Dosing patterns of ponatinib in patients with chronic-phase chronic myeloid leukemia and effect on treatment: analysis of specialty pharmacy data in the United States

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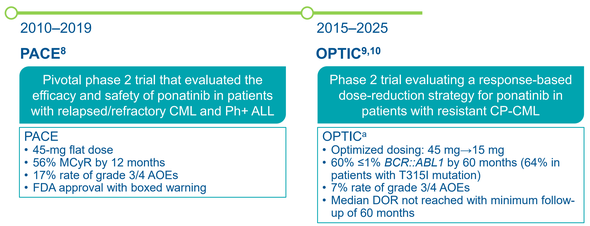
Background

- Approximately 10,000 people are diagnosed with chronic myeloid leukemia (CML) each year, representing ~15% of all new cases of leukemia in the US annually, with an average age at diagnosis of 66 years[1,2]
- Tyrosine kinase inhibitors (TKIs) are the mainstay of treatment, but 23%–40% of cases progress from first- to second-line treatment, and another 32%–50% progress from second to third line[3-6]
  - *BCR::ABL1* mutations are the most common cause of TKI resistance[7]
  - Mutation testing and appropriate choice of TKI are critical for patient care
- Ponatinib was approved by the US (United States) Food and Drug Administration (FDA) in 2012 and is the only BCR::ABL1 TKI with no contraindicated mutations
- Ponatinib has been evaluated in patients with chronic-phase (CP) CML that was resistant or who were intolerant to prior TKIs or who had a T315I mutation in 2 large, global, phase 2 studies (**Figure 1**)[8,9]
  - PACE (NCT01207440) evaluated ponatinib at a 45-mg once daily (QD) flat dose, showing a 56% MCyR by 12 months but with a 17% grade 3/4 AOE rate, resulting in FDA approval with a boxed warning[8]
  - OPTIC (NCT02467270) was conducted to optimize the dosage to maximize efficacy while reducing safety concerns
    - In patients with CP-CML, OPTIC showed that 45 mg QD administered until achievement of ≤1% *BCR::ABL1* and then reduced to 15 mg QD resulted in a 52% ≤1% *BCR::ABL1* rate by 12 months and 60% rate by 60 months, with a 5% grade 3/4 AOE rate in the 12-month analysis and a 7% rate in the 60-month analysis[9,10]
    - This optimal risk:benefit ratio, in a heavily pretreated population, was achieved through appropriate down-dosing from 45 mg QD to 15 mg QD upon clinical benefit

Figure 1: Ponatinib clinical trial history



[a]60-month data are shown, as reported in the US prescribing information.[10]

AOE, arterial occlusive event; DOR, duration of response; MCyR, major cytogenetic response; Ph+ ALL, Philadelphia chromosome-positive acute lymphoblastic leukemia.

- This study aimed to explore how ponatinib is being dosed across the US. By utilizing supply chain analytics, researchers analyzed dosage patterns to understand if and how patients are being down-dosed and the implications thereof

Methods

- Ponatinib prescription information from specialty pharmacy shipment data was analyzed
- Patients with CML with new ponatinib specialty pharmacy shipment data between January 2021 and March 2024 were included
- De-identified patients receiving the FDA-recommended dosage of 45 mg QD reduced to 15 mg QD versus other dosing regimen variations were determined by establishing a window of first and final dosage strength (**Figure 2**)
- New patient starts (NPS) and restarts with >3 shipments were included to ensure sufficient length of patient journey
- Patients were grouped into cohorts by starting year and month
- For the purpose of this analysis, a patient was said to have discontinued treatment if they did not receive any subsequent shipment beyond 90 days of the last expected refill, or if there was a >90-day gap either between the current refill and next shipment or between the last expected refill and the end of the data observation period; patients were considered restarts if they subsequently resumed treatment
  - Last expected refill date = last shipment date + days of supply in the last shipment
- Mean duration of therapy by starting dose and titration type was calculated using cohort-based persistency method
- All metrics were evaluated 12 months following the month of NPS

Question

Are patients receiving ponatinib following the OPTIC FDA-approved dosage titration, and is there a greater benefit to following approved dosing in the real-world setting?

Study design

Data analyzed → NPS and discontinuation rates by start dosage and titration type; Average and median duration of treatment by start dosage and titration type; Year-over-year NPS and discontinuation rates by start dosage

Results

~48% of new CML patients started on the FDA-approved starting dose of 45 mg QD

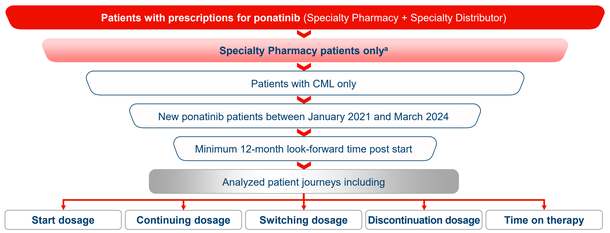
13% of new total patients with CML are following the FDA-approved dosage titration of 45 mg → 15 mg QD

8 months longer mean duration of treatment among patients who down-titrated vs patients who did not

Key Takeaway

- The ponatinib 45 mg → 15 mg dosing regimen identified in OPTIC and specified in FDA-approved labeling results in 8 more months of therapy compared with other dosing patterns
- However, only 13% of patients in the US are being treated with the recommended dosing regimen
- These findings highlight the need for education on the FDA-approved dosing regimen for ponatinib

Figure 2: Analysis flow chart

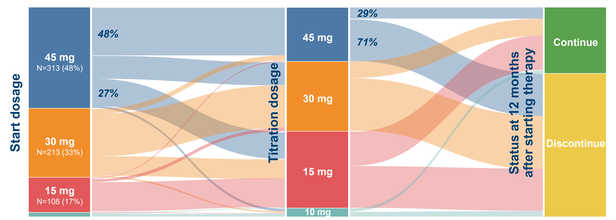


[a]Does not capture patients who switched between specialty pharmacy and specialty distributor.

Results

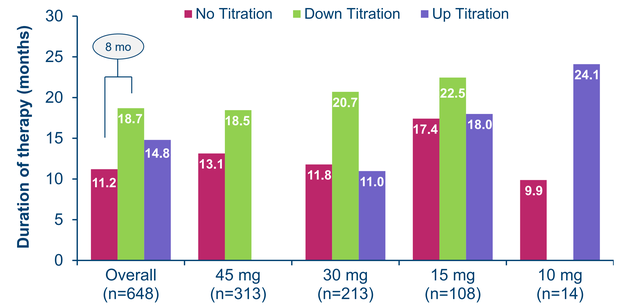
- A total of 648 patients with CML were included in the analysis
- 313 patients with CML (48%) who started new therapy with ponatinib received the FDA-recommended starting dose of 45 mg QD as their initial dose; among these patients, 84 (27%) dose-reduced to 15 mg QD (**Figure 3**)
  - Of all patients in this analysis, 13% (84/648) were treated with the FDA-recommended dosage regimen of 45 mg QD with reduction to 15 mg QD upon achievement of ≤1% *BCR::ABL1*

Figure 3: Patient distribution across starting dosage



- Of the remaining patients who started on 45 mg QD, 149 (48%) remained on 45 mg QD; 73 (23%) and 7 (2%) patients had dose reductions to 30 mg and 10 mg QD, respectively
  - Mean time to dose reduction to 30 mg, 15 mg, and 10 mg was 4.3, 6.3, and 9.7 months, respectively
- A total of 213 (33%) patients started ponatinib at 30 mg QD, and most (132 patients; 62%) remained on that dose
  - 60 (28%) and 5 (2%) patients had dose reductions to 15 mg and 10 mg QD, respectively; mean time to dose reduction to 15 mg and 10 mg was 7 and 6.1 months, respectively
  - 16 (8%) patients titrated up to 45 mg QD; mean time to dose increase was 0.9 months
- Of the 108 (17%) patients who started treatment on 15 mg QD, 91 (84%) remained on that dose
  - 11 (10%) and 3 (3%) patients titrated up to 30 mg and 45 mg QD, respectively; mean time to dose increase to 30 mg and 45 mg was 2.1 and 10.5 months, respectively
  - 3 (3%) patients had dose reduction to 10 mg QD; mean time to dose reduction was 6.1 months
- Of 14 patients who started treatment on ponatinib 10 mg, 11 (79%) patients remained on 10 mg QD and 3 (21%) patients titrated up to 15 mg QD; mean time to dose increase was 4.2 months
- Mean duration of ponatinib therapy for all patients with dose reductions was 8 months longer than that of patients who did not (19 vs 11 months), regardless of starting dose

Figure 4: Mean duration of therapy



Conclusions

- Ponatinib was approved in 2012 with a flat-dosing regimen of 45 mg QD, resulting in nearly half of patients in the heavily pretreated setting deriving clinical benefit, but adverse events limited use in some patients
- The OPTIC study led to the FDA-recommended regimen of 45 mg→15 mg upon achieving ≤1% *BCR::ABL1* as the optimal dosing regimen to maximize efficacy and minimize AOE risk
  - However, this analysis demonstrated that only 13% of patients in the US are being treated with the recommended dosage regimen
- In this analysis, starting ponatinib at 45 mg QD or 30 mg QD and down-dosing to 15 mg QD provides 8 more months of therapy, possibly because of optimized risk:benefit
- Limitations of this analysis include use of specialty pharmacy shipment data as the primary data source and use of anonymized data that does not allow further investigation into timing or reason for dose reduction (eg, safety, reaching a response) or discontinuation due to safety concerns
- OPTIC 5-year results suggest that ponatinib may be able to prevent the emergence of *BCR::ABL1* mutations; therefore, ponatinib should be implemented as early as indicated and dosed according to the FDA-approved dosage of 45 mg QD reduced to 15 mg QD upon clinical benefit

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