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First-line tyrosine kinase inhibitor response in chronic myeloid leukemia: A retrospective study from Iraqi Kurdistan

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Abstract:

BACKGROUND: Chronic myeloid leukemia (CML) is a malignant blood disorder characterized by BCR-ABL1 transcript production, which results in constitutive tyrosine kinase activity. The use of tyrosine kinase inhibitors (TKIs), notably imatinib, has greatly improved patient outcomes. However, treatment resistance, intolerance, and adherence remain significant concerns.

OBJECTIVES: This study aimed to assess the hematological and molecular responses of patients with CML in Iraqi Kurdistan treated with first-line imatinib while also identifying factors related to resistance, intolerance, and adherence.

MATERIALS AND METHODS: This retrospective descriptive study included 161 CML patients diagnosed since 2010 across three major hematology/oncology centers in Duhok, Erbil, and Sulaymaniyah. Data were collected from patient records, including demographics, clinical presentation, laboratory findings, BCR-ABL1 transcript levels, comorbidities, treatment regimens, and follow-up response at 3, 6, 12, and 15 months. Data analyses were carried out using SPSS version 26, with significance set at $P < 0.05$.

RESULTS: Of 161 patients, 140 (86.9%; 95% confidence interval [CI]: 81.1–91.3) achieved complete hematological response at 3 months. At 15 months, 93 patients (57.8%; 95% CI: 49.7–65.6) attained optimal molecular response, including 40 (24.8%) with major molecular response, 37 (23.0%) with deep molecular response, and 16 (9.9%) with complete molecular response. Resistance occurred in 46 patients (28.6%), significantly associated with delayed diagnosis ($P = 0.021$). Imatinib intolerance was observed in 13 (8.1%), poor adherence in 7 (4.3%), and T315I mutation in 3 (1.9%).

CONCLUSION: While imatinib remains an effective first-line treatment, resistance and adherence issues necessitate early molecular monitoring and consideration of second-generation TKIs. Future research should focus on genetic profiling, treatment modifications, and socioeconomic interventions to enhance CML management in Iraqi Kurdistan.

Keywords:

Chronic myeloid leukemia, imatinib, molecular response, treatment resistance, tyrosine kinase inhibitors

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Introduction

The clonal spread of malignant precursor cells with the Philadelphia (Ph) chromosome is a hallmark of chronic myeloid leukemia (CML). This abnormality is brought on by a mutual translocation between chromosomes 9 and 22, which results in the BCR-ABL1 fusion gene. By producing a constitutively active tyrosine kinase that encourages uncontrolled cell proliferation, this fusion gene mainly impacts the granulocytic lineage in the bone marrow. The primary pathogenic driver in CML, the BCR-ABL1 gene, is the primary target of tyrosine kinase inhibitors (TKIs).[1,2]

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The development of TKIs has fundamentally altered the treatment of CML, one of the most successful types of targeted cancer therapy. Imatinib, the first TKI developed to precisely target the BCR-ABL1 kinase, revolutionized the treatment of CML by significantly improving survival and turning the disease into a chronic condition that the majority of patients could manage after it was approved for clinical use.[3,4] Second- and third-generation TKIs, such as dasatinib, nilotinib, bosutinib, and ponatinib, were later developed to address the cases of imatinib resistance or intolerance and improve therapeutic results in CML patients.[5,6]

In order to improve long-term results, stop progression, and optimize treatment, it is essential to evaluate responsiveness to TKI therapy. The three main categories of response criteria are molecular, cytogenetic, and hematologic responses. Blood count normalization is the first indicator of TKI effectiveness, whereas cytogenetic reaction assesses the decrease or eradication of Ph chromosome-positive cells. The most sensitive metric, molecular response, uses real-time quantitative polymerase chain reaction (qPCR) to assess BCR-ABL1 transcript levels, enabling accurate monitoring of minimal residual disease.[7,8]

The prognosis in CML is significantly influenced by the speed and severity of the response. Early molecular response at 3 months, often indicated by a BCR-ABL1 level of ≤10% on the International Scale (IS), is significantly associated with good long-term outcomes, even if failure to meet response milestones may suggest a need for therapy modification. Hematologists can utilize this structured approach to guide medication adjustments and enhance patient care by combining clinical and molecular criteria.[9,10]

There are still issues, particularly in regard to intolerance and treatment resistance to TKI. The failure to react initially is known as primary resistance, but the lack of reaction following early effectiveness is known as secondary resistance. BCR-ABL1 kinase domain mutations are frequently linked to secondary resistance.[11] Molecular mutation testing helps refine treatment, especially when response is inadequate, because second- and third-generation TKIs are designed to target specific resistant mutations.[12]

While international trials have established the efficacy of imatinib and subsequent TKIs, treatment outcomes can vary by region due to differences in diagnostic timing, socioeconomic status, healthcare infrastructure, and access to molecular monitoring. In Iraqi Kurdistan, challenges such as delayed diagnosis, limited access to routine qPCR monitoring, and economic barriers to switching therapy may impact patient outcomes.[13] To date, there is a paucity of region-specific data on CML treatment response, creating uncertainty about how closely international benchmarks apply to this population. Local data are therefore essential to identify gaps in care, adapt therapeutic strategies, and guide policy decisions for optimizing CML management in this resource-constrained setting. The present study aimed to evaluate hematological and molecular responses to first-line imatinib therapy in CML patients in Iraqi Kurdistan.

Materials and Methods

This retrospective descriptive study was conducted to assess responses to first-line TKI therapy in patients with CML. Patients were identified from the three main hematology/oncology referral centers in the Iraqi Kurdistan Region – Duhok, Erbil, and Sulaymaniyah – between January 2010 and December 2023.

Inclusion and exclusion criteria

Eligible patients were adults (≥18 years) diagnosed with CML in chronic phase, confirmed by the presence of the BCR-ABL1 fusion gene, who received imatinib as first-line therapy. Patients were excluded if they (1) presented with accelerated or blast phase at diagnosis, (2) had received any prior TKI therapy before imatinib initiation, or (3) had incomplete medical records that precluded assessment of treatment response.

Sample size and handling of missing data

As this was a retrospective cohort, all eligible patients available in the study period were included (n = 161). Therefore, no formal sample size or power calculation was performed.

Patients with missing follow-up data at a specific time point were excluded from that particular analysis but retained in other available analyses. Missing data were not imputed.

Data collection

Demographic variables (age, sex, and residence), clinical features at presentation (symptoms, splenomegaly, and blood counts), laboratory findings (hemoglobin, white blood cell, platelets, and peripheral blasts), BCR-ABL1 transcript levels, comorbidities, treatment details (imatinib dose, modifications, and discontinuation), and follow-up responses were extracted from hospital records. Response assessments included hematological and molecular responses. Cytogenetic outcomes were not consistently available and were therefore not included in the final analysis.

Baseline prognostic assessment was performed using the Sokal score,[14] which incorporates age, spleen size, platelet count, and peripheral blood blast percentage. Patients were stratified into low-, intermediate-, and high-risk groups according to standard definitions. The relationship between Sokal risk category and treatment response (hematological and molecular) was analyzed.

Outcome definitions

- Complete hematological response (CHR): normalization of peripheral blood counts and disappearance of clinical signs (e.g., splenomegaly)
- Optimal molecular response (OMR): BCR-ABL1 transcript levels ≤0.1% on the IS by 12–15 months, which included major molecular response (MMR), deep molecular response (DMR), and complete molecular response (CMR)
- Treatment failure: Resistance, intolerance, or poor adherence leading to discontinuation or suboptimal response.

Statistical analysis

Data analysis was performed using SPSS version 26 (IBM Corp., Armonk, NY, USA). Continuous variables were assessed for normality and summarized as mean ± standard deviation or median. Categorical variables were presented as frequencies and percentages with 95% confidence intervals (CIs). Adjustments for multiple testing were applied, given the exploratory nature of the study.

Ethical approval

The study protocol was reviewed and approved by the Scientific and Ethical Committee of the Kurdistan Board for Medical Specialization (Ref. No.: 901, dated April 30, 2023). Written informed consent was obtained from all patients at initial registration.

Results

A total of 161 patients with CML in chronic phase were included. The cohort consisted of 75 males and 86 females (M:F ratio = 1:1.15), with a median age of 47 years (range: 20–84). The most common presenting symptom was fatigue (47.8%), followed by abdominal pain (29.8%) [Table 1]. Notably, 21.1% of patients were diagnosed incidentally during evaluation for unrelated conditions.

Table 1: Presenting clinical features among enrolled patients

Main clinical feature	Number of patients (%)
Incidental	34 (21.12)
Fatigue	77 (47.83)
Abdominal pain	48 (29.81)
Night sweat	32 (19.88)
Weight loss	28 (17.39)
Fever	20 (12.42)
Loss of appetite	20 (12.42)
Headache	12 (7.45)
Bleeding	9 (5.59)
Joint pain	8 (4.97)
Early satiety	5 (3.11)
Itching	5 (3.11)
Back pain	4 (2.48)
Visual disturbance	4 (2.48)
Dyspnea	3 (1.86)
Diarrhea	2 (1.24)
Splenomegaly	110 (68.32)
Pallor	14 (8.70)
Sokal score	
Low risk	129 (80.1)
Intermediate risk	25 (15.5)
High risk	7 (4.4)

Hematological response

At 3 months, 140 patients (86.9%; 95% CI: 80.9–91.3) achieved CHR. CHR rates did not differ significantly by sex (male 85.3% vs. female 88.4%, $P = 0.59$) or residence (urban 88.1% vs. rural 84.2%, $P = 0.51$).

Molecular response

By 15 months, 93 patients (57.8%; 95% CI: 50.0–65.6) achieved an OMR. Among these, 40 (24.8%; 95% CI: 18.8–32.1) achieved MMR, 37 (23.0%; 95% CI: 17.2–30.1) DMR, and 16 (9.9%; 95% CI: 6.2–15.5) CMR. Patients with delayed diagnosis (>6 months from symptom onset) had significantly lower OMR rates than those diagnosed earlier (48.0% vs. 65.9%, $P = 0.021$).

Treatment resistance and failure

Resistance occurred in 46 patients (28.6%; 95% CI: 22.0–36.1). Among these, 3 patients (1.9%) carried the T315I mutation. Resistance was significantly associated with delayed diagnosis ($P = 0.021$) and poor adherence ($P < 0.01$). Thirteen patients (8.1%) discontinued imatinib due to intolerance, mainly cytopenias, musculoskeletal pain, or gastrointestinal symptoms. Seven patients (4.3%) exhibited poor adherence, often due to financial constraints or pill burden. Two patients (1.2%) experienced drug–drug interactions leading to treatment interruption.

At diagnosis, the distribution of Sokal risk categories was as follows: low risk in 129 patients (80.1%), intermediate risk in 25 patients (15.5%), and high risk in 7 patients (4.4%). Hematological response at 3 months was achieved in 93.0% of low-risk, 76.0% of intermediate-risk, and 14.3% of high-risk patients ($P < 0.001$). Similarly, OMR at 15 months was significantly higher in the low- and intermediate-risk groups compared to high-risk patients (85.4% vs. 14.3%, $P < 0.01$). Resistance was more common among high-risk patients (85.7%) compared with intermediate (56.0%) and low-risk groups (20.9%) ($P = 0.01$).

Flowchart of patient outcomes

A flowchart summarizing treatment response and failure pathways is provided in Figure 1. The figure provides a detailed stepwise depiction of patient inclusion, treatment response at each time point, and reasons for treatment discontinuation.

Discussion

The introduction of TKIs has transformed the prognosis of CML, achieving long-term survival rates that were previously unattainable.[3,4] In this retrospective cohort from Iraqi Kurdistan, the majority of patients achieved CHR by 3 months, consistent with international benchmarks.[2,9] However, only 57.8% reached OMR at 15 months, which is lower than some Western cohorts reporting rates above 64%. This discrepancy highlights the importance of regional context in evaluating treatment outcomes.[2,15]

Compared with trials such as IRIS and DASISION, which demonstrated high response rates with imatinib and dasatinib, respectively,[9,16] our results suggest that a considerable proportion of patients in Kurdistan face barriers to achieving timely molecular milestones. Several local healthcare factors likely contribute. First, delayed diagnosis was frequent, with over 20% of patients diagnosed incidentally, suggesting limited awareness and access to early hematologic testing. Second, routine qPCR monitoring is not universally available in public hospitals, leading to delayed detection of suboptimal responders. Third, access to second-generation TKIs is restricted by cost and supply limitations, leaving patients with resistance – particularly those harboring mutations such as T315I – with few therapeutic alternatives.[11] These realities underscore the need for tailored strategies that extend beyond drug efficacy alone.[17,18]

The resistance rate in this study (28.6%) was higher than the 15%–20% typically reported in Western cohorts.[11] In addition to biological factors, such as undetected mutations beyond T315I,[12] healthcare system challenges likely amplify this problem. Limited access to plasma drug monitoring, financial constraints affecting adherence, and variability in drug supply chains can reduce treatment efficacy. Similarly, intolerance and poor adherence, observed in 8.1% and 4.3% of patients, respectively, mirror findings from regional studies in Turkey and Asia where socioeconomic and educational barriers strongly influence compliance.[19,20] Addressing these challenges will require interventions such as patient education, improved side effect management, and policy measures to subsidize both medications and molecular testing.[21,22]

Our findings reinforce the prognostic value of the Sokal score in predicting treatment outcomes with first-line imatinib. Patients in the low- and intermediate-risk categories achieved higher rates of both hematological

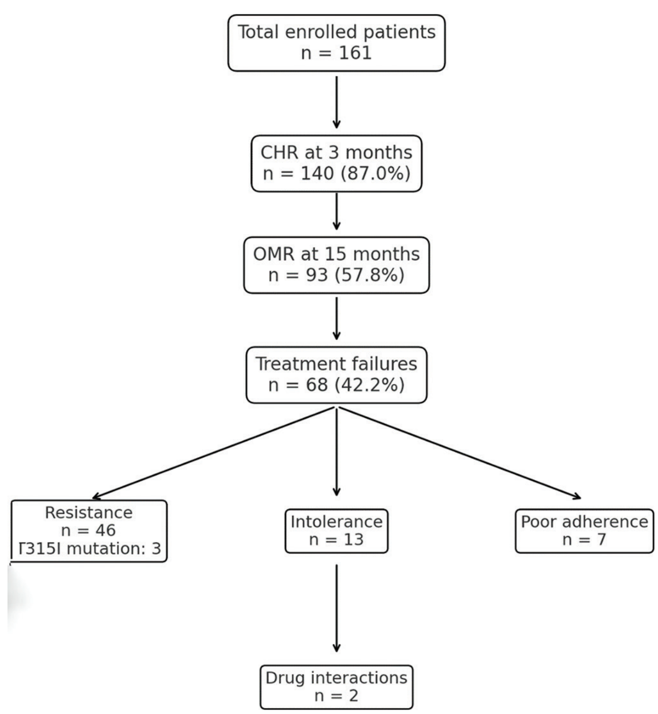

Figure 1: Flowchart of patient outcomes following first-line imatinib therapy. Of 161 enrolled patients, 140 (86.9%) achieved complete hematological response at 3 months. At 15 months, 93 patients (57.8%) achieved an optimal molecular response, including major, deep, and complete molecular responses. Treatment failures occurred in 68 patients (42.2%), most commonly due to resistance (*n* = 46, including 3 with T315I mutation), intolerance (*n* = 13), poor adherence (*n* = 7), and drug interactions (*n* = 2). CHR = Complete hematological response, OMR = Optimal molecular response

and molecular responses compared with high-risk patients, who were more likely to develop resistance. This is consistent with previous international reports that demonstrated poorer outcomes in high-risk Sokal groups, even in the era of TKIs.[14]

In the context of Iraqi Kurdistan, where delayed diagnosis and limited access to molecular monitoring are already major challenges, the presence of a high Sokal score further stratifies patients into a group with particularly poor prognosis. This highlights the importance of incorporating Sokal risk assessment into routine practice, not only to predict treatment outcomes but also to guide decisions on early switching to second-generation TKIs when feasible.

This study has several limitations. The retrospective design introduces potential information bias, as data collection relied on medical records rather than standardized follow-up protocols. Missing molecular monitoring data at certain time points reduced analytic precision. Furthermore, because all cases were recruited from tertiary referral centers, selection bias is possible, as these centers may receive patients with more advanced disease compared to the general population. Cytogenetic response was not systematically available and therefore excluded from the analysis, which limits comparison with other cohorts where cytogenetic milestones remain important.[7,8]

Despite these limitations, the findings provide valuable insights into real-world CML management in Iraqi Kurdistan. Strengthening laboratory infrastructure for routine qPCR monitoring, ensuring the availability of second-generation TKIs, and integrating patient education programs could improve outcomes. These measures would align regional practice more closely with European LeukemiaNet recommendations.[7,10] At the health policy level, our results highlight the importance of resource allocation toward molecular monitoring and subsidized drug programs to bridge the gap between international guidelines and local practice.

Conclusion

Most CML patients in Iraqi Kurdistan achieve early hematological response with imatinib, but OMR remains suboptimal and resistance is common. Early diagnosis, adherence monitoring, and routine molecular testing are essential for clinicians, while policymakers should prioritize access to qPCR facilities and second-generation TKIs. These measures are critical to align local practice with international standards and improve patient outcomes.

Authors' contributions

Shirzad Yousif collected samples and performed a large part of the work. Zeki Ali Mohamed analyzed data and wrote the manuscript. All authors declare that all data were generated in-house and that no paper mill was used.

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Conflicts of interest

There are no conflicts of interest.

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