, F317/F35V (1, each). All of them retained the same mutation at ponatinib discontinuation except for the patient with T315I/L298V who had only L298V detected at discontinuation.

^^ -Of the 10 patients who had clonal evolution at ponatinib discontinuation, 4 out of 7 patients with CML-AP and 1 out of 3 patients with CML-BP had no detected baseline chromosomal abnormalities in their Ph+ metaphases at start of ponatinib therapy

Table 2:

Disease characteristics and therapies at ponatinib discontinuation

First Rx after Ponatinib discontinuation	Overall (N = 36)	TKI (N = 13)	SCT (N = 9)	Best supportive (N = 10)	Other chemoRx** (N = 4)
Causes of ponatinib discontinuation, *N*(%)					
Resistance	29 (81)	9 (69)	9^^ (100)	7 (70)	4 (100)
Toxicity	7 (19)	4 (31)	0 (0)	3 (30)	0 (0)
Toxicities leading to ponatinib discontinuation	Stroke = 2 Pancreatitis = 2 Thrombocytopenia = 1 Other = 2	Stroke = 1 Pancreatitis = 2 Headache = 1	-	Stroke = 1 Thrombocytopenia = 1 Nausea = 1	-
Median months on ponatinib therapy (Range)	17 (1–61)	25 (1–61)	14 (7–39)	15 (1–51)	29 (3–53)
CyR at the time of ponatinib discontinuation, %					
CCyR	10	0	11	20	0
PCyR	3	0	0	10	0
mCyR	33	20	66	20	25
No CyR	54	80	22	50	75
MolR at the time of ponatinib discontinuation, %					
MMR	0	0	0	10	0
No MMR	100	100	100	90	100
Phase of CML at discontinuation, *N*(%)					
CML CP	17 (47)	7 (54)	4 (44)	4 (40)	2 (50)
CML-AP	14 (39)	5 (38)	3 (33)	5 (50)	0 (0)
CML-BP	5 (14)	1 (18)	2 (23)	0 (0)	2 (50)
Post-ponatinib therapies	-	BMS = 5, BMS + DAC = 3, BMS + Nivolumab = 1, STI = 1, AMN = 1, DAC + SKI =1, DAC + AMN = 1	SCT = 9***	Hydrea = 2, HD-Ara-C = 1, None = 8	Omacetaxine = 2, Fludarabine + AraC = 1, Mitoxantrone + VP −16 + ponatinib = 1

Abbreviations: BSC−Best supportive care; Rx−therapy; SCT-transplant; BMS−Dasatinib; AMN−Nilotinib; STI−Imatinib; SKI-Bosutinib; DAC-Decitabine; HD−Ara−C−High dose cyatarabine; VP−16−Etoposide; PVD-Peripheral vascular disease; FAMP–Fludarabine; MXT-Mitoxantrone. *-Two pts on hydoxyurea, 1 pt received 1 cycle of high dose ara-C;**−2 pts received omacetaxine, 1 pt received Fludarabine+ cytarabine, 1 pt received Mitoxantrone + VP-16+ Ponatinib. ***−2 CML-BP pts required cytotoxic chemotherapy (Hyper CVAD in both) + TKI (pt #1 BMS, pt # 2 AMN) to reinsert remission to permit allo-SCT. Patient # 1 had T315I mutation at discontinuation of PO and was continued on PO during cycle # 5 & 6 of Hyper-CVAD. Both pts survived about 12 mos post SCT. ^^ Two patients got transplanted on a suboptimal response. * Ipilimumab administered for concomitant malignant melanoma.

*-Two pts on hydroxyurea, 1 pt received 1 cycle of high dose ara-C;

**−2 pts received omacetaxine, 1 pt received fludarabine+ cytarabine, 1 pt received mitoxantrone + VP-16 + ponatinib.

*** −2 CML-BP pts required cytotoxic chemotherapy (Hyper CVAD in both) + TKI (pt # 1 BMS, pt # 2 AMN) to reinsert remission to permit allo-SCT. Pt # 1 had T315I mutation at d/c of PO and was continued on PO during cycle # 5 & 6 of Hyper-CVAD. Both pts survived about 12 mos post AP-d/c.

^^ Two pts got transplanted on a suboptimal response/warning.

Table 3:

Outcomes of patients after ponatinib discontinuation

First Rx after Ponatinib discontinuation	Overall (n = 36)	TKI (n = 13)	SCT (n = 9)	Best supportive (n = 10)	Other chemoRx (n = 4)
Number of therapies required after ponatinib discontinuation, *N*(%)					
One	23 (64)	9 (70)	7 (77)	3 (30)	4 (100)
Two	4 (11)	2 (15)	2 (23)	0 (0)	0 (0)
Three	2 (6)	2 (15)	0 (0)	0 (0)	0 (0)
none	7 (19)	0 (0)	0 (0)	7 (70)	0 (0)
Best CyR after subsequent therapy, %					
CCyR	45	0	100	25	33
PCyR	15	42	0	13	0
mCyR	20	28	0	25	0
No CyR	20	28	0	37	66
MolR after subsequent therapy, %					
MMR	36	14	70	12	33
No MMR	64	86	30	88	66
Events, *N*(%)					
Death	24 (67)	7 (54)	6 (66)	8 (80)	3 (75)
Loss of McyR	3 (8)	3 (23)	-	-	-
Cardiac or vascular adverse events post ponatinib[^], *N*(%)	5	4 (80)	-	-	1 (20)
Deaths, *N*(%)	24	10 (41)	6 (25)	8 (35)	4 (19)
Causes of death, *N*(%)					
sepsis	3 (13)	1 (10)	2 (33)	-	-
Disease related	10 (41)	3 (30)	2 (33)	3 (37)	2 (50)
IC bleed	1 (4)	-	-	-	1 (25)
Ipilimumab toxicity[*]	1 (4)	-	-	1 (13)	-
unidentified	9 (39)	6 (60)	2 (33)	4 (50)	1 (25)
Median follow up post ponatinib in months [range]	30 [5–70]	19 [5–70]	48 [25–63]	42 [29–55]	12 [5–21]
12-month Kaplan-Meier survival probability (%) and median survival (months):					
Overall survival	54%, 16.6	74%, 33	56%, 13	30%, 1.7	50%, 7.8
Event free survival	40%, 8.9	47%, 12	44%, 11.8	23%, 1.7	50%, 7.8
Failure free survival	32%, 8.8	32%, 8.8	44%, 11.8	12%, 1.7	50%, 7.8
Transformation free survival	52%, 13	85%, 26.3	44%, 11.8	23%, 1.7	50%, 7.8

[*] - Ipilimumab administered for concomitant malignant melanoma.

[^] Vascular adverse events: Four pts had grade 3–4 vascular adverse events after ponatinib discontinuation: 1) one developed PVD on ponatinib, had a vascular bypass 18 months later; no further signs of arterial insufficiency have occurred after 25 months of follow-up since discontinuation. 2) One patient developed giant cell arteritis (documented by temporal artery biopsy). 3) One patient was diagnosed with pulmonary hypertension during therapy; pulmonary pressures normalized over six months after discontinuation. She also had Raynaud phenomenon well controlled with

nifedipine after ponatinib discontinuation. 4) One patient with ocular ischemic syndrome soon after taking ponatinib. Fifteen days after discontinuation, she suffered a left cerebrovascular accident.