Treatment Patterns, Tolerance, and Clinical Response of Chronic Phase Chronic Myeloid Leukemia (CML-CP) Patients (Including Those Harboring the T315I Mutation) Experiencing Multiple Tyrosine Kinase Inhibitor Failure: A Multi-Center Retrospective Chart Review Analysis

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Abstract #4343 – Poster Presentation
Background and Objectives

Background

• Adenosine triphosphate-competitive tyrosine kinase inhibitors (TKIs) are an effective treatment for chronic phase chronic myeloid leukemia (CML-CP)\(^1,2\)

• However, a substantial proportion of CP-CML patients treated with TKIs eventually switch to an alternative TKI after developing intolerance or resistance, representing a major clinical burden\(^3,4\)

• The presence of the *BCR::ABL1* T315I mutation, which is associated with worse prognosis, further complicates the clinical management of patients with CML-CP\(^5\)

Objectives

• To describe real-world treatment patterns, clinical outcomes, and adverse events (AEs) in French CML-CP patients receiving 3 or more lines of therapy (3L+) and those with the *BCR::ABL1* T315I mutation
Methods

• Study design (Figure 1)

• A retrospective chart review study was conducted at 3 large clinical institutions for CML in France:
  • Centre Léon Bérard (Lyon)
  • Hématologie Institut Bergonié (Bordeaux)
  • Institut Universitaire du Cancer Toulouse (Toulouse)

• De-identified demographic and clinical data for adult patients diagnosed with CML-CP and treated in 3L+ or harboring the T315I mutation between 2006 and 2021 were abstracted from medical charts using an electronic case report form
Methods

- **Study population**
  - Inclusion criteria:
    - Age ≥ 18 years at CML-CP diagnosis
    - **For 3L CML patients**: initiated 3L therapy after failing 2 prior therapies (allogeneic stem cell transplantation, bosutinib, dasatinib, imatinib, nilotinib, or ponatinib) between 2006 and 2021
    - **For T315I mutation patients**: evidence of T315I mutation and treatment with TKI or allogeneic stem cell transplantation
    - Non-opposition of patients recruited for participation in the study
  - Exclusion criteria:
    - History of other active malignancy within 3 years prior to CML-CP diagnosis
    - Received anti-cancer therapies for any other malignancies prior to time of 3L therapy initiation or at the time of treatment initiation after identification of T315I mutation
    - Enrollment in a clinical trial at the time of 3L therapy initiation or at the time of treatment initiation after identification of T315I mutation

- **Statistical analysis**
  - Descriptive statistics were used to summarize patient characteristics, treatment patterns, clinical outcomes, and AEs
  - Kaplan–Meier analysis was performed to determine the cumulative incidence of patients with a major molecular response (MMR [0.01% < \( BCR::ABL \leq 0.1\% \)]) or deep molecular response (MR4.0 or MR4.5; standardized and expressed on the international scale [IS])
  - Factors associated with overall survival (OS) were evaluated by multivariate Cox regression analysis
Results

Table 1. Demographic characteristics of patients with 3L+

<table>
<thead>
<tr>
<th>Demographic Characteristic</th>
<th>N = 157</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) at CML-CP diagnosis, mean ± SD [median]</td>
<td>52.8 ± 15.7 [55.7]</td>
</tr>
<tr>
<td>Age (years) at index date, mean ± SD [median]</td>
<td>59.3 ± 15.6 [62.1]</td>
</tr>
<tr>
<td>Year of CML-CP diagnosis, n (%)</td>
<td></td>
</tr>
<tr>
<td>Before 2010</td>
<td>88 (56.1)</td>
</tr>
<tr>
<td>On or after 2010</td>
<td>69 (43.9)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>88 (56.1)</td>
</tr>
<tr>
<td>Female</td>
<td>69 (43.9)</td>
</tr>
<tr>
<td>Medical center, n (%)</td>
<td></td>
</tr>
<tr>
<td>Centre Léon Bérard, Lyon</td>
<td>65 (41.4)</td>
</tr>
<tr>
<td>Hématologie Institut Bergonié, Bordeaux</td>
<td>61 (38.9)</td>
</tr>
<tr>
<td>Institut Universitaire du Cancer Toulouse, Toulouse</td>
<td>31 (19.7)</td>
</tr>
<tr>
<td>Length of follow-up (month), mean ± SD [median]</td>
<td>66.9 ± 43.3 [59.3]</td>
</tr>
</tbody>
</table>

ABBREVIATIONS: 3L+, three or more lines of therapy; CML-CP, chronic myeloid leukemia in chronic phase.

NOTE: Follow-up time was defined as the time from the index date to the date of death from any cause or date of last follow-up.

- Risk scores at CML-CP diagnosis:
  - Sokal: 22% low, 34% intermediate, 29% high, 15% unknown
  - EUTOS long-term survival (ELTS): 40% low, 25% intermediate, 11% high, 24% unknown/not assessed
- 24/157 patients (15%) had additional chromosomal abnormalities at CML-CP diagnosis
- Molecular profile:
  - 142/157 patients (90%) had major BCR::ABL1 rearrangement
  - 7/89 patients (8%) with mutation status assessed had T315I mutation
Figure 2. Sankey diagram of treatment patterns for CML-CP patients with ≥3 lines of therapy.

- Mean ± SD [median] number of lines of therapy (N=157) was 3.6 ± 0.9 [3.0]; 16% of patients had 5L+
- The most frequent treatment sequences (Figure 2) were:
  - Imatinib – nilotinib – dasatinib (17%)
  - Imatinib – dasatinib – nilotinib (10%)
  - Imatinib – dasatinib – bosutinib (6%)
  - Imatinib – dasatinib – ponatinib (6%)
- TKIs received in 3L (median duration: 17 [5–47] months) were dasatinib (32%), nilotinib (19%), imatinib (18%), ponatinib (17%), and bosutinib (14%)
- 50% of patients discontinued 3L therapy; reasons for discontinuation included AEs/intolerance (69%) and resistance (23%)
Results

Clinical outcomes of patients with 3L+

- AEs were documented in 139/157 patients (89%) in 3L
  - The median number of AEs per patient was 2 in 3L; infections (18%) and asthenia (13%) were the most common AEs
- Treatment-free remission (TFR) was observed in 16 (10%) patients in 3L (median duration: 45 months); the last reported treatments were dasatinib (n=10) and nilotinib (n=6) for these patients
  - Among the 16 patients in TFR, 5 (31%) were intolerant to 3L TKI
- In 145 patients with documented responses in 3L, the rate of achieving MMR, MR4.0, and MR4.5 at 12 months was 42%, 27%, and 14%, respectively
  - MMR in 3L was achieved by 79/145 (54.5%) patients; median time to reach MMR was 20.8 months
- The median OS since 3L treatment initiation was 12 (8–16) years
- Age at index date, additional chromosomal abnormalities at CMP-CP diagnosis, and achievement of MMR in 3L were statistically significant factors impacting OS in the multivariate Cox regression model (Table 2)
Table 2. Multivariate Cox regression model of OS

<table>
<thead>
<tr>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) at index date</td>
<td>1.07 (1.02, 1.13)</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Male (ref: female)</td>
<td>0.86 (0.27, 2.80)</td>
<td>0.81</td>
</tr>
<tr>
<td>ELTS risk score at CML-CP diagnosis (ref: low risk)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>0.91 (0.14, 6.10)</td>
<td>0.92</td>
</tr>
<tr>
<td>High risk</td>
<td>2.69 (0.30, 23.65)</td>
<td>0.37</td>
</tr>
<tr>
<td>Not assessed or unknown</td>
<td>2.28 (0.49, 10.63)</td>
<td>0.29</td>
</tr>
<tr>
<td>Additional chromosomal abnormalities at CML-CP diagnosis (ref: no additional abnormalities)</td>
<td>5.67 (1.71, 18.82)</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>MMR was achieved in 3L (ref: MMR was not achieved in 3L)</td>
<td>0.10 (0.02, 0.47)</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Ponatinib (ref: non-ponatinib)</td>
<td>1.35 (0.18, 10.04)</td>
<td>0.77</td>
</tr>
<tr>
<td>Reason for terminating 2L is resistance or lack of efficacy (ref: no)</td>
<td>1.60 (0.33, 7.67)</td>
<td>0.56</td>
</tr>
<tr>
<td>Reason for terminating 2L is intolerance or management of AEs (ref: no)</td>
<td>0.91 (0.18, 4.51)</td>
<td>0.91</td>
</tr>
</tbody>
</table>

ABBREVIATIONS: 2L, second line; CI, confidence interval; CML-CP, chronic myeloid leukemia in chronic phase; ELTS, EUTOS long-term survival; MMR, major molecular response; OS, overall survival; ref, reference category.

[1] 12 Patients were not tested for molecular response in 3L and were therefore not included in the analysis.
Results

Baseline characteristics of patients with T315I mutation

• Of the 17 patients harboring the T315I mutation, median age [interquartile range] at diagnosis was 52 [39–59] years; 24% of patients were female

• Risk scores at CML-CP diagnosis:
  • Sokal: 6% low, 12% intermediate, 65% high, 18% unknown
  • ELTS: 18% low, 24% intermediate, 41% high, 18% unknown

• The T315I mutation was identified in 2L (N=6, 35%), 3L (N=5, 29%), 4L (N=4, 24%), and 5L (N=2, 12%)
Results

Treatment patterns and clinical outcomes of patients with T315I mutation

- 41% of patients with T315I mutation had ≥5 lines of therapy (Figure 3)
  - Mean duration of line of therapy identified as the T315I line of interest was 18.5 months
  - Ponatinib was the most frequently used TKI (N=10, 59%) following identification of the mutation, followed by dasatinib (N=3, 18%), allogeneic stem cell transplantation (N=2, 12%), and asciminib (N=2, 12%)
  - In the last line of therapy, the most common treatments were ponatinib (N=7, 41%) and asciminib (N=3, 18%) through compassionate use or clinical trial
  - 65% of patients (N=11) discontinued treatment, mainly due to AEs/intolerance [N=9, 82%] and resistance [N=4, 36%])
  - Thrombocytopenia (18%) was the most common AE
  - The median (range) OS since T315I identification was 5 (3–10) years
41% of patients with T315I mutation had ≥5 lines of therapy (Figure 3).

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Thrombocytopenia (18%) was the most common AE.

The median (range) OS since T315I identification was 5 (3–10) years.
Limitations

- Because of the retrospective and nonrandomized study design, the results may have been influenced by uncontrolled confounding; reporting, selection, or recall bias; or non-random missing data (e.g., data on comorbidities and AEs not recorded in patient charts)
  - Selection bias was minimized by including data from eligible patients (currently living or deceased) up until the date of last contact or date of death
- The three clinical sites included in the study may not be representative of all such sites in France or in other countries with different reimbursement or practice patterns
Conclusions

- In this chart review, CML-CP patients with 3L+ received up to 7 lines of therapy, and those harboring the T315I mutation received up to 6 lines.

- In both 3L+ and T315I cohorts, patients switched between first-, second-, and third-generation TKIs.

- The most common reasons for treatment discontinuation in 1L, 2L, and 3L—including in patients with T315I mutation—were intolerance and resistance; In 2L and 3L, we observed a numerically higher proportion of patients discontinued treatment due to intolerance than resistance.

- Earlier lines of treatment lasted <2 years in CML-CP patients in 3L and <1 year in patients harboring the T315I mutation, suggesting a need for novel therapeutics with improved safety and efficacy profiles earlier in the treatment course.

- CML-CP patients who discontinued treatment due to resistance/lack of efficacy in 2L exhibited worse OS/PFS than patients who discontinued for other reasons.
Acknowledgments and References

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References


