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A Retrospective-Prospective Study of Second-Line Nilotinib versus Ponatinib in CML Patients Resistant or Intolerant to Imatinib

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Abstract

Objective: To compare the efficacy, safety, and progression-free survival (PFS) of nilotinib versus ponatinib as second-line therapy in chronic-phase chronic myeloid leukemia (CP-CML) patients resistant or intolerant to imatinib and negative for the T315I mutation.

Methodology: A single-center retrospective -prospective cohort study was conducted between January 2008 and 2023, enrolling 35 CP-CML patients resistant or intolerant to first-line imatinib and confirmed negative for T315I mutation. Patients received nilotinib or ponatinib per clinical guidelines. The primary outcomes were major molecular response (MMR) rates and PFS, analyzed using Kaplan–Meier survival curves with log-rank testing. Adverse events were recorded according to standardized criteria.

Results: Nineteen patients received nilotinib and sixteen received ponatinib. Baseline risk scores were comparable (p=0.491). After second-line treatment, MMR was achieved in 15.8% of nilotinib patients and 37.5% of ponatinib patients (p=0.245). PFS showed a numerical trend favoring ponatinib, but without statistical significance (p=0.743). No deaths occurred during the observation period. Adverse events included mild allergic reactions in both groups, with thyroiditis observed only in nilotinib-treated patients and dermatitis in ponatinib-treated patients.

Conclusions: Both nilotinib and ponatinib demonstrated durable disease control as second-line therapies in imatinib-resistant or intolerant CP-CML patients negative for T315I, with acceptable safety profiles. While ponatinib showed a trend toward improved PFS, differences were not statistically significant.

Key Words: Gender-Related Characteristics, Chronic Myeloid Leukemia, progression-free survival (PFS), Nilotinib, Ponatinib, Second-line therapy

Introduction

Chronic myeloid leukemia (CML) is a clonal myeloproliferative neoplasm arising from a reciprocal translocation between chromosomes 9 and 22—t (9;22) (q34;q11)—that generates the BCR-ABL1 fusion gene, a constitutively active tyrosine kinase that drives uncontrolled proliferation of myeloid lineage cells.[1] This hallmark molecular lesion, also known as the Philadelphia chromosome, has transformed CML from a diagnostic and prognostic enigma into a model for targeted therapy in oncology.

The introduction of tyrosine kinase inhibitors (TKIs), beginning with imatinib mesylate, revolutionized CML therapy, achieving profound cytogenetic and molecular remissions and transforming patient survival to near-normal life expectancy.[2,3] However, despite the remarkable success of imatinib, clinical resistance or intolerance develops in approximately 30–40% of patients, requiring the use of second-line therapies.[4,5]

Second-generation TKIs such as nilotinib and dasatinib were developed to overcome the limitations of imatinib. Nilotinib, a structurally modified analog of imatinib, exhibits higher selectivity and potency against BCR-ABL1 and is effective in many cases of imatinib resistance or intolerance—except for mutations such as T315I, which confer high-level resistance.[6] Third-generation TKIs, notably ponatinib, were designed to overcome even these highly resistant mutations and have demonstrated robust activity across a broad mutation spectrum, including the T315I gatekeeper mutation, which remains refractory to all other approved TKIs.[7,8]

While ponatinib's broad efficacy makes it a potent agent in refractory settings, its clinical use is tempered by a notable risk of serious vascular events, including arterial thrombosis and hypertension, particularly at higher doses.[9,10] Dose-adjustment strategies—such as those tested in the OPTIC trial—have aimed to optimize the balance between efficacy and safety, but concerns

Authorship Contribution: [1]critically reviewed and edited the manuscript, [2]conception and design of the study, performed data collection and analysis, and prepared the initial draft of the manuscript. [3]responsible for genetic response evaluation. [1,4]critically reviewed and edited the manuscript. All authors read and approved the final version.

Funding Source: none
Conflict of Interest: none
Received: July 06, 2025
Accepted: Oct 12, 2025

persist regarding patient selection and long-term tolerability.[11]

In contrast, nilotinib has a more favorable side-effect profile in many patients but lacks activity against certain kinase domain mutations, limiting its utility in mutation-driven resistance. It is also associated with metabolic and cardiovascular complications, including QT prolongation, hyperglycemia, and lipid disturbances, which must be considered in risk stratification.[12]

Given these complexities, the choice between nilotinib and ponatinib as second-line therapy after imatinib failure is far from straightforward. Factors such as mutation profile, disease kinetics, cardiovascular risk, treatment goals, and comorbid conditions must be weighed carefully. However, direct comparative data between nilotinib and ponatinib in the second-line setting remain limited, and there is no universally accepted algorithm for selecting one over the other in T315I-negative patients.

This article aims to critically review and compare nilotinib and ponatinib as second-line treatment options in chronic-phase CML patients who are resistant or intolerant to imatinib but do not harbor the T315I mutation. By analyzing key efficacy outcomes, safety data and clinical decision-making parameters, we seek to clarify their relative benefits and risks in this important therapeutic niche.

Methodology

This was a single-center observational study, combining retrospective and prospective data, to evaluate the outcomes of nilotinib and ponatinib as second-line therapies in patients with chronic-phase chronic myeloid leukemia (CP-CML) following first-line imatinib failure due to resistance or intolerance. The study was conducted at the National Hematology and Blood Transfusion Center, from January 2008 to 2023. Ethical approval was obtained from the institutional review board (an approval code was not assigned), and written informed consent was collected from all prospectively enrolled patients in accordance with the Declaration of Helsinki.

Eligible patients were adults aged 18 years or older, diagnosed with CP-CML based on World Health Organization 2016/2022 criteria. Inclusion criteria required documented resistance or intolerance to first-line imatinib therapy and confirmed absence of the T315I BCR-ABL1 mutation by standardized molecular testing before second-line initiation. Patients were excluded if they had progressed to accelerated phase or blast crisis, received more than one prior second- or third-generation TKI, demonstrated significant organ dysfunction precluding TKI therapy (defined as left ventricular ejection fraction <40% or serum creatinine >2.0 mg/dL), or were pregnant or breastfeeding. Consecutive sampling was used to minimize selection bias.

In total, 35 patients were analyzed. Limited access to second-line TKIs in the country before 2019 restricted the eligible cohort size during the earlier years of the study. Data were collected retrospectively through patient medical records between 2008 and 2019, while prospective enrollment was conducted from 2019 onward. Collected data included demographic characteristics (mean age ± standard deviation, sex distribution), baseline disease features including Sokal risk scores, and details of prior imatinib therapy such as duration and response. Further variables included the choice of second-line TKI (nilotinib or ponatinib), serial molecular monitoring results (BCR-ABL1 international scale at defined timepoints), time to and rates of major molecular response (MMR), progression-free survival (PFS), and overall survival (OS). Adverse events were documented using standard definitions and graded according to internationally accepted criteria.

Nilotinib was administered orally at 400 mg twice daily, and ponatinib was initiated at 45 mg once daily with subsequent dose adjustments based on toxicity and therapeutic response, in line with OPTIC trial recommendations. All patients were monitored according to European LeukemiaNet guidelines, including scheduled BCR-ABL1 transcript quantification by real-time PCR, hematologic assessments, routine electrocardiography, and metabolic laboratory monitoring where indicated.

Descriptive statistics summarized baseline characteristics and treatment outcomes. Continuous variables were presented as means with standard deviations or medians with interquartile ranges as appropriate, and categorical variables as frequencies with percentages. Response rates were compared using the Chi-square test or Fisher’s exact test. Time-to-event outcomes including PFS and OS were analyzed using Kaplan–Meier survival curves and compared with the log-rank test, while Cox proportional hazards regression was performed to explore the impact of key variables on survival. A p-value of less than 0.05 was considered statistically significant. Statistical analyses were

performed using SPSS software version 31 (IBM Corp., Armonk, NY, USA) Ethics Statement: Ethical approval was granted by the National Hematology and Blood Transfusion Center Research Committee; however, no formal approval number was issued according to local committee procedures.

Results

A total of 35 patients with chronic-phase CML who were resistant or intolerant to first-line imatinib were included. Of these, 19 received nilotinib and 16 received ponatinib as second-line therapy. Baseline characteristics are summarized in Table I.

In the nilotinib group, there were 4 males (21%) and 15 females (79%), with a mean age of 43 years. According to the Sokal scoring system, 47% were classified as intermediate risk and 53% as low risk. The median duration of prior imatinib treatment was 99.5 months (range 51–180). Following transition to nilotinib, 3 patients (15.8%) achieved major molecular response (MMR), while 4 patients (21%) experienced treatment failure and required third-line therapy. An additional 3 patients (15.8%) showed only hematologic response, and the remainder demonstrated hematologic improvement without achieving MMR. Mild allergic reactions were observed in 2 patients, and thyroiditis developed in 2 patients.

In the ponatinib group, 6 patients (37.5%) were male and 10 (62.5%) female, with a mean age of 37 years. Sokal scoring showed 31% intermediate-risk and 69% low-risk patients. The median duration of prior imatinib therapy was 90.1 months (range 12–173). After switching to ponatinib, 6 patients (37.5%) achieved MMR, while 1 patient (6%) failed treatment. Four patients (25%) achieved only hematologic response, and the remainder had hematologic improvement. Adverse effects included mild allergic reactions in 4 patients and dermatitis in 2 patients.

Risk score distributions were comparable between treatment groups (p=0.491). The difference in MMR rates following second-line therapy, 15.8% for nilotinib and 37.5% for ponatinib, did not reach statistical significance (p=0.245).

During the median follow-up of 31 months, no deaths were recorded in either treatment group, and therefore median overall survival was not reached, with 100% survival probability maintained throughout the observation period.

Progression-free survival (PFS), analyzed using the Kaplan–Meier method (Figure I), showed a numerical trend favoring ponatinib, with fewer progression events observed compared to nilotinib. The nilotinib group showed a gradual decline in PFS beyond 20 months, with additional drops over a 60-month period, while the ponatinib group maintained a relatively stable curve despite shorter follow-up in some cases. The difference in PFS between groups was not statistically significant (p=0.314). Median PFS was not reached in either cohort within the available follow-up.

Table I: Baseline Characteristics and Treatment Outcomes of Chronic-Phase CML Patients Treated with Second-Line TKIs.

Parameter	Nilotinib (n=19)	Ponatinib (n=16)	p-value
Age, mean (years)	43	37	—
Sex, n (%)			
Male	4 (21%)	6 (37.5%)	—
Female	15 (79%)	10 (62.5%)	—
Sokal Risk Score, n (%)			0.491
Intermediate	9 (47%)	5 (31%)	
Low	10 (53%)	11 (69%)	
Median prior imatinib treatment duration, months (range)	99.5 (51–180)	90.1 (12–173)	—
Mean time to MMR on imatinib, months (range)	86.7 (27–171)	48.2 (12–180)	—
MMR achieved after second-line, n (%)	3 (15.8%)	6 (37.5%)	0.245
Treatment failure after second-line, n (%)	4 (21%)	1 (6%)	0.347
Hematologic response after second-line, n (%)	3 (15.8%)	4 (25%)	0.677
Adverse events			
Mild allergic reactions	2 (11%)	4 (25%)	0.379
Thyroiditis	2 (11%)	0	0.489
Dermatitis	0	2 (12.5%)	0.202
Progression-free survival (log-rank p)	—	—	0.743
Median overall survival	Not reached	Not reached	—
Deaths during study	0	0	—

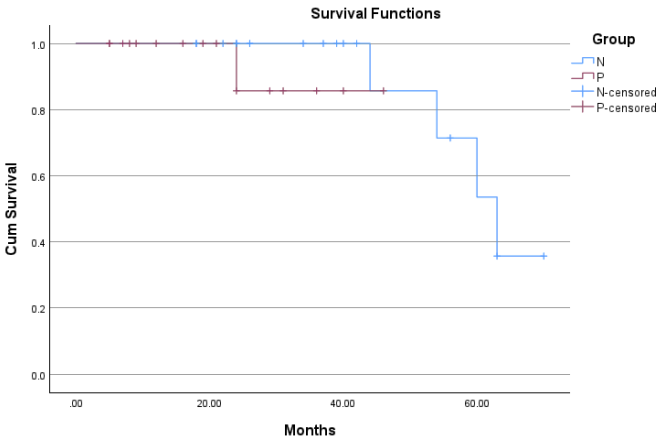

Figure I. Progression-Free Survival in Chronic-Phase CML Patients Receiving Second-Line TKIs.

Overall, both nilotinib and ponatinib demonstrated durable disease control in most patients receiving second-line therapy.

Discussion

This retrospective-prospective cohort study compared the effectiveness, safety, and progression-free survival of second-line nilotinib versus ponatinib in patients with chronic-phase chronic myeloid leukemia (CML) who were resistant or intolerant to first-line imatinib. Both treatment options provided satisfactory disease control, and no statistically significant differences were observed in major molecular response (MMR) rates or progression-free survival (PFS) between groups.

Although ponatinib showed a higher proportion of patients achieving MMR and a numerically favorable trend in PFS, these differences did not reach statistical significance, likely due to the small sample size and limited number of progression events. These findings partially support the initial hypothesis that ponatinib could offer superior disease control after imatinib failure; however, confirmation requires larger cohorts.

Our results align broadly with previous data. The ENESTnd and ENESTcmr trials have shown nilotinib to achieve durable molecular responses in chronic-phase CML with acceptable tolerability profiles.[6,13] Nonetheless, nilotinib lacks efficacy against the T315I mutation, which is a key cause of treatment failure.[14] Conversely, ponatinib, designed to inhibit even the T315I gatekeeper mutation, has demonstrated substantial activity against a wide range of resistant clones, supporting its role in second-line and beyond settings.[8,15] However, the risk of vascular and thrombotic complications with ponatinib remains a concern, leading to adoption of dose-optimization approaches such as those tested in the OPTIC trial.[16]

Regarding safety, the adverse event profiles observed in our cohort were consistent with previous studies.[17,18] Mild allergic reactions and thyroiditis were noted in nilotinib-treated patients, while ponatinib was associated with mild allergic reactions and dermatologic toxicities. These patterns emphasize the importance of close safety monitoring and individualized risk-benefit assessment in treatment selection.

Our findings underscore the continuing challenges in choosing second-line therapy after imatinib failure. While nilotinib remains an appropriate option, especially for patients with favorable cardiovascular profiles and without high-risk mutations, ponatinib may be preferred for patients with complex or compound kinase domain mutations, provided cardiovascular risk is thoroughly evaluated and mitigated. International guidelines increasingly recommend comprehensive molecular profiling before second-line treatment initiation to personalize therapy and optimize outcomes.[19,20]

A key strength of this study is its real-world design incorporating both retrospective and prospective data over an extended period. However, limitations include its single-center nature, small sample size, and the lack of broad molecular mutation analysis beyond T315I. These factors may have reduced the power to detect statistically significant differences and limit generalizability.

Limitations: Limitations of our study include its single-center nature, relatively small cohort, absence of comprehensive mutation testing beyond T315I, and a modest number of progression events limiting statistical power. Nevertheless, this cohort adds to the limited real-world data comparing these two agents head-to-head in the second-line setting, particularly among patients without T315I mutation. Small cohort size partly reflects the limited availability of second-line tyrosine kinase inhibitors in our country prior to 2019. Many patients were unable to access these agents until more recently, constraining the number of cases eligible for second-line treatment during the early phases of the study. This may have affected the statistical power to detect differences between treatment groups.

Conclusion

This study provides real-world evidence on the outcomes of nilotinib and ponatinib as second-line therapies for chronic-phase CML patients resistant or intolerant to imatinib. Both agents showed acceptable safety profiles and maintained disease control in most patients, with no statistically significant differences observed in major

molecular response rates or progression-free survival. While ponatinib demonstrated a numerical trend toward improved disease control, this was not statistically confirmed, likely due to the small sample size and limited number of events. Further multicenter prospective studies with broader mutation profiling and longer follow-up are warranted to optimize second-line treatment strategies in this patient population.

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