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Treatment outcome of the tyrosine kinase inhibitor (bosutinib) in previously treated chronic myeloid leukemia patients (sample of Iraqi patients)

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Abstract:

BACKGROUND: Chronic myeloid leukemia (CML) is a type of myeloproliferative neoplasm characterized by the excessive accumulation of malignant myeloid cells in the bone marrow and peripheral blood. This condition is primarily triggered by a specific chromosomal translocation known as *t*(9;22) (q34.13;q11.23), which leads to the formation of the BCR-ABL fusion gene. The treatment landscape for CML has undergone significant changes with the approval of tyrosine kinase inhibitors (TKIs) targeting the BCR-ABL1 kinase activity. One such inhibitor is bosutinib, which has been available for several years to treat patients with chronic, accelerated, and blast-phase CML who have shown resistance or intolerance to previous therapies.

OBJECTIVES: The aim of this study was to assess efficacy and safety of Bosutinib as a 2nd line therapy in CML patients, in addition to effect of adherence to treatment on patients response.

PATIENTS AND METHODS: Eighty-five patients with CML were enrolled in a prospective cohort study from October 2021 to October 2022 at Hematology Center in Medical City Complex – Baghdad. All patients failed to at least one TKI, and all of them started escalated dose of bosutinib. The patients were followed-up by assessing molecular and cytogenetic response at 3 and 6 months and monitored carefully for adverse events (AEs) which were graded by common terminology IX criteria for AEs version 5. Adherence to bosutinib was also monitored by a specific adherence scale to optimize the response rate to treatment.

RESULTS: The mean age of patients was 47.3 ± 14.9 (range: 18–77), with male:female ratio 1.4:1. Status of CML patients showed that 89.4% were in the chronic phase, 5.8% in accelerated phase, and 4.7% in blast phase. Regarding the number of previous TKIs before bosutinib, 72.9% of patients failed to prior one TKI (imatinib). At 6 months (72.3%), patients achieve optimal response according to European Leukemia Net criteria 2013. Gastrointestinal symptoms and dermatological manifestations were the most common nonhematological AEs of bosutinib. According to 9-item Morisky Medication Adherence Scale, 42% of patients were adherent to medication which showed a significant association with a higher number of optimal response ($P = 0.0001$).

CONCLUSION: Bosutinib is effective with a high and promising response as a subsequent line treatment in CML patients, and it is generally safe and associated with mild-to-moderate tolerable and manageable AEs. Adherence to the drug plays a significant role in optimal response to bosutinib.

Keywords:

Bosutinib, chronic myeloid leukemia, treatment response

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Introduction

Chronic myeloid leukemia (CML) is a type of myeloproliferative neoplasm characterized by the excessive accumulation of malignant myeloid cells in the bone marrow and peripheral blood. This condition is primarily triggered by a specific chromosomal translocation known as *t*(9;22) (q34.13;q11.23), which leads to the formation of the BCR-ABL fusion gene.[1,2]

The treatment landscape for CML has undergone significant changes with the approval of tyrosine kinase inhibitors (TKIs) targeting the BCR-ABL1 kinase activity. One such inhibitor is bosutinib, which has been available for several years to treat patients with chronic, accelerated, and blast-phase CML who have shown resistance or intolerance to previous therapies.[3]

Bosutinib's AE profile differs from that of other TKIs. The most common side effect associated with bosutinib treatment is diarrhea, along with rash and liver enzyme elevations. However, cardiac events, fluid retention, and electrolyte abnormalities are infrequent.[4]

To achieve the best response to bosutinib, it is crucial for patients to adhere to the treatment regimen, which relies, in part, on effectively managing the associated toxicities. By doing so, patients can optimize the benefits of bosutinib therapy and improve their overall outcomes.[4]

Hence, the aim of this study was to assess the efficacy and safety of bosutinib as a subsequent therapy in CML patients, with the assessment of the drug adherence on response criteria.

Patients and Methods

A prospective cohort study was conducted on 85 Iraqi CML patients treated with bosutinib at Hematology Center of Medical City Complex in Baghdad. The study period was from October 2021 to October 2022.

Inclusion criteria

1. Age ≥18 years
2. Prior treatment with resistance to ≥1 TKIs
3. Good hepatic and renal functions
4. Patients with any phase of disease (chronic, accelerated, and blast phase).

Exclusion criteria

1. Patients with a history of chronic diarrhea and inflammatory bowel diseases
2. Pregnant and breastfeeding women
3. Patients that received hematopoietic stem cell transplantation.

Data collection

The demographic data were collected directly from each patient by a specific questionnaire list involving age, sex, number of treatment lines before bosutinib, status of CML at time of diagnosis, initial complete blood picture, initial polymerase chain reaction (PCR), date of starting bosutinib, and duration of disease. All patients were treated using a dose escalation regimen; initially, bosutinib was orally administrated at 200 mg once daily then escalated 100 mg every week, till reaching a dose of 500 mg/day based on patient tolerance and response. Dose of bosutinib was conducted based on adverse events (AEs) grade. For example, at the time of onset for grade 1–2 AEs, the bosutinib therapy was continued using the same dose with an appropriate supporting therapy while observing each patient's condition. While for Grade 3 AEs, the bosutinib therapy was temporarily discontinued until each AE disappeared; then, the patient received the same dose, or the dose was reduced by 100 mg. Dose escalation of bosutinib to 600 mg/day was permitted for 12% of patients due to unsatisfactory response or signs of disease progression in the absence of any Grade 3 or more. Dose reduction to 400, 300, or 200 mg/day due to toxicity/tolerability was permitted. The change and switching to other TKIs than bosutinib was permitted according to doctor preference following the guidelines response. Assessment of response according to ELN criteria 2013[5] done at baseline, 3 months, and 6 months by complete blood picture, PCR (done by GeneXpert fully automated real-time PCR, Cepheid – USA), and fluorescence *in situ* hybridization (FISH) study (done by Ikaros and Isis meta-system using BCR/ABL dual color dual fusion probe). Because of limited laboratory resource, PCR was done for only 40 patients at 3 months but for all 76 patients at 6 months (9 patients stopped bosutinib before 6 months due to variable causes and according to their doctors' advices). FISH study was done when patients do not reach PCR <1 at 3 and 6 months.

AEs, along with their grades of toxicity, were assessed by history, laboratory tests (complete blood picture, renal function, liver function, serum electrolytes, and random blood sugar) which was done weekly in the first 2 months and then done according to each patient status. Electrocardiogram was done at baseline, after 2 months then when indicated and for symptomatic patients with echo study. All adverse effects were graded according to common terminology criteria for adverse events Version 5.0, and interruption of treatment was allowed according to each AE happened.[6]

Patients adherence was evaluated using the nine-item Morisky Medication Adherence Scale which is

one of the most commonly used techniques for adherence assessment. Questionnaires were prepared in the Arabic language, with scores ranging from 1 to 13, and patients scoring 11 or above classified as adherent.

Statistical analysis

Statistical analysis was performed with the IBM-SPSS 26 statistical software program. Univariate data were summarized using standard descriptive statistics, tabulation of categorical variables and histograms of numerical variables. Associations between categorical variables were assessed via cross-tabulation and chi-square test. Mann Whitney Test (a non-parametric equivalent of the independent samples *t*-test), Wilcoxon signed rank test (a non-parametric equivalent of the paired *t*-test) and Kruskal-Wallis test (a non-parametric equivalent to one-way ANOVA) were used to compare means of continuous variables. Exact tests were used to calculate the *p*-value. In all statistical analyses, a *p*-value < 0.05 was considered significant.

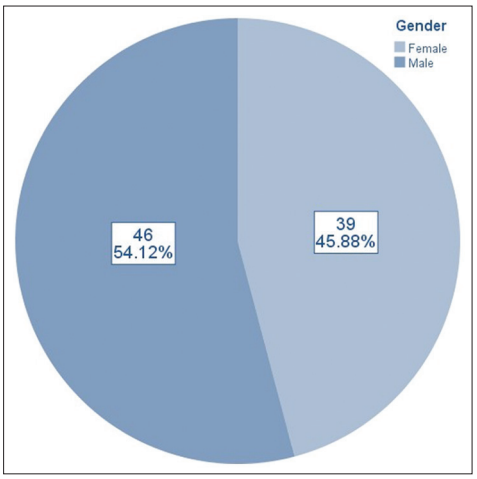

Figure 1: Sex distribution across participants

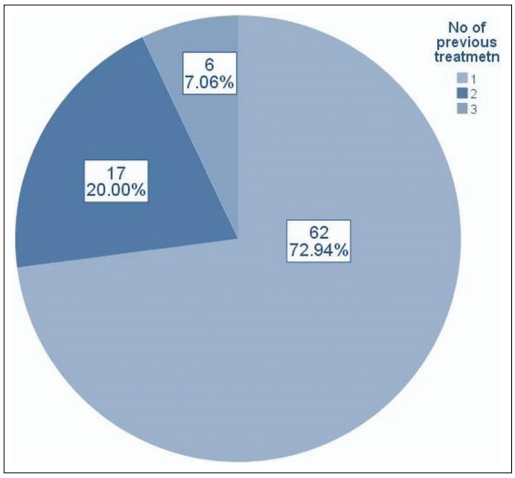

Figure 3: Number of previous treatment distribution across participants

Ethical considerations

The official approvals for this study were attained, represented by the approval of the Iraqi Council of Medical Specialties, in addition to the necessary approvals from the relevant Health facilities. After a thorough explanation of the study objectives to the patients, a written informed consent was taken from each one of them to participate in the study. The patients were given a pledge that all the information taken will be reserved strictly confidential, and would not be used by anyone other than the researchers, and for any purpose other than research work.

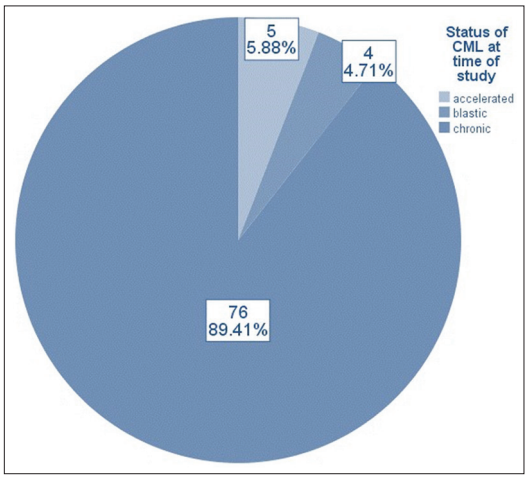

Figure 2: Patients status. CML: Chronic myeloid leukemia

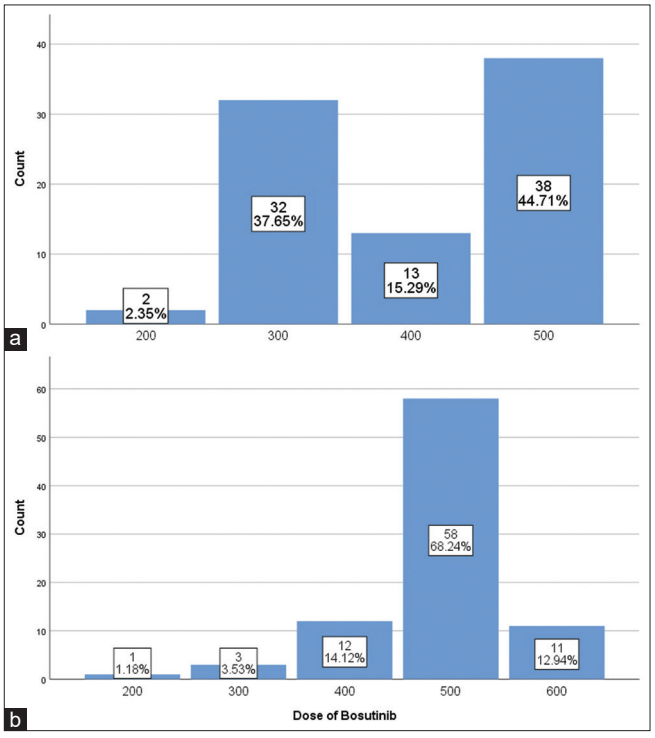

Figure 4: (a) Dose of bosutinib in mg across participants at the end of the first month, (b) Dose of bosutinib in mg across participants at 6 months

Results

The mean age of patients was 47.3 ± 14.9 years (range: 18–77 years). Males and females represented 54.1% and 45.8% of patients, respectively, with male:female ratio 1.4:1 [Figure 1 and Table 1].

The mean duration from diagnosis till bosutinib initiation was 5.4 ± 4.5 years (range: 6 months–21 years). The mean percentage of PCR at baseline was 43.4 ± 38.5 (range: 0.4%–98%). The characteristics of CBC are given in Table 2.

The status of CML patients at the time of study showed that majority of patients (89.4%) were on chronic phase (CP) CML, 5 (5.8%) patients were on accelerated phase CML, and 4 (4.7%) patients were on blastic phase CML [Figure 2].

Table 1: Descriptive statistics of age

Age group (years)	Frequency (%)
18–39	20 (23.5)
40–59	48 (56.5)
≥60	17 (20)

Table 2: Descriptive statistics of duration, complete blood count and baseline polymerase chain reaction

	n	Minimum	Maximum	Mean±SD
Hb	85	6.80	16.30	11.36±1.78
WBC	85	1.70	65.50	9.35±9.43
Platelet	85	16.2	1419.0	219.9±175.78
Percentage PCR at baseline	85	0.45	98.00	43.43±38.59
Duration of CML disease (year)	85	6 months	21	5.40±4.5

CML=Chronic myeloid leukemia, PCR=Polymerase chain reaction, SD=Standard deviation, WBC=White blood cell, Hb=Hemoglobin

Table 3: Type of tyrosine kinase inhibitor before bosutinib

Type of TKI	Frequency (%)
Imatinib	62 (72.9)
Imatinib, nilotinib	16 (18.8)
Imatinib, dasatinib	1 (1.2)
Imatinib, nilotinib, dasatinib	5 (5.9)
Imatinib, nilotinib, ponatinib	1 (1.2)
Total	85 (100.0)

TKI=Tyrosine kinase inhibitor

Table 4: European leukemia net 2013 response classification (response to second line therapy in case of failure of imatinib) at 6-months duration

	Frequency (%)
Failure	21 (27.6)
Optimal	55 (72.3)
Total	76 (100.0)

ELN=European leukemia net

For the number of previous treatment, 72.9% of patients failed for 1 TKI (imatinib only), 20% of patients failed on 2 TKIs, and only 7% of patients failed for 3 TKIs [Figure 3].

Type of medication that patients failed previously is shown in Table 3.

Dose of bosutinib

The dose of bosutinib at 1 and 6 months is showed in Figure 4a and b.

Assessment of response at 3 and 6 months

The assessment of response based on ELN 2013 showed that 55 patients had optimal response (which is defined as BCR-ABL1 ≤10% and/or Ph+ <35%) at 6 months of bosutinib out of 76 patients who had assessment after 6 months of bosutinib initiation [Table 4].

At 3 months, 48% (19 out of 40 patients) achieve molecular response ≤1% and at 6 months 53% (40 out of 76 patients) achieve molecular response ≤1%, as shown in Figure 5a and b.

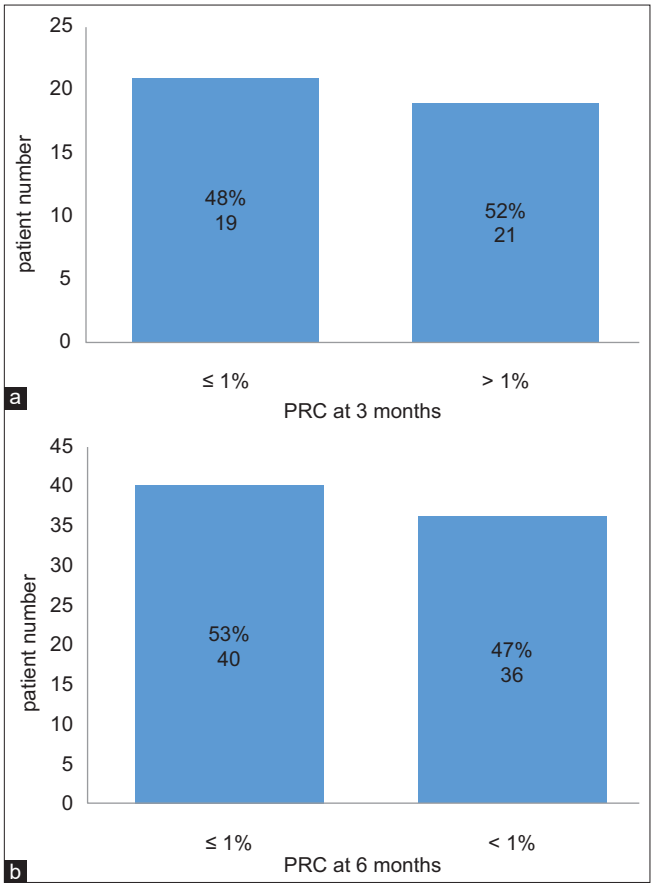

Figure 5: (a) Polymerase chain reaction (PCR) at 3 months among 40 patients on bosutinib who achieve major molecular response (MMoR) (PCR ≤1%), (b) PCR at 6 months among 76 patients on bosutinib who achieve MMoR (PCR ≤1). PCR: Polymerase chain reaction

The types of molecular and cytogenetic responses at 3 and 6 months are given in Table 5.

There was no association between initial hematological assessment and 6-month response ($P = 0.19$) [Table 6].

The assessment of response after 3 months of initiation of bosutinib, only 40 patients had PCR test at 3 months [Table 7], the mean PCR at 3 months was 11% ± 25% (0.01%–98%). The assessment after 6 months showed that only 76 patients had PCR results, the mean PCR was 12.3% ± 22% (0.00%–98%).

The comparison of PCR at baseline and PCR at 3 and 6 months showed that there was a significant reduction after 3 and 6 months of bosutinib initiation ($P < 0.001$); also, the reduction was in PCR from 3 to 6 months ($P = 0.04$) [Table 8].

Factors associated with ELN 2013 response

The assessment of factors associated with response at 6 months showed that optimal response was associated significantly with imatinib failure (one TKI failure) ($P < 0.05$), other factors, sex, status of CML patients, and hematological response at 3 months did not demonstrate significant association [Table 9].

The high white blood cell (WBC) count and high PCR% at baseline were associated significantly with failure in response ($P < 0.05$), whereas age, duration, hemoglobin, and platelet did not demonstrate a significant difference between optimal and failure in response at 6 months of bosutinib initiation [Table 10].

Adherence to medication

There were 42% of patients who were fully adherent to medication [Figure 6].

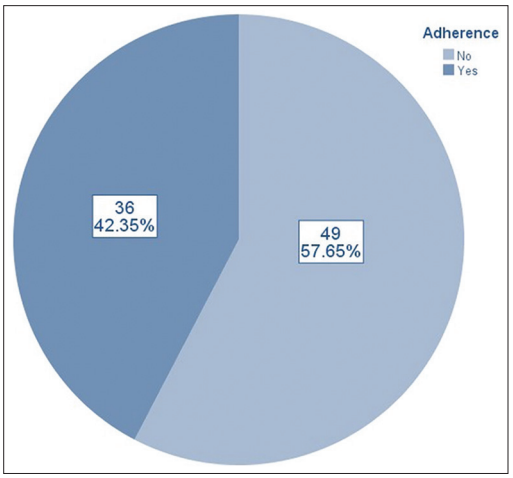

Figure 6: Adherence of patients to medication

The adherence showed significant association with response to treatment in which patients whom were adherent to medication have a significant higher number optimal response ($P = 0.0001$) [Table 11].

The cause for discontinuation of treatment showed that three patients discontinued due to AEs and other three patients due to disease progression [Figure 7].

Table 5: Type of response at 3 and 6 months

Response type	3 months, *n* (%)	6 months, *n* (%)
Minor CyR	10 (25)	21 (27.6)
MCyR	11 (27.5)	15 (19.7)
CCyR	14 (35)	19 (25)
MMoR	5 (12.5)	21 (27)
Total	40	76

CyR=Cytogentic response, MCyR=Major CyR, CCyR=Complete CyR, MMoR=Major molecular response

Table 6: Comparison between initial hematological assessment and 6 month's response

Initial assessment	Number of patients at 6 months response		Total
	Failure	Optimal	
FMoR	15	42	57
FMoR + FHR	6	13	19
Total	21	55	76

FMoR=Failure molecular response, FHR=Failure hematological response

Table 7: Descriptive statistics of polymerase chain reaction at 3 and 6 months after bosutinib initiation

	Minimum	Maximum	Mean±SD
Percentage PCR at 3 months (%)	0.01	98.0	11.42±25.56
Percentage PCR at 6 months (%)	0.00	98.0	12.37±22.67

PCR=Polymerase chain reaction, SD=Standard deviation

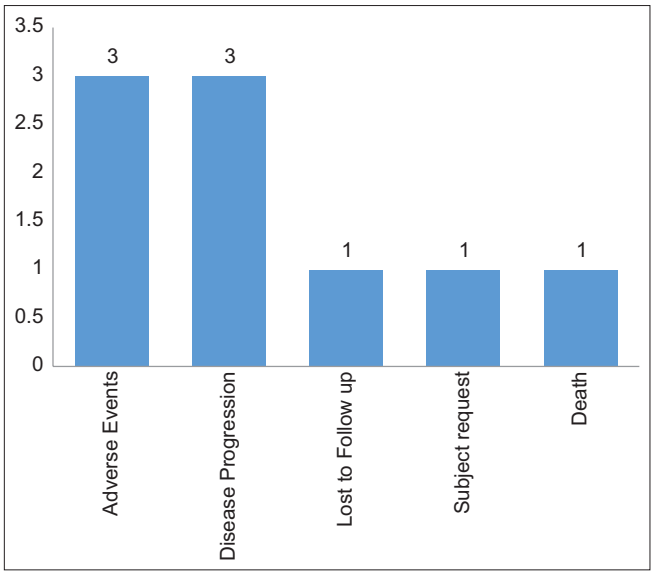

Figure 7: Causes for discontinuation of bosutinib in chronic myeloid leukemia patients

Table 8: Paired samples statistics comparison for polymerase chain reaction at 0, 3, 6 months of initiation of bosutinib

	Mean±SD	*P**
Pair 1 (for 40 patients)		
Percentage of PCR 0	39.75±42.11	0.0001
Percentage of PCR 3	11.42±25.56	
Pair 2 (for 76 patients)		
Percentage of PCR 0	44.86±39.51	0.0001
Percentage of PCR 6	12.37±22.67	
Pair 3 (for 40 patients)		
Percentage of PCR 3	11.42±25.92	0.04
Percentage of PCR 6	6.12±18.84	

*Paired sample *t*-test. SD=Standard deviation, PCR=Polymerase chain reaction

Table 9: Factors associated with European leukemia net 2013 response

	ELN 6 months response count, *n* (%)		*P**
	Failure	Optimal	
Sex			
Female	10 (28.6)	25 (71.4)	0.86
Male	11 (26.8)	30 (73.2)	
Number of previous treatment			
1	11 (19.6)	45 (80.4)	0.028
≥2	10 (50)	10 (50)	
Status of CML at time of study			
Accelerated	3 (75.0)	1 (25.0)	0.094
Blastic	1 (25.0)	3 (75.0)	
Chronic	17 (25.0)	51 (75.0)	
Hematological response at 13 month			
No	4 (40.0)	6 (60.0)	0.34
Yes	17 (25.8)	49 (74.2)	

*Chi-square test. CML=Chronic myeloid leukemia, ELN=European leukemia net

Table 10: Group statistics test of association for European leukemia net criteria response at 6 months with patients baseline data

	ELN response	*n*	Mean±SD	*P**
Age (year)	Optimal	55	48.60±15.99	0.08
	Failure	21	42.67±11.54	
Duration since diagnosis to bosutinib (years)	Optimal	55	5.09±4.22	0.53
	Failure	21	5.76±4.18	
Hb baseline	Optimal	55	11.49±1.75	0.54
	Failure	21	11.20±1.89	
WBC baseline $\times 10^9$	Optimal	55	7.90±5.32	0.03
	Failure	21	13.31±16.23	
Platelet baseline $\times 10^9$	Optimal	55	216.2±115.97	0.65
	Failure	21	237.4±292.58	
Percentage PCR baseline	Optimal	55	34.32±37.05	0.0001
	Failure	21	72.46±32.27	

*Independent sample *t*-test. PCR=Polymerase chain reaction, SD=Standard deviation, WBC=White blood cell, ELN=European leukemia net, Hb=Hemoglobin

Side effect

The assessment of side effect and adherence is given in Table 12.

Discussion

Bosutinib is an oral, second-generation BCR-ABL1 TKI. Bosutinib was first 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, nilotinib, and dasatinib are not considered appropriate treatment options or in patients resistant or intolerant to prior therapy, according to guidelines of the European Medicines Agency and US Food and Drug Administration, respectively.[7,8]

The mean age of patients was 47.3 years (range: 18–77 years), and this was in line with another local study by Ahmed *et al*. that showed a mean age of in the forties with a median of 36 years old.[9] While the age was lower than other global studies that showed a higher mean of age, they reported a median age of 72 years and more than 50% of their participants were above 60 years old.[10,11]

Males and females represented 54.1% and 45.8% of patients, respectively, with male:female ratio 1.4:1 in this study, and it was in line with other regional studies,[12] and global studies that showed a slight predominance of the male sex.[13-15] The median duration of CML disease was 5.4 years from diagnoses since switching to besutimb (only one patient was diagnosed since 2005 and he was on imatinib, and due to loss of follow-up and financial causes, he could not switch to other TKIs). In this study, at the end of 1st month, the majority of patients were on 300 mg or 400 mg with a mean dose of 400 mg. While at the end of 6 months (the mean dose was 488 mg), the majority of patients were on 500 mg with 12% of patients have been increased the dose to 600 mg. Upon the start of therapy, some patients may experience AEs that may prompt treatment interruptions, dose adjustments, and even early discontinuation of treatment or nonadherence to medication. Some physicians tailored the starting dose, usually guided by anticipated AEs. This is expected to help improve adherence, and it is possible to maintain efficacy at lower doses. Furthermore, the 500 mg dose was approved in ≥2 L treatment on the basis that this was the dose used in pivotal studies and secondary analyses of both the ≥2 L phase 1/2 study and 1 L treatment in bosutinib trial in first-line chronic myelogenous leukemia treatment (BFORE) suggest maintained efficacy even with bosutinib 200 mg QD.[16,17]

Assessment of response

BCR-ABL1 transcripts were measured in peripheral blood samples, at the time of starting bosutinib and then

Table 11: The effect of adherence on response of chronic myeloid leukemia patients on bosutinib at 6 month

Response	Adherence, count (%)		Total, count (%)	*P**
	No	Yes		
Failure	18 (85.7)	3 (14.3)	21 (100.0)	0.0001
Optimal	23 (41.8)	32 (58.2)	55 (100.0)	
Total	41 (57.6)	35 (42.4)	76 (100.0)	

*Chi-square=16

every 3 months thereafter using Real-Time quantitative PCR as previously described.

Initially, in this study, all patients who started bosutinib were in failure molecular response to one or more TKIs, and 22.3% patients of them were in failure hematological response. At end of 3 months of bosutinb treatment, 85.8% of patients were achieved/maintained complete hematological response (CHR). The mean PCR at baseline was 43% ± 38% for all participants. After 3 months of initiation of bosutinib, only 40 patients had PCR test at 3 months, the mean PCR at 3 months was 11% ± 25% (0.01%–98%) with 48% of them had PCR <1%. The assessment after 6 months showed that 76 patients had PCR results, the mean PCR was 12.3% ± 22% (0.00%–98%) with 53% of them had PCR <1%. The comparison of PCR at baseline and PCR at 3 and 6 months showed that there was a significant reduction after 3 and 6 months of bosutinib initiation ($P < 0.001$), also, there was a significant reduction in PCR for 40 patients from 3 to 6 months (from 11.4% to 6.1%) ($P = 0.04$). The assessment of response based on ELN 2013 showed that 72.3% of patients had an optimal response at 6 months of bosutinib.

By FISH study which was done at 3 and 6 months for patients not reach optimal molecular response. At 3 months, 27.5% of patients achieve major cytogenetic response (MCyR), whereas 35% of patients achieve complete cytogenetic response (CCyR). At 6 months, 19.7% of patients achieve MCyR, and 25% of patients achieve CCyR. Major Molecular Response (MMoR) was achieved in 12.5% and 27% of patients in 3 and 6 months, respectively.

Bosutinib treatment for patients with CML has been studied in three large trials. For second-line and subsequent-line (≥2 L) treatment, a phase 1/2 study studied bosutinib 500 mg once daily (QD) in patients with imatinib-resistant or imatinib-intolerant CML.[18] The study analyzed two groups based on their treatment history: a 2 L cohort of patients previously treated with imatinib only, and ≥3 L cohort of patients previously treated with imatinib plus dasatinib and/or nilotinib.[18]

In the ≥2 L phase 1/2 study, 31% of patients in the 2 L cohort achieved MCyR at 24 weeks with bosutinib 500 mg QD, and 86% of patients achieved complete hematologic remission at the longer-term follow-up (after a median of 24.2 months).[19] In the ≥3 L cohort, 32% of patients achieved MCyR, 24% CCyR, and 73% complete hematologic response.[20]

In the ongoing phase 4 BYOND study, 163 CML patients resistant/intolerant to prior TKIs received bosutinib 500 mg once daily (starting dose). As of ≥1 year after the last enrolled patient, 56.4% of Ph+ CP CML patients remained on bosutinib. The primary endpoint of cumulative confirmed MCyR rate by 1 year was 75.8% in Ph+ CP CML patients after one or two prior TKIs and 62.2% after three prior TKIs. Cumulative CCyR and major molecular response (MMR) rates by 1 year were 80.6% and 70.5%, respectively, in Ph+ CP CML patients overall. The majority of patients had confirmed MCyR by 1 year and MMR by 1 year, further supporting bosutinib use for Ph+ CP CML patients resistant/intolerant to prior TKIs.[21]

In our study, the assessment of factors associated with response at 6 months showed that optimal response was associated significantly with failure to prior one TKI ($P < 0.05$) rather than ≥2 TKIs, while high WBC count and high PCR% at baseline was associated significantly with failure in response ($P < 0.05$).

Adverse events

In this study, the most common AEs that associated with bosutinib were related to gastrointestinal, being diarrhea (77.6%), 65.8% of them less than grade three, nausea (48.7%), vomiting (35.5%), and abdominal pain (35.5%) were the most common AEs, and the majority of those AEs were with grade one/two. These results compared with Cortes *et al*. in which the most common no hematologic treatment-emergent AEs were diarrhea (84%), nausea (44%), and vomiting (35%).[18]

Pharmacologic strategies include supportive care with antidiarrheal, antiemetic, or anti-nausea medications; bosutinib dose reductions or interruptions; and avoidance of concomitant use with PPIs.[22,23] In our study, the second-most common nonhematological AEs were skin manifestation in the form of (pruritus, hyperpigmentation, and rash [22.4%]), dry skin (18.4%), acne form lesions (7.8%), and this was comparable to that of Hochhauss *et al*.[21] in which 25% of patients develop skin rash and 17% developed pruritus. Transaminitis in the form of elevated liver enzymes shows that aspartate transaminase (AST) elevated in 14.5%, AST elevated in 13.2% which was compared to Gambacorti-Passerini *et al*.,[19] in which patient treated with ≥2 L treatment, in the 2 L cohort, increased alanine transaminase occurred in 22.2% and increased AST in 19.7%. The hematological AEs in this study in the form of myelosuppression include thrombocytopenia (29%), anemia (31.6%), and leukopenia (6.6%) was comparable with Ault *et al*. in which anemia occurs in 27% of patients,

Table 12: Side effect assessment

	Number of patients (%)
Gastrointestinal	
Diarrhea	
Grade 1	23 (30.3)
Grade 2	27 (35.5)
Grade ≥3	9 (11.8)
Total	59 (77.6)
Nausea	
Grade 1	16 (21.1)
Grade 2	18 (23.7)
Grade ≥3	3 (3.9)
Total	37 (48.7)
Vomiting	
Grade 1	19 (25.0)
Grade 2	8 (10.5)
Total	27 (35.5)
Abdominal pain	
Grade 1	8 (10.5)
Grade 2	17 (22.4)
Grade 3	2 (2.6)
Total	27 (35.5)
Wight loss	
Grade 1	1 (1.3)
Grade 2	4 (5.3)
Grade 3	3 (3.9)
Total	8 (10.5)
Anorexia	
Grade 1	12 (15.8)
Grade 2	7 (9.2)
Grade 3	3 (3.9)
Total	22 (28.9)
Hematological	
Anemia	
Grade 1	17 (22.4)
Grade 2	3 (3.9)
Grade 3	4 (5.3)
Total	24 (31.6)
Thrombocytopenia	
Grade 1	11 (14.5)
Grade 2	5 (6.6)
Grade 3	6 (7.9)
Total	22 (29)
Leukopenia	
Grade 1	2 (2.6)
Grade 2	3 (3.9)
Total	5 (6.6)
Dermatological	
Pruritus	
Grade 1	5 (6.6)
Grade 2	10 (13.2)
Grade 3	2 92.6)
Total	17 (22.4)
Rash	
Grade 1	8 (10.5)
Grade 2	9 (11.8)
Total	17 (22.3)
Hyperpigmentation	
Grade 1	7 (9.2)
Grade 2	10 (13.2)
Total	17 (22.4)
Acne form lesion	
Grade 1	2 (2.6)
Grade 2	3 (3.9)
Grade 3	1 (1.3)
Total	6 (7.8)
Dry skin	
Grade 1	5 (6.6)
Grade 2	9 (11.8)
Total	14 (18.4)
Liver	
ALT	
Grade 1	4 (5.3)
Grade 2	5 (6.6)
Grade 3	2 (2.6)
Total	11 (14.5)
AST	
Grade 1	6 (7)
Grade 2	4 (5.3)
Total	10 (13.2)
ALK PH	
Grade 1	1 (1.3)
TSB	
Grade 2	1 (1.3)
Grade 3	1 (1.3)
Total	2 (2.6)
Atrial flutter	
Grade 2	1 (1.3)
Total	1 (1.3)
Others	
Hypokalemia	
Grade 1	2 (2.6)
Total	2 (2.6)
Serum creatinine elevation	
Grade 1	1 (1.3)
Grade 2	1 (1.3)
Total	2 (2.6)
Bone pain	
Grade 1	1 (1.3)
Grade 2	3 (3.9)
Total	4 (5.2)

ALT=Alanine transaminase, AST=Aspartate transaminase, ALK PH=Alkaline phosphatase, TSB=Total serum bilirubin

thrombocytopenia 42%, and leukopenia 16%.[24] The causes for permanent discontinuation of bosutinib in our study showed that 3 patients discontinued bosutinib due to AEs, the other 3 patients due to disease progression, 1 patient due to lost to follow-up, one patient switch bosutinib on his request and one died (was already in blast phase and has no human leukocyte antigen matching donor). This was comparable with Hochhaus *et al*. that show most common primary reason for

permanent treatment discontinuation were AEs in 25%, and insufficient clinical response in 5.1% patients.[21]

Other considerations for treatment selection

Additional considerations for treatment selection in patients with CML include the impact of treatment adherence on clinical outcomes, for example, nonadherence to treatment has been associated with poorer response rates, deteriorations in quality of life, and increased healthcare costs.[25,26] In this study, the adherence (42%) showed a significant association with response to treatment in which patients whom were adherent to medication had a significant higher number optimal response ($P = 0.0001$).

Limitations of study

1. The most important limitation of our study was the short duration of follow-up
2. Limited laboratory recourses to afford molecular study to all patients at 3-month assessment
3. Lack of mutational analysis.

Conclusion

Based on study results, we concluded the following:

- The assessment of response based on ELN 2013 showed that more than 2/3 of the patient had optimal response at 6 months of bosutinib when used as a subsequent TKI therapy
- Dose escalation of bosutinib was efficacious and tolerable for patients with CML
- Main AEs were GIT symptoms
- Patients' adherences played a significant role in optimal response to bosutinib.

Recommendations

Based on study results, we recommended the following:

- Use of bosutinb for a large number of patients and for prolonged period
- Using mutational analysis before initiation second line TKIs
- Increase patients' awareness about the importance of drug adherence to achieve optimal response.

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Conflicts of interest

There are no conflicts of interest.

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