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Efficacy of Bosutinib therapy as a second line in the treatment of chronic myeloid leukemia: A single-center study

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Abstract:

BACKGROUND: Chronic myeloid leukemia (CML), a myeloproliferative neoplasm caused by genetic abnormality resulted in BCR-ABL1 fusion gene, leading to constitutive tyrosine kinase activity. Despite improved treatment outcomes of tyrosine kinase inhibitors (TKIs), resistance to these agents due to mutations in targeted BCR-ABL gene is still a challenge. Bosutinib is consider one of TKI, it inhibit both Sarcoma kinase and Ablson kinase (SRC/ABL), It is approved for patients for whom frontline TKIs is failed or undergo adverse effects.

OBJECTIVE: This study aims to evaluate the efficacy of bosutinib as a second-line treatment for CML patients who have previously failed or experienced intolerance to other TKIs.

MATERIALS AND METHODS: A cross-sectional study was conducted from October 2021 to December 2023 at the National Center of Hematology. Thirty CML patients were enrolled, all of whom had received bosutinib following failure or intolerance to prior TKI treatments (imatinib and/or nilotinib). Data collected included patient demographics, prior treatment history, and laboratory results. BCR-ABL levels were quantitatively measured using polymerase chain reaction at baseline and 6 months posttreatment. Statistical analyses included paired *t*-tests and correlation assessments.

RESULTS: The study included 30 CML patients (12 males and 18 females) with a median age of 49.5 years. Most patients (60%) had received imatinib only prior to bosutinib. A significant decrease in mean BCR-ABL levels was observed after 6 months of bosutinib treatment ($P < 0.0001$), with 53% of patients achieving optimal molecular response as per the European LeukemiaNet criteria. Correlation analyses indicated significant relationships between BCR-ABL level and white blood cell count ($P = 0.006$) and between treatment duration and hemoglobin level ($P = 0.001$). In addition, patients previously treated solely with imatinib responded to bosutinib significantly better than those who had received both imatinib and nilotinib ($P = 0.0272$).

CONCLUSION: Bosutinib demonstrated significant efficacy as a second-line treatment for CML in patients who showed failure response to prior TKI therapies. These findings support bosutinib usage in managing CML, particularly in patients with a history of single TKI treatment, and underscore the necessity for ongoing research into resistance mechanisms and alternative therapies.

Keywords:

BCR-ABL level, bosutinib, chronic myeloid leukemia, tyrosine kinase inhibitors

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Introduction

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm manifested with proliferation and differentiation of granulocytes without achieving complete maturation. Pathogenesis of CML is associated with characteristic cytogenetic abnormality resulting from t (9;22)(q34;q11) translocation (Philadelphia chromosome), leading to the formation of BCR-ABL1

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transcript. This fusion gene codes for BCR-ABL1, a chimeric protein with constitutive tyrosine kinase activity that promotes the proliferation of leukemia cells through multiple mechanisms.[1,2] Annual incidence of CML is estimated to range from around 0.4 to 1.75 cases per 100,000 people globally, varying by region. Higher-income areas, such as North America and Europe, report CML rates closer to 1–2 cases per 100,000, while lower rates, often under one case per 100,000, are found in regions with limited access to health care, such as parts of Africa and Latin America.[3] It has been shown that CML is mainly affecting the elderly (the mean age is 60 years in the west and 50 years in Asia and Africa), indicating an age-related pathogenesis.[4] In addition, age group with 1–20 years represents <10% of CML and approximately 3% of all pediatric leukemia. Disease predisposition has not been found in families with rare co-occurrence as well as no concordance in identical twins has been reported.[5] Global CML incidence rate is estimated at 52 and 36 per 10,000 in males and females, respectively.[6]

The Iraqi Cancer Registry (ICR) in 2019 reported that the total number of registered cases of CML was 338, representing 0.94% of total number of cancer cases (incident rate of 0.86% per 100,000) in Iraqi population. Among 338 cases, 221 (65.38%) were males and 117 (34.62%) were females, indicating higher incidence rate in males versus females (1.12 vs. 0.60, respectively).[7]

Since the US Food and Drug Administration (FDA) approved imatinib, the first (tyrosine kinase inhibitor [TKI]),[8] CML treatment began new era due to the remarkable success of imatinib compared with previous treatments. Subsequently, imatinib has become the first-line therapy for CML treatment for patients in all stages. Imatinib selectively inhibits ABL and BCR-ABL transcripts.[9,10] However, development of a group of mutations within BCR-ABL oncogene causes resistance to TKIs by changing binding sites at BCR-ABL protein. So far, more than 100 different resistance mutations have been characterized and existed in a large group of patients with imatinib failure.[11,12] For this reason, development of new TKIs with better targeting activity is a very active area of research. This leads to the emerging of new TKIs with various binding properties such as nilotinib, bosutinib, asciminib, and ponatinib.[10,13] Imatinib along with dasatinib and nilotinib represent frontline therapy for treatment of CML at chronic, accelerated, or blast phase, while other TKIs represent salvage therapy when patients experience resistance or intolerance to the frontline TKIs. Patients respond differently to TKIs depending on disease stage, BCR-ABL level, cytogenetic, and other comorbidities.[10]

Bosutinib (Bosulif) is a TKI that selectively targets both SRC and ABL. Bosutinib was approved by the FDA in 2012 for patients for whom imatinib and nilotinib fail to achieve response or experience intolerance to these TKIs at any stage of CML.[12,14] Studies and clinical trials evaluated bosutinib treatment outcome in patients with postimatinib and/or nilotinib failure at various clinical settings showed successful outcomes. Regarding safety, despite discontinuation of treatment due to intolerable adverse events in a proportion of patients, bosutinib-associated side effects are tolerable and can be managed, making bosutinib a suitable alternative in patients who discontinued from imatinib and/or nilotinib due to either efficacy or safety issues.[15] Due to the limited data in Iraqi medical health settings, we conducted this study to reveal the effect of bosutinib as a second-line treatment in Iraqi CML patients.

Materials and Methods

Patients

This study was performed at the National Center of Hematology from October 2021 to December 2023. Among CML patients admitted to our center, 30 cases with complete profiles were included in this study. Patients involved in this study were those who started receiving TKI bosutinib (Pfizer, Germany) following failure or experience of adverse effects imatinib mesylate and/or nilotinib. Bosutinib treatment dose was selected on the basis of patients' response and tolerance. Out of 30 patients, 17 received 500 mg/day, 3 received 400 mg/day, and 10 received 300 mg/day. The study followed standards and regulations and was approved by the review ethical committee at the National center of hematology (NCH) (reference: Nch-erc-21-17). Consent was obtained from all the participants to use their data for research purposes. Clinical and laboratory data were collected either directly from patients or from NCH database. These include age, diagnosis date, number of previous TKI treatments, previous BCR-ABL records, current medication type, treatment dose, and complete blood count (CBC).

Sample collection and preparation

Samples from patients (peripheral blood) were collected in anticoagulation (ethylenediaminetetraacetic acid) tubes for blood count and polymerase chain reaction (PCR) analysis. RNA extraction and sample preparation for PCR were performed using (GXBCRABL-10, Cepheid, USA) kit according to manufacturer instructions. Fresh samples were used for PCR analysis.

BCR-ABL measurement by quantitative polymerase chain reaction

BCR-ABL fusion gene was quantitatively determined

in International Scale unit using GeneXpert PCR system (Cepheid, USA) along with (GXBCRABL-10, Cepheid, USA) kit according to manufacturer instructions. BCR-ABL1 level was measured in patients at two time points: at starting point of bosutinib treatment (baseline) and at least 6 months posttreatment. Some patients underwent the test 2–4 months after due date because of unavailability of laboratory resource.

Statistical analysis

Patients' data were collected directly and from archives in database software. GraphPad Software, Inc., (v6.0) (San Diego, California, United States) and SPSS software (IBM Corporation, Armonk, New York, United States) were used for statistical analysis. The probability was calculated using paired *t*-test. The Mann–Whitney and Fisher's exact tests were used for nonparametric and categorical data, respectively. Pearson test was performed to calculate the correlation between parameters. P <0.05 was considered a significant difference.

Table 1: Demographic and laboratory parameters of chronic myeloid leukemia patients (baseline)

Characteristics	Analyzed patients (*n*=30)
Age, median (range)	49.5 (18–75)
Age group, *n* (%)	
≤40	4 (13.33)
>40	26 (86.67)
Sex, *n* (%)	
Male	12 (40)
Female	18 (60)
Previous treatment, *n* (%)	
Imatinib only	18 (60)
Imatinib then nilotinib	12 (40)
Duration from diagnosis to bosutinib treatment (years) (mean±SD) (range)	6.75±5.72 (3 months–22 years)
BCR-ABL baseline level (IS) (mean±SD)	27.59±18.5
HGB (g/dL), median (range)	12.0 (6.4–16.7)
WBC (×10^3/μL), median (range)	7.55 (1.9–21.7)
Platelet (×10^3/μL), median (range)	228.5 (23–436)

WBC=White blood cell, HGB=Hemoglobin, IS=International Scale, SD=Standard deviation

Results

The basic demographic and laboratory data of 30 CML patients were analyzed at the baseline of bosutinib treatment. There were 12 males and 18 females with a median age of 49.5 years. The majority of them were older than 40 years. Among 30 patients, 18 and 12 cases were previously treated with imatinib only and both imatinib and nilotinib, respectively. All patients demonstrated molecular response failure, and the majority presented with high BCR-ABL transcript levels. Generally, patients were characterized with normal blood parameters, as shown in Table 1.

Analysis of BCR-ABL levels before and after bosutinib treatment was performed by quantitative PCR [Figure 1]. Results showed a remarkable decrease in mean BCR-ABL level compared with baseline (P < 0.0001). After 6 months of bosutinib treatment, out of 30 patients, 16 cases achieved a BCR-ABL1 level of <1, and 14 cases showed a BCR-ABL1 level of >1 (considered a molecular response cutoff at 6 months based on the European LeukemiaNet 2013 [ELN]).

We then performed correlation analysis of patients' data postbosutinib treatment [Table 2]. Results showed a moderate positive correlation between BCR-ABL level and white blood cell (WBC) count (P = 0.006) as well as between bosutinib dose and hemoglobin (HGB) level (P = 0.007). Additionally, there was a mild negative correlation between BCR-ABL levels and hemoglobin (HGB) levels (P = 0.035), as well as between HGB levels and white blood cell (WBC) count (P = 0.011). Duration of bosutinib treatment course was high positively correlated with both BCR-ABL and WBC (P = 0.002 for both) and high negatively correlated with HGB (P = 0.001). No correlation was seen between the duration of previous TKI treatment and other parameters [Table 2].

Table 2: Correlation between patients' parameters (Post-Bosutinib treatment)

	Age	BCR-ABL	HGB	WBC	PLT	Bosutinib dose	Bosutinib period	Previous TKI period	Diagnosis to bosutinib
Age		0.23	−0.30	0.08	−0.11	−0.14	0.01	0.13	0.11
BCR-ABL	0.23		−0.42*	0.54**	−0.35	−0.04	0.55**	0.20	0.29
HGB	−0.30	−0.42*		−0.49*	0.07	0.52**	−0.59***	0.11	0.01
WBC	0.08	0.54**	−0.49*		−0.34	0.25	0.57**	0.03	0.06
PLT	−0.11	−0.35	0.07	−0.34		−0.06	−0.48*	−0.21	−0.12
Bosutinib dose	−0.14	−0.04	0.52**	0.25	−0.06		−0.16	−0.13	−0.12
Bosutinib period	0.01	0.55**	−0.59***	0.57**	−0.48*	−0.16		−0.01	0.00
Previous TKI period	0.13	0.20	0.11	0.03	−0.21	−0.13	−0.01		0.86****
Diagnosis to bosutinib	0.11	0.29	0.01	0.06	−0.12	−0.12	0.00	0.86****	

*P≤0.05, **P≤0.01, ***P≤0.001, ****P≤0.0001. Numbers represent (*r*) value of Pearson correlation. Positive and negative *r* values represent positive and negative correlation, respectively. *R* values of 0.9–1 (very high), 0.7–0.9 (high), 0.5–0.7 (moderate), 0.3–0.5 (low), and 0–0.3 (negligible) indicate level of correlation. TKI=Tyrosine kinase inhibitor, WBC=White blood cell, PLTs=Platelet, HGB=Hemoglobin

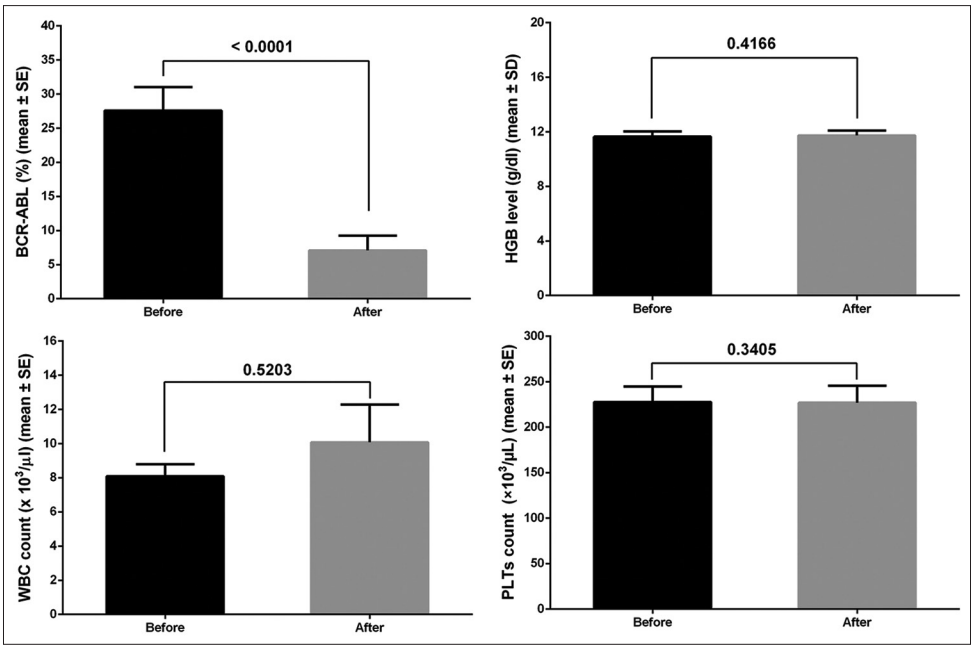

Figure 1: BCR-ABL level, hemoglobin, white blood cell, and platelet count at baseline and Post-Bosutinib treatment (all patients). SE = Standard error, SD = Standard deviation, WBC = White blood cell, PLT = Platelet, HGB = Hemoglobin, IM = Imatinib mesylate

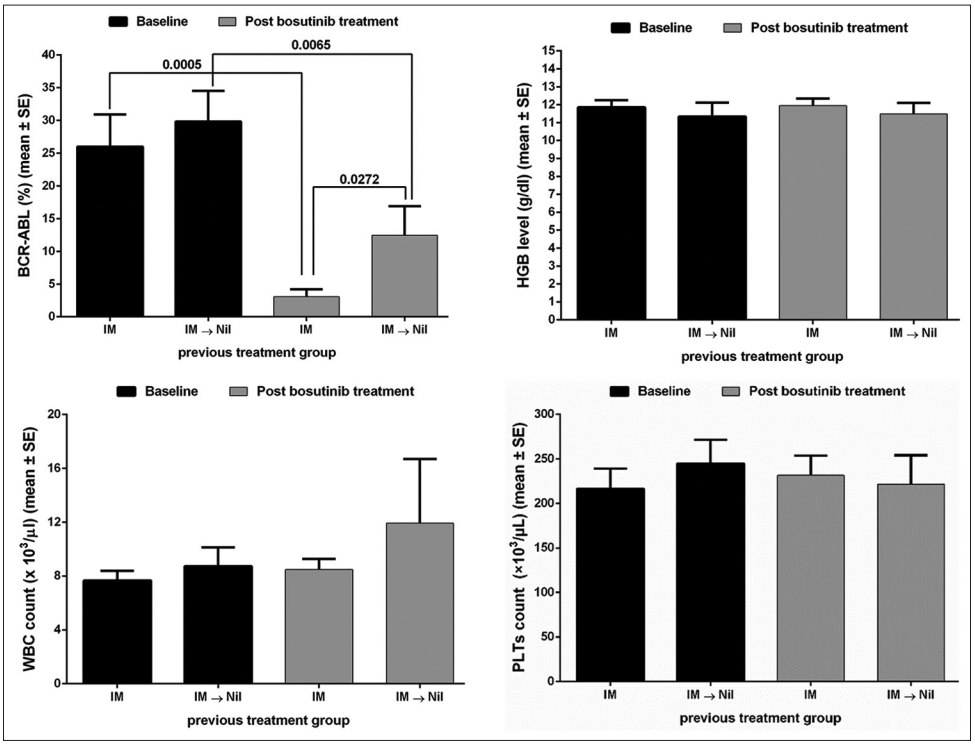

Figure 2: BCR-ABL level, hemoglobin, white blood cell, and platelet count at baseline and Post-Bosutinib treatment (grouped by previous treatment). SE = Standard error, WBC = White blood cell, PLT = Platelet, HGB = Hemoglobin, IM = Imatinib mesylate

We also analyzed patients' data by comparing bosutinib treatment outcome on the basis of previous treatment (imatinib only vs. imatinib then nilotinib) [Table 3 and Figure 2]. The analysis showed that patients who previously underwent two TKIs (imatinib mesylate then nilotinib) responded to bosutinib treatment significantly less than those who previously underwent single tyrosine response (only imatinib mesylate) ($P = 0.0272$) [Figure 2]. No significant difference was seen between the two groups in terms of other parameters (age, sex distribution, HGB, WBC, and platelet [PLT]) [Table 3].

Table 3: Laboratory parameters of patients (postbosutinib treatment)

Characteristics	Previous treatment group		*P*
	IM group (*n*=18)	IM → Nilotinib (*n*=12)	
Age, mean±SE	51.33±2.932	50.75±3.411	0.8988
Age group, *n* (%)			
≤40	2 (11.11)	2 (16.67)	1.00
>40	16 (88.89)	10 (83.33)	
Sex, *n* (%)			
Male	9 (50)	3 (25)	0.2599
Female	9 (50)	9 (75)	
BCR-ABL level (IS), mean±SE	3.066±1.129	12.47±4.413	0.0272
HGB level (g/dL), mean±SE	11.95±0.395	11.48±0.625	0.5217
WBCs count (×10^3/μL), mean±SE	8.487±0.779	11.93±4.765	0.4490
PLTs count (×10^3/μL), mean±SE	231.4±22.24	221.6±32.43	0.7999

IM=Imatinib mesylate, WBC=White blood cell, PLT=Platelet, IS=International Scale, SE=Standard error, HGB=Hemoglobin

Discussion

Bosutinib is a TKI with a dual SRC/ABL targeting activity.[16] Bosutinib was approved by the FDA in 2012 for treatment of CML patients for whom frontline TKIs are not suitable due to efficacy or safety reasons.[17] The current study involved 30 CML patients who were primarily in chronic phase (CP) in consistent with literature data that most admitted patients are in CP.[10] Patients started on bosutinib after single TKI (imatinib) or two TKIs (imatinib and nilotinib) treatment failure (18 and 12, respectively). The mean age of patients was 51.1 ± 12 years, with an age group frequency of 13%, 66.7%, and 23.33% for ≤20 years, 40–60 years, and ≥60 years, respectively. This is similar with global incidence trend that CML is associated with age and mainly affects the elderly.[4,18,19] Locally, according to the ICR data for 2019, the percentage of males and females ≥40 years was 63.8% and 73.5%, respectively.[7] In the current study, the male: female ratio was 1.5:1, in agreement with male: female ratio of ICR (2022) data of 1.58:1, as well as local and global data of sex distribution of CML patients whereby male is more prevalent.[4,5,20] At baseline, generally, the majority of patients were characterized with normal CBC without molecular response. Similar data were reported previously.[20] The mean duration from diagnosis to bosutinib treatment was 6.75 ± 5.72 years.

At baseline, all patients were characterized by molecular failure (mean BCR-ABL level = 27.59 ± 18.5). BCR-ABL level analysis by quantitative PCR after 6 months showed a remarkable decrease in mean BCR-ABL level compared with baseline ($P < 0.0001$), with 16 (53%) patients achieving optimal response according to ELN optimal response recommendations.[21] This is consistent with previous Phase I/II clinical trials that demonstrated the efficacy of bosutinib following treatment failure with imatinib and/or nilotinib TKIs.[14,22] In one such trial involving 547 patients who had previously failed to respond to a single TKI, 33% achieved a major cytogenetic response (MCyR). Another clinical trial showed MCyR in 25% of treated patients.[14,22] Findings of these two studies were confirmed by publishing the final results of Phase I/II over another 5 years.[23] *In vitro* studies showed that therapeutic activity of bosutinib to CML was due to the prevention of BCR-ABL phosphorylation, resulting in inhibition of cell proliferation and differentiation pathways associated with CML.[24,25]

To clarify any association between treatment settings and certain patients' parameters, we performed correlation analysis after bosutinib treatment [Table 2]. The positive correlation between WBC count and BCR-ABL levels is particularly notable, as elevated WBC counts are often associated with disease activity in CML. $P = 0.006$ suggests a statistically significant relationship, reinforcing the understanding that higher BCR-ABL levels correlate with leukocytosis in CML patients. In addition, the negative correlation between bosutinib treatment duration and HGB and PLT counts aligns with clinical observations that prolonged treatment can sometimes lead to cytopenias. Conversely, the positive correlation of treatment duration with WBC and BCR-ABL levels further supports the notion that inadequate response to therapy may be reflected in these parameters, indicating either disease progression or inadequate management.[25]

The study showed that patients previously treated with imatinib solely responded better to bosutinib than those previously treated with both imatinib and nilotinib ($P = 0.0272$) [Figure 2]. This finding is consistent with previous findings that the ratio of cases with major or complete cytogenetic response after bosutinib as second-line treatment is higher than those who underwent bosutinib treatment in third- or fourth-line settings. This was also shown by Phase 4 BYOND study.[26]

Limitation of study

This study had number of limitations including single-center enrollment, limited sample size, short

follow-up period, and variation in treatment dosing which may introduce variability in treatment outcomes and complicate the analysis of dosage effects.

Limited Evaluation of Adverse Events: While safety was mentioned, the study may not have comprehensively assessed or reported all potential adverse events associated with bosutinib treatment. Finally, detailed information about the adverse effects of bosutinib is out of scope of this study.

Conclusion

The findings from this study highlight bosutinib efficacy as a second-line treatment for CML in patients for whom first-line TKI treatment results in failure response or adverse effects. A significant reduction in BCR-ABL levels after 6 months of bosutinib treatment underscores its therapeutic potential, particularly in patients previously treated solely with imatinib, who showed better responses compared to those who had also been treated with nilotinib. These results suggest that bosutinib can serve as a viable alternative for managing CML, contributing to improved patient outcomes in the Iraqi healthcare context. However, further research is necessary to explore the long-term effects of bosutinib, investigate the underlying mechanisms of resistance, and optimize treatment strategies for CML patients.

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Conflicts of interest
There are no conflicts of interest.

References

1. Bain BJ. Leukaemia Diagnosis. Hoboken (NJ): Wiley; 2017.p. 371-416.
2. Quintás-Cardama A, Cortes J. Molecular biology of bcr-abl1-positive chronic myeloid leukemia. Blood 2009;113:1619-30.
3. Hochhaus A, Saussele S, Rosti G, Mahon FX, Janssen JJ, Hjorth-Hansen H, *et al*. Chronic myeloid leukaemia: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2017;28:v41-51.
4. Mendizabal AM, Younes N, Levine PH. Geographic and income variations in age at diagnosis and incidence of chronic myeloid leukemia. Int J Hematol 2016;103:70-8.
5. Nguyen LT, Guo M, Naugler C, Rashid-Kolvear F. Incidence of chronic myeloid leukemia in Calgary, Alberta, Canada. BMC Res Notes 2018;11:780.
6. Ning L, Hu C, Lu P, Que Y, Zhu X, Li D. Trends in disease burden of chronic myeloid leukemia at the global, regional, and national levels: A population-based epidemiologic study. Exp Hematol Oncol 2020;9:29.
7. Iraqi Cancer Board, Ministry of Health and Environment, Republic of Iraq. Annual report of Iraqi cancer registry (2019). Iraqi Cancer Board; 2019. Available from: https://moh.gov.iq/?page=35. [Last accessed 2024 September 12].
8. Druker BJ. Translation of the Philadelphia chromosome into therapy for CML. Blood 2008;112:4808-17.
9. Chauhan R, Sazawal S, Pati HP. Laboratory monitoring of chronic myeloid leukemia in patients on tyrosine kinase inhibitors. Indian J Hematol Blood Transfus 2018;34:197-203.
10. Jabbour E, Kantarjian H. Chronic myeloid leukemia: 2022 update on diagnosis, therapy, and monitoring. Am J Hematol 2022;97:1236-56.
11. Shanmuganathan N, Hiwase DK, Ross DM. Treatment of chronic myeloid leukemia: Assessing risk, monitoring response, and optimizing outcome. Leuk Lymphoma 2017;58:2799-810.
12. Cuellar S, Vozniak M, Rhodes J, Forcello N, Olszta D. BCR-ABL1 tyrosine kinase inhibitors for the treatment of chronic myeloid leukemia. J Oncol Pharm Pract 2018;24:433-52.
13. Saglio G, Jabbour E. First-line therapy for chronic phase CML: Selecting the optimal BCR-ABL1-targeted TKI. Leuk Lymphoma 2018;59:1523-38.
14. Khoury HJ, Cortes JE, Kantarjian HM, Gambacorti-Passerini C, Baccarani M, Kim DW, *et al*. Bosutinib is active in chronic phase chronic myeloid leukemia after imatinib and dasatinib and/or nilotinib therapy failure. Blood 2012;119:3403-12.
15. Syed YY, McCormack PL, Plosker GL. Bosutinib: A review of its use in patients with Philadelphia chromosome-positive chronic myelogenous leukemia. BioDrugs 2014;28:107-20.
16. Puttini M, Coluccia AM, Boschelli F, Cleris L, Marchesi E, Donella-Deana A, *et al*. *In vitro* and *in vivo* activity of SKI-606, a novel Src-Abl inhibitor, against imatinib-resistant Bcr-Abl+neoplastic cells. Cancer Res 2006;66:11314-22.
17. Cortes JE, Khoury HJ, Kantarjian HM, Lipton JH, Kim DW, Schafhausen P, *et al*. Long-term bosutinib for chronic phase chronic myeloid leukemia after failure of imatinib plus dasatinib and/or nilotinib. Am J Hematol 2016;91:1206-14.
18. Huang X, Cortes J, Kantarjian H. Estimations of the increasing prevalence and plateau prevalence of chronic myeloid leukemia in the era of tyrosine kinase inhibitor therapy. Cancer 2012;118:3123-7.
19. GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: A systematic analysis for the global burden of disease study 2017. Lancet 2018;392:1789-858.
20. Ahmed AM, Matti BF. Treatment outcome of the tyrosine kinase inhibitor (bosutinib) in previously treated chronic myeloid leukemia patients (sample of Iraqi patients). Iraqi J Hematol 2024;13:12-21.
21. Cross NC, Ernst T, Branford S, Cayuela JM, Deininger M, Fabarius A, *et al*. European LeukemiaNet laboratory recommendations for the diagnosis and management of chronic myeloid leukemia. Leukemia 2023;37:2150-67.
22. Cortes JE, Kantarjian HM, Brümmendorf TH, Kim DW, Turkina AG, Shen ZX, *et al*. Safety and efficacy of bosutinib (SKI-606) in chronic phase Philadelphia chromosome-positive chronic myeloid leukemia patients with resistance or intolerance to imatinib. Blood 2011;118:4567-76.
23. Gambacorti-Passerini C, Cortes JE, Lipton JH, Kantarjian HM, Kim DW, Schafhausen P, *et al*. Safety and efficacy of second-line bosutinib for chronic phase chronic myeloid leukemia over a five-year period: Final results of a phase I/II study. Haematologica 2018;103:1298-307.
24. Doan V, Wang A, Prescott H. Bosutinib for the treatment of chronic myeloid leukemia. Am J Health Syst Pharm 2015;72:439-47.
25. García-Gutiérrez V, Gómez-Casares MT, Xicoy B, Casado-Montero F, Orti G, Giraldo P, *et al*. Critical review of clinical data and expert-based recommendations for the use of bosutinib in the treatment of chronic myeloid leukemia. Front Oncol 2024;14:1-12.
26. Hochhaus A, Gambacorti-Passerini C, Abboud C, Gjertsen BT, Brümmendorf TH, Smith BD, *et al*. Bosutinib for pretreated patients with chronic phase chronic myeloid leukemia: Primary results of the phase 4 BYOND study. Leukemia 2020;34:2125-37.