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Safety and efficacy of bosutinib in chronic myeloid leukemia patients after failure of previous tyrosine kinase inhibitors: A prospective study from Basrah, Iraq

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Abstract:

BACKGROUND: Tyrosine kinase inhibitors (TKIs) have significantly improved the prognosis of chronic myeloid leukemia (CML). However, resistance or intolerance to first- and second-generation TKIs remains a clinical challenge.

OBJECTIVE: The objective of this study was to evaluate the safety and efficacy of bosutinib in CML patients following failure of previous TKIs (imatinib and/or nilotinib).

MATERIALS AND METHODS: In this prospective cohort study, 35 CML patients in chronic or accelerated phase were treated with bosutinib at the Basrah Center of Hematology between August 2021 and January 2024. Patients were followed for 1 year and evaluated for hematologic and molecular responses, as well as treatment-related adverse events (AEs).

RESULTS: The majority were female (60%), with a mean age of 45.6 years. Bosutinib was primarily indicated for molecular response failure (60%). Complete hematologic response was achieved in 74% of patients, and major molecular response was observed in 40.7% at 12 months. The most common AEs were gastrointestinal (e.g., diarrhea in 80% and nausea in 51%). Most AEs were Grade 1–11. Severe hematologic toxicities were rare.

CONCLUSION: Bosutinib demonstrated a favorable safety and efficacy profile in CML patients with prior TKI failure. It remains a viable treatment option in resource-constrained settings where mutation analysis may be unavailable.

Keywords:

Adverse events, bosutinib, chronic myeloid leukemia, Iraq, molecular response, tyrosine kinase inhibitor resistance

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Introduction

Chronic myeloid leukemia (CML) is a clonal myeloproliferative disorder driven by the presence of the Philadelphia chromosome, resulting from a reciprocal translocation t (9;22) (q34;q11). This cytogenetic abnormality gives rise to the *BCR-ABL1* fusion gene, which encodes a constitutively active tyrosine kinase that promotes uncontrolled myeloid proliferation and survival. CML accounts for approximately 7%–15% of adult leukemias, with the majority of cases diagnosed in the chronic phase. Without effective treatment, CML inevitably progresses to the accelerated phase (AP) or blast phase (BP), which are associated with poor outcomes and limited therapeutic options.[1]

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The introduction of tyrosine kinase inhibitors (TKIs) revolutionized the treatment landscape of CML. Imatinib, the first-generation TKI, was the prototype-targeted therapy and dramatically improved long-term survival, transforming CML from a life-threatening disease into a manageable chronic condition. Subsequently, second-generation TKIs such as dasatinib, nilotinib, and bosutinib were developed to overcome resistance and improve efficacy. These agents have further reduced disease-related mortality, and patients with Philadelphia chromosome-positive (Ph+) CML can now expect near-normal life expectancy with appropriate treatment.[2]

Despite these advances, therapeutic challenges remain. A significant subset of patients experiences primary or secondary resistance or intolerance to TKI therapy. Mechanisms of resistance include point mutations in the *BCR-ABL1* kinase domain, pharmacokinetic variability, and clonal evolution. Adverse events (AEs) such as cardiovascular complications, hepatotoxicity, or hematological toxicities may also necessitate treatment discontinuation. In such cases, switching to an alternative TKI is essential to maintain disease control and prevent progression.[3]

Bosutinib is an orally available dual Src/ABL kinase inhibitor approved in 2012 for patients with Ph+ CML resistant or intolerant to prior TKI therapy. Unlike other second-generation TKIs, bosutinib exhibits minimal activity against platelet-derived growth factor receptor and c-KIT, which are thought to contribute to off-target toxicities. It has demonstrated activity against most imatinib-resistant *BCR-ABL1* mutations, with the exception of T315I and V299L, and has shown efficacy in chronic, accelerated, and BPs of CML. Clinical trials and real-world data suggest that bosutinib provides durable hematologic and molecular responses, with a manageable toxicity profile primarily characterized by gastrointestinal side effects.[4]

Treatment response in CML is primarily monitored by quantitative polymerase chain reaction of *BCR-ABL1* transcripts, standardized to the International Scale. According to European Leukemia Network recommendations, achievement of molecular milestones at 3, 6, and 12 months is a strong predictor of long-term outcome. Responses are categorized as optimal, warning, or failure, providing a framework for timely therapeutic adjustments. Patients who fail to achieve molecular milestones benefit from early intervention, including switching to an alternative TKI such as bosutinib.[5]

Although data from international clinical trials are well established, real-world evidence from Middle Eastern populations remains scarce. Variability in healthcare infrastructure, treatment accessibility, and patient characteristics may influence therapeutic outcomes. Therefore, evaluating the safety and efficacy of bosutinib in local settings is important to complement global data and guide regional treatment practices. This study reports the experience of the Basrah Center of Hematology, Iraq, in using bosutinib as a second- or third-line treatment in patients with CML who experienced treatment failure or intolerance with prior TKIs.

Patients and Methods

Study design and setting

This was a prospective cohort study conducted at the Basrah Center of Hematology between August 2021 and January 2024.

Participants

Inclusion criteria

Adults (≥18 years) with Ph+ CML in chronic or AP, who had failed, or who were intolerant to imatinib or nilotinib were included in the study.

Exclusion criteria

Organ failure, pregnancy/lactation, or noncompliance with follow-up was excluded from the study.

Treatment protocol

Bosutinib (Bosulif; Pfizer) was initiated at 300 mg/day and escalated to 500 mg/day per clinical tolerance. Response evaluations and laboratory testing were performed quarterly.

Endpoints

- Primary: Complete hematologic response (CHR) and major molecular response (MMR) at 6 and 12 months
- Secondary: AEs graded per CTCAE v5.0.

Ethical approval

This study was reviewed and approved by the Institutional Review Board/Ethics Committee of the Arab Board of Health Specializations. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee.

Data analysis

Statistical analysis was done using software version 25.0 (SPSS, Chicago, Illinois, USA). $P < 0.05$ was considered statistically significant.

Results

The study involved 35 patients diagnosed with CML, with 10 patients receiving imatinib and 25 receiving imatinib and nilotinib.

Table 1 represents the details of demographic characteristics and indications of bosutinib therapy.

The patients' mean age at the time of the study was 45.6 years, with a mean age at diagnosis of CML 39.94 years and a mean duration since diagnosis of 68 months.

Most participants were female (60%), and the majority had a normal body mass index (57.1%). Regarding medical conditions, 68% of the patients did not have any concurrent medical conditions, while hypertension and diabetes mellitus were present in 17% and 14% of patients, respectively.

Bosutinib was primarily prescribed due to failure of molecular response (60%), followed by indications such as acceleration (20%), hematological failure (11.4%), and intolerance to previous TKIs (8.6%).

The baseline patient and disease characteristics were evaluated in the current study [Table 2]. Among the patients, 91.4% had an Eastern Cooperative Oncology Group performance status of 0, indicating that they were fully active. The Sokal score distribution at the time of diagnosis showed that 34.3% had a low risk, 45.7% had an intermediate risk, and 20% had a high risk. Similarly, the European Treatment and Outcome Study (EOTUS) score (also at time of diagnosis) indicated that 62.9% had a low risk, while 37.1% had a high risk.

Regarding treatment discontinuation, 8% of patients stopped treatment as a result of death from causes unrelated to either the bosutinib therapy or the CML disease and 5.7% due to side effects.

Hematological parameters revealed varying averages among the groups, with mean white blood cell counts ($\times 10^9$/l) of 31.1 ± 77.9, mean platelet counts ($\times 10^9$/l) of 201 ± 98.8, and mean hemoglobin levels (g/dl) of 12.2 ± 1.8. These findings highlight the heterogeneity in baseline characteristics among patients receiving imatinib or receiving imatinib and nilotinib. Such variations may influence treatment outcomes and underscore the importance of individualized therapeutic approaches in managing CML.

The comparison [Table 3] evaluates the efficacy of bosutinib as a second- or third-line treatment in two

Table 1: The baseline patient demographic data and indication of bosutinib (*n*=35)

Characteristic	Imatinib (*n*=10), *n* (%)	Imatinib and nilotinib (*n*=25), *n* (%)	Total
Age at time of the study (years)			
Mean±SD	42±16.4	47±12.5	45.6±13.6
Median	43	47	45
Range	19-67	21-76	19-76
Age at diagnosis of CML (years)			
Mean±SD	39.6±15.5	40±11.4	39.94±12.5
Median	42	40	41
Range	18-66	18-64	18-66
Duration from diagnosis (months)			
Mean±SD	27.1±36.6	84±49.6	68±52.7
Median	9	88	73
Range	6–123	9–204	6–204
Sex			
Male	5 (50)	9 (36)	14 (40)
Female	5 (50)	16 (64)	21 (60)
BMI			
Normal	5 (50)	15 (60)	20 (57.1)
Overweight	2 (20)	5 (20)	7 (20)
Obese I	3 (30)	2 (8)	5 (14.3)
Obese II	0	2 (8)	2 (5.7)
Obese III	0	1 (4)	1 (2.9)
Medical conditions			
None	8 (80)	16 (64)	24 (68)
Hypertension	1 (10)	5 (20)	6 (17)
Diabetes mellitus	1 (10)	4 (16)	5 (14)
Indication of bosutinib			
Acceleration	1 (10)	6 (17.1)	7 (20)
Failure of molecular response	5 (50)	16 (64)	21 (60)
Hematological failure	3 (30)	1 (4)	4 (11.4)
Intolerance	1 (10)	2 (8)	3 (8.6)

BMI=Body mass index, SD=Standard deviation, CML=Chronic myeloid leukemia

patient cohorts: those treated solely with imatinib and those receiving imatinib and nilotinib.

Across all evaluated patients, both the groups demonstrated a total CHR rate of 74%, slightly edging out the imatinib-only group's rate of 70%. Similarly, among patients lacking a baseline CHR, CHR rates were closely aligned, with 65.4% observed in the imatinib and nilotinib group and 66.6% in the imatinib-only group.

Table 2: Baseline patient and disease characteristics

Characteristics	Imatinib (*n*=10), *n* (%)	Imatinib and nilotinib (*n*=25), *n* (%)	Total, *n* (%)
ECOG performance			
0	9 (90)	23 (92)	32 (91.4)
1	1 (10)	1 (4)	2 (5.7)
2	0	1 (4)	1 (2.9)
Sokal score			
Low	3 (30)	9 (36)	12 (34.3)
Intermediate	4 (40)	12 (48)	16 (45.7)
High	3 (30)	4 (16)	7 (20)
EOTUS score			
Low	5 (50)	17 (68)	22 (62.9)
High	5 (50)	8 (32)	13 (37.1)
Discontinuation from the treatment			
Death	0	3 (12)	3 (8)
Side effect	1 (10)	1 (4)	2 (5.7)
White blood cell count $\times 10^9$/L			
Mean±SD	56±125.8	21±47.9	31.1±77.9
Median	9.8	7.2	8
Range	5.4–412	4.4–223	4.4–412
Platelet count $\times 10^9$/L			
Mean±SD	199±128	202±87	201±98.8
Median	167	192	188
Range	50–453	74–426	50–453
Hemoglobin level (g/dL)			
Mean±SD	12.5±2.2	12±1.7	12.2±1.8
Median	12.9	12.1	12.5
Range	8.7–15.5	7.8–15.6	7.8–15.6

SD=Standard deviation

Table 3: Best cumulative response to bosutinib

	Imatinib	Imatinib and nilotinib	Total	*P*
Hematologic response*				0.9
Evaluable patients	10	25	35	
Complete response	7 (70)	19 (76)	26 (74)	
Hematologic response among patients with no baseline CHR				1
Evaluable patients	9	17	26	
Complete response	6 (66.6)	11 (64.7)	17 (65.4)	
Molecular response				
Evaluable patients	9	18	27	
Response after 6 months				
Optimal	4 (44.4)	9 (50)	13 (48.1)	0.9
Warning	2 (22.2)	4 (22.2)	6 (22.2)	
Failure	3 (33.3)	5 (27.7)	8 (29.6)	
Response after 12 months				
Optimal (MMR)**	3 (33.3)	8 (44.4)	11 (40.7)	0.7
Optimal (CMR)***	2 (22.2)	4 (22.2)	6 (22.2)	
Warning	2 (22.2)	2 (11.1)	4 (14.8)	
Failure	4 (44.4)	8 (44.4)	12 (44.4)	

*Evaluable patients with CHR at baseline qualified for further evaluation, they were deemed responders if they sustained their CHR for two consecutive postbaseline assessments 4 weeks apart, **MMR, *BCR-ABL1* <0.1% IS (qPCR), ***CMR, *BCR-ABL1/ABL1* ratio levels undetectable by (qPCR) with assay sensitivity at least 4.5 logs below baseline IS (MR4.5 <0.0032%). CHR=Complete hematologic response, CMR=Complete molecular response, MMR=Major molecular response, qPCR=Quantitative polymerase chain reaction, IS=International Scale

Molecular response rates after 6 and 12 months were also analyzed. After 6 months, complete responses were seen in 44.4% of patients in the imatinib group and 50% in the imatinib and nilotinib group. After 12 months, similar trends persisted, with 33.3% complete responses in the imatinib group compared to 44.4% in the imatinib and nilotinib group. However, warning and failure rates showed no significant difference between the two groups at both time points. Overall, while there were slight variations in response rates between the two treatment groups, statistical analysis (*P* values) indicated no significant difference.

Table 4 represents the proportion of patients experiencing each AE at different severity levels. Most AEs were primarily grading I–II, with diarrhea being the most common, affecting 80% of patients to some extent, followed by nausea (51%) and vomiting (48%). Less common AEs, occurring in fewer than 10% of patients, included elevated alanine aminotransferase, elevated aspartate aminotransferase, elevated alkaline phosphatase, elevated creatinine, and hyperglycemia, all at Grade I–II. Anemia was observed in 25.7% of patients, with 22.8% experiencing Grade I–II symptoms and 2.8% experiencing Grade III–IV symptoms. This finding indicates that anemia is relatively common but usually mild. Thrombocytopenia affected 22.8% of patients, with 17% experiencing Grade I–II symptoms and 5.7% experiencing severe symptoms (Grade III–IV). Leukopenia was less common, occurring in 5.7% of patients, with equal distribution between Grade I–II and Grade III–IV severities.

Table 4: Treatment-related adverse events

Adverse event	Grade I–II, *n* (%)	Grade III–IV, *n* (%)	Total, *n* (%)
Diarrhea	24 (68.6)	4 (11.4)	28 (80)
Nausea	14 (40)	4 (11.4)	18 (51)
Vomiting	15 (42.9)	2 (5.7)	17 (48)
Abdominal pain	16 (45.7)	0	16 (45.7)
Fatigue	13 (37.1)	0	13 (37.1)
Loss of appetite	8 (22.9)	0	8 (22.9)
Rash	5 (14.3)	0	5 (14.3)
Fever	6 (17.1)	0	6 (17.1)
Arthralgia	9 (25.7)	0	9 (25.7)
Myalgia	8 (22.9)	0	8 (22.9)
Headache	6 (17.1)	0	6 (17.1)
TSB	1 (2.8)	0	1 (2.8)
Elevated ALT	2 (5.7)	0	2 (5.7)
Elevated AST	1 (2.8)	0	1 (2.8)
Elevated alkaline phosphatase	1 (2.8)	0	1 (2.8)
Elevated creatinine	1 (2.8)	0	1 (2.8)
Hyperglycemia	1 (2.8)	0	1 (2.8)
Anemia	8 (22.8)	1 (2.8)	9 (25.7)
Thrombocytopenia	6 (17)	2 (5.7)	8 (22.8)
Leukopenia	1 (2.8)	1 (2.8)	2 (5.7)

TSB=Total serum bilirubin, ALT=Alanine aminotransferase, AST=Aspartate aminotransferase

Severe AEs Grade III–IV (also gastrointestinal symptoms) were (5%–10%) across all the patients.

Table 5 illustrates the treatment response based on various factors in patients receiving bosutinib. Optimal response rates varied across different parameters, with notable differences observed in age, duration from diagnosis, and previous treatment received. Patients aged <45 years showed slightly higher optimal response rates compared to those aged >45 years, although this difference was not statistically significant ($P = 0.29$). Similarly, duration from diagnosis <1 year exhibited lower optimal response rates compared to those with 1–7 years or >7 years, with no significant differences detected ($P = 0.38$). Notably, patients previously treated with imatinib and nilotinib demonstrated higher optimal response rates compared to those treated solely with imatinib ($P = 0.7$). While variations in response rates were observed across different parameters, no statistically significant associations were found.

Discussion

Bosutinib is a second-generation *BCR-ABL1* TKI initially approved in 2012 for the treatment of chronic, accelerated, and blast-phase CML in patients previously treated with one or more TKIs and for whom imatinib or nilotinib were deemed unsuitable options.[3]

The present study aimed to evaluate the safety and efficacy of bosutinib in a cohort of patients with CML who had failed previous TKI therapies. The findings provide important insights into the therapeutic potential of bosutinib as a second- or subsequent-line treatment option.

A total of 35 patients were analyzed, with approximately one-third receiving imatinib alone and the remainder treated with both imatinib and nilotinib. The demographic characteristics of the cohort were consistent with other local studies, with a mean age of 45.6 years, closely aligning with previously reported data (mean age: 47.3 years) and an age range of 18–77 years.[6] Most patients were female and had a normal body mass index, while a smaller proportion were classified as overweight or obese. Comorbidities were relatively infrequent, with hypertension and diabetes being the most commonly reported.

Bosutinib was most commonly initiated due to a failure to achieve molecular response, followed by disease progression, hematologic failure, and intolerance to prior TKIs. Risk stratification using the Sokal score classified approximately one-third of patients as low risk, nearly half as intermediate risk, and the remainder as high risk.

Table 5: Factors influencing treatment response in bosutinib therapy

Variables	Optimal response (*n*)*	Warning response (*n*)*	Failure response (*n*)	*P*
Age				
<45	6	3	4	0.29
>45	5	1	8	
Age at diagnosis				
<45	8	4	7	0.39
>45	3	0	5	
Duration from diagnosis (years)				
<1	2	3	3	0.38
1–7	5	0	4	
>7	4	1	5	
Sex				
Male	4	3	5	0.5
Female	7	1	7	
BMI				
Normal	6	3	7	0.7
Overweight	2	0	3	
Obese I	1	1	2	
Obese II	2	0	0	
Indication of bosutinib				
Acceleration	0	0	2	0.62
Failure of molecular response	9	3	9	
Chronic hematological failure	1	0	1	
Intolerance	1	1	0	
SOKAL score				
Low	4	2	2	0.7
Intermediate	5	1	7	
High	2	1	3	
EOTUS score				
Low	7	3	6	0.6
High	4	1	6	
Previous treatment				
Imatinib	3	2	4	0.7
Imatinib and nilotinib	8	2	8	
White blood cell count				
Normal	11	4	8	0.21
Leukocytosis	0	0	3	
Leukopenia	0	0	1	
Platelet				
Normal	8	2	7	0.7
Thrombocytopenia	3	2	4	
Thrombocytosis	0	0	1	
Hemoglobin				
Normal	7	3	9	0.8
Anemia	4	1	4	

*Response to TKIs can be classified as.[13] Optimal → treatment continues with survival expected to be normal or near-normal. Failure → switch to another TKI or consider allo-SCT. Warning → an intermediate zone requiring closer monitoring and possible adjustment of therapy. BMI=Body mass index, TKIs=Tyrosine kinase inhibitors

In contrast, the European Treatment and Outcome Study (EUTOS) score identified the majority of patients as low risk, with the rest categorized as high risk.

Efficacy outcomes observed in our study were encouraging. The overall CHR rate was 74%, suggesting a robust treatment effect, comparable to earlier findings in which 84% of evaluable patients achieved CHR.[7,8] Verified CHR was 73% after a median follow-up of 28.5 months.[9,10]

Molecular response outcomes were also favorable. At 6 and 12 months of therapy, MMR was achieved in 48% and 40% of patients, respectively. These results are comparable to local data where 53% of patients achieved *BCR-ABL1* transcript levels below 1% at 6 months, though that study had a shorter duration of follow-up.[4] In addition, the BYOND study, with a median follow-up of 30.4 months, reported a 12-month MMR rate of 41% and a cumulative MMR of 74.4% at 60 months, further reinforcing bosutinib's efficacy.[6,10,11]

Although there were minor variations in treatment response between patients receiving imatinib alone and those treated with both imatinib and nilotinib, statistical analysis did not reveal any significant differences in warning or failure rates between the two groups.

In terms of safety, the AE profile of bosutinib was consistent with previously published data. Gastrointestinal side effects – including diarrhea, nausea, and vomiting – were the most frequently reported, typically of Grade I–II severity. Severe AEs (Grade III–IV) were rare. Diarrhea was the most prevalent AE, reported in 80% of patients, which is consistent with previous findings that noted diarrhea in up to 84% of cases.[6,9] Management strategies for these events included supportive pharmacologic measures such as antidiarrheals and antiemetics, as well as temporary dose adjustments. Concomitant use of proton-pump inhibitors was discouraged due to potential drug interactions.[12,13]

Hematological AEs were also observed, with anemia and thrombocytopenia occurring in approximately 25% of patients, primarily presenting as mild cases. Leukopenia was reported in 5.7% of patients and ranged from mild to severe. These findings align with existing literature that has reported similar rates of hematologic toxicities associated with bosutinib therapy.[2,6,7] Routine monitoring remains essential for early identification and management of both preexisting and treatment-emergent adverse effects.[14]

Our analysis also explored potential predictors of response to bosutinib but found no statistically significant associations with baseline characteristics, including age, duration of prior TKI therapy, or prognostic scores.[6,7]

These findings emphasize the multifactorial nature of treatment response in CML and highlight the need for further investigation to identify predictive biomarkers and optimize individualized treatment strategies.

Limitations

- Lack of mutational analysis to stratify resistance profiles (absence of resistance mutation testing)
- Limited molecular monitoring due to laboratory constraints
- Small sample size and single-center setting
- Short follow-up duration may underestimate long-term efficacy and toxicity.

Conclusion

Bosutinib is a safe and effective therapeutic option in CML patients with prior TKI resistance or intolerance. Its tolerable safety profile and promising molecular responses make it suitable for use in low-resource environments. Further multicenter studies are recommended.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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