BMC Research Notes

RESEARCH NOTE Open Access

Late presentation of chronic myeloid leukaemia patients in a low-income country: the prognostic implications and impact on treatment outcome

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Abstract

Background In Nigeria, since 2002, Imatinib mesylate (glivec®) has been available freely to chronic myeloid leukaemia (CML) patients but only at a tertiary health care centre in the southwestern part of the country. Despite this, it is not readily accessible to many patients due to the distance and other challenges including low socioeconomic status and political problems, preventing timely access to specialist care. This study evaluated the effect of the baseline characteristics on the prognostic implication and treatment outcome of CML patients in Nigeria.

Method This study retrospectively evaluated the baseline characteristics, clinical presentations and treatment outcomes of 889 CML patients over 18 years (2002–2020). Of these, 576 (65%) patients had complete information with up-to-date BCR::ABL1 records. These 576 patients were categorized based on their responses to Imatinib therapy into three groups viz.; Optimal response (OR) defined as BCR::ABL1 ratio of < 0.1% or major molecular remission (≥ 3-log reduction of BCR::ABL1 mRNA or BCR::ABL1 ratio of < 0.1% on the International Scale), Suboptimal response (SR) with BCR::ABL ratio of 0.1–1%, and Treatment failure (TF) when MMR has not been achieved at 12 months. The variables were analyzed using descriptive and inferential statistics and a p-value < 0.05 was considered statistically significant.

Results The result revealed a median age of 37 years at diagnosis with a male-to-female ratio of 1.5:1. The majority (96.8%) of the patients presented with one or more symptoms at diagnosis with a mean symptom duration of 12 ± 10.6 months. The mean Sokal and EUTOS scores were 1.3 ± 0.8 and 73.90 ± 49.09 respectively. About half of the patients presented with high-risk Sokal (49%) and EUTOS (47%) scores. Interestingly, both the Sokal ($r = 0.733$, $p = 0.011$) and EUTOS ($r = 0.102$, $p = 0.003$) scores correlated positively and significantly with the duration of symptoms at presentation. Based on response categorization, 40.3% had OR while 27.1% and 32.6% had SR and TF respectively.

Conclusion This study observed a low optimal response rate of 40.3% and treatment failure rate of 32.6% in our CML cohort while on first-line Imatinib therapy. This treatment response is strongly attributable to the long duration

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of symptoms of 12 months or more and high Sokal and EUTOS scores at presentation. We advocate prompt and improved access to specialist care with optimization of tyrosine kinase inhibitor therapy in Nigeria.

Keywords Chronic myeloid leukaemia, Low-income country, Sokal score, Imatinib Mesylate, Treatment outcomes

Background

Chronic myeloid leukaemia (CML) is a clonal, acquired genetic disorder of haemopoietic stem cells commonly defined by the presence of the Philadelphia chromosome (Ph+), detected in about 95% of patients [1]. The Ph+arises from the reciprocal translocation of genetic material between chromosomes 9 and 22. The resultant BCR::ABL1 oncoprotein is a constitutively active tyrosine kinase that activates numerous signal transduction pathways, leading to uncontrolled cell proliferation and reduced apoptosis [1, 2]. In the United States, the age-adjusted incidence is 1–2 cases per 100,000, accounting for about 15% of newly diagnosed cases of leukaemia in adults [2].

The natural history of CML is that of a triphasic disease, comprising the chronic phase (CP), accelerated phase (AP) and the final blastic phase (BP) [1, 2]. Most patients present during the chronic phase, and the transition from CP to more advanced stages (AP and BP) is believed to result from genomic instability [3]. Some patients are diagnosed asymptomatically during routine medical evaluation but may present with clinical features related to anaemia, weight loss, abdominal swelling/discomfort or other complications related to advanced disease [2].

The stage at presentation and the presenting clinical features may significantly affect the overall outcome of treatment. Thus, the prognostic score at presentation needs to be evaluated and the Sokal score has shown to be very useful in pre-determining patients' response to imatinib treatment [4, 5].

Treatment of CML with tyrosine kinase inhibitor (TKI) has been reported to induce a good response with durable remission and prolonged survival [6–8]. At 12 months of treatment with TKI, the European Leukaemia Net (ELN) defines optimal treatment response as being able to achieve a BCR::ABL1 ratio of <0.1% (major molecular remission, MMR) and/or progressive increasing molecular remission after 12 months. The suboptimal response is defined by a BCR::ABL1 ratio of 0.1–1% at 12 months of commencement of TKI while treatment failure is defined by non-achievement of MMR (BCR::ABL1 ratio>1%) at 12 months of commencement of TKI, or thereafter a loss of MMR or presence of clonal disease progression [9].

In Nigeria, most CML patients are treated in a referral tertiary health care centre where imatinib mesylate (Glivec®) is given to CML patients free via the Glivec International Patient Assistance Program (GIPAP), however, many of these patients present late before they can have access to Glivec® and this invariably affects the overall response to treatment and treatment outcome. It is on this premise that we evaluated the baseline characteristics of our CML patients and the effect on their treatment response.

Methods

The study retrospectively evaluated the baseline characteristics, clinical presentation, and response to imatinib treatment of CML patients managed at a referral centre between the years 2002 and 2020. After ethical approval, 889 medical records were reviewed to extract the demographic and baseline information (age, sex distribution, symptoms and duration of symptoms, platelet count, blast cell count, spleen size, and the phase at presentation) of the patients at diagnosis. BCR::ABL1 transcript quantification was performed using the Reverse Transcriptase Quantitative Polymerase Chain Reaction (RT-qPCR-TaqMan Chemistry) method. In contrast, the transcript variant was performed using the Seeplex Leukaemia BCR::ABL1 transcript kit (Seegene, Seoul, Korea). In summary, the quantification steps involved include RNA extraction from whole blood/buffy coat using the Zymo-Research® extraction kit followed by RNA transcription to produce cDNA and finally quantitative PCR assay (Agilent Stratagene –Mx3005P by Agilent Technologies, USA). Both transcript quantification and variant assay are mandatory at diagnosis, and quantification is recommended every 3–6 months for monitoring. The patients were categorized into various prognostic risk categories using the Sokal and EUTOS scores. The Sokal score was determined using the age, spleen size, platelet count and blast count and was calculated using the formula: - Sokal score=Exp [0.0116 × (age in years −43.4)+0.0345 × (spleen size −7.51)+0.188 9 ([platelet count/700]2–0.563)+0.0887 × (blast cell counts −2.10)], where Exp is the exponential function. The patients were categorized into the three risk groups based on their Sokal score as proposed by Sokal et al. Low-risk (Sokal score of less than 0.8), intermediate-risk (Sokal score between 0.8 and 1.2), and high-risk (Sokal score greater than 1.2) [10]. The European Treatment and Outcome Study (EUTOS) risk score for CML uses the spleen size (cm) and the peripheral basophil percentage and was calculated using the formula: (7 x basophil [%]) + (4 x spleen [cm]). Two risk groups were identified as proposed by EUTOS and used to categorize the patients into low-risk (score of less than 87) and high-risk (score of greater

Table 1 Baseline characteristics of 889 CML patients at presentation

1	Age (years) [mean ± SD; range]	38.3 ± 12.9; 6.0–80.0
2	Gender	
	Male (M) (n, %)	541 (61)
	Female (F) (n, %)	348 (39)
	M:F	1.5:1
3	Asymptomatic [n, %]	28 (3.2)
	Symptomatic [n, %]	861 (96.8)
4	Duration of symptoms (months) [mean ± SD; range]	12.2 ± 10.6; 0–96
	(0 – 12 months) (n, %)	545 (61)
	(> 12 months) (n, %)	344 (39)
5	Spleen size (cm) [mean ± SD; range]	10.2 ± 6.6; 0–32
	< 10 cm [n,%]	467 (52)
	≥ 10 cm [n,%]	422 (48)
6	Platelet count (x 10^9cells/L) [mean ± SD; range]	413.8 ± 290.4; 54-2120
7	Blast count (%) [mean ± SD; range]	4.1 ± 5.7; 0–46
8	Sokal risk score [mean ± SD; range]	1.3 ± 0.8; 0.29–6.96
	Low (< 0.8) [n, %]	157 (18)
	Intermediate (0.8–1.2) [n, %]	294 (33)
	High (> 1.2) [n, %]	438 (49)
9	Eutos risk score [mean ± SD; range]	73.90 ± 49.09 ;0-274
	Low (< 87) [n, %]	471 (53)
	High (≥ 87) [n, %]	418 (47)
10	Phase at presentation	
	Chronic [n, %]	762 (86)
	Accelerated [n, %]	98 (11)
	Blastic [n, %]	29 (3)

Table 2 Baseline symptoms of 889 CML patients at presentation

S/N	Presenting symptoms	Frequency (*n*)	Percentage (%)
	Asymptomatic	28	3.2
1	Abdominal swelling/ distention	591	66.5
2	Abdominal pain/discomfort	382	42.9
3	Easy satiety	411	46.1
4	Weight loss	314	35.3
5	Fever	268	30.2
6	Excessive sweating	196	22.1
7	Body weakness	173	19.5
8	Body pains	123	13.8
9	Bone pains	64	7.1
10	Head ache	59	6.6
11	Dizziness	72	8.1
12	Leg swelling	66	7.4
13	Breathlessness	54	6.1
14	Easy fatiguability	169	19.0
15	Cough	51	5.7
16	Bleeding diathesis	32	3.5
17	Skin rashes/itching	25	2.8
18	Granulocytic sarcoma	21	2.4
19	Hearing impairment	17	1.9
20	Visual impairment	8	0.8
21	Priapism	37	4.2
22	Tinnitus	40	4.5
23	Blurred vision	49	5.5
	Number of patients with symptoms	861	96.8

than or equal to 87) [11]. Using the European Leukaemia Network (ELN) and the National comprehensive cancer network (NCCN) criteria, 576 patients with regular clinic visit and at least 2 BCR::ABL1 results for at a minimum of one year) were subsequently categorized into 3 groups; optimal responders, suboptimal responders, and the treatment failure groups based on their BCR::ABL1 results. Optimal response at 1 year was defined as a BCR::ABL1 ratio of <0.1% or the achievement of MMR (≥3-log reduction of BCR::ABL1 mRNA or BCR::ABL1 ratio of <0.1% on the International Scale)while suboptimal response was defined as a BCR::ABL1 ratio of 0.1-1%. Treatment failure was defined as a BCR::ABL1 ratio of >1% [12, 13]. Statistical analysis was done using IBM SPSS version 23(SPSS, Chicago, IL, http://www.spss.com). Variables were presented as mean, median, range, and percentages. Pearson's correlation was calculated to test the correlation between the duration of symptoms at diagnosis and the risk stratification score.

Results

Table 1 shows the baseline characteristics of the 889 cases reviewed. The median age at diagnosis was 37 years, range (6-80years). The male-to-female ratio was 1.5:1. Twenty-eight (3.2%) patients were asymptomatic at diagnosis while 861 (96.8%) presented with one or more symptoms. The commonest symptoms were those related to splenomegaly. The mean duration of symptom(s) at presentation was 12±10.6 months, range (0–96). The majority of the patients (86%) were diagnosed in the chronic phase of the disease while 11% and 3% presented in accelerated and blastic phases respectively. The mean Sokal score was 1.3±0.8 with almost half (49%) presenting with a high score, while 33% and 18% presented with intermediate and low scores respectively. Similarly, the European Treatment Outcome Study (EUTOS) score was used for the risk stratification of the patients and a mean score of 73.90±49.09 was observed. About half of the patients (47%) presented with a score of ≥87 and were categorized as high risk, while the remaining 53% had scores less than 87 and were classified as low risk.

Table 2 shows the symptoms at presentation. Twenty-eight (3.2%) cases were asymptomatic and were diagnosed on routine medical screening while 861 (96.8%) presented with one or more symptoms at diagnosis. The commonest symptoms were those related to splenomegaly (abdominal swelling/discomfort/pain, and easy satiety).

Table 3 shows the relationship between the duration of symptoms and the risk stratification scores (Sokal and EUTOS). The duration of symptoms had a statistically significant and positive correlation with both Sokal (r=0.733, p-value=0.011) and EUTO (r=0.102, p-value=0.003) scores at diagnosis. The corresponding Scatter plots between the duration of symptoms (months) and baseline Sokal and EUTOS scores at presentation are depicted in Figs. 1 and 2 below.

Figure 3 shows the categorization and proportion of 576 CML patients with Optimal response (OR), Suboptimal response (SR), and Treatment failure (TF). Of the 576 patients, 232 (40.3%) belong to the OR category while 156 (27.1%) and 188(32.6%) were categorized as SR and TF respectively.

Table 3 Correlation between risk stratification scores and duration of symptoms

Risk Stratification scores	Duration of symptoms (Months)	
	r-value	*p*-value
Sokal Score	0.733	0.011*
EUTOS score	0.102	0.003*

**p*-value significant at < 0.05

Discussion

This study evaluated the characteristics of CML patients at a referral center from a low- and middle-income country (LMIC) where CML patients received free imatinib via the Glivec International Patient Assistance Program (GIPAP) now the Max Solution (MAS), fronted by Novartis pharmaceutical and the Max Foundation. A review of the medical records of 889 CML patients revealed a median age of diagnosis of 37 years. This result is similar to other studies where the median age at diagnosis among CML patients of African descent was not more than 40 years [14, 15]. This value is lower than what was obtained from studies from the Western world where CML is a disease of older age [16–18]. The lower age incidence pattern of CML patients in this study is believed to be due to the age distribution of the African population rather than any other inherent biological characteristics [11]. The Male to Female ratio of 1.5:1 reported from this study is similar to the ratio reported from similar studies

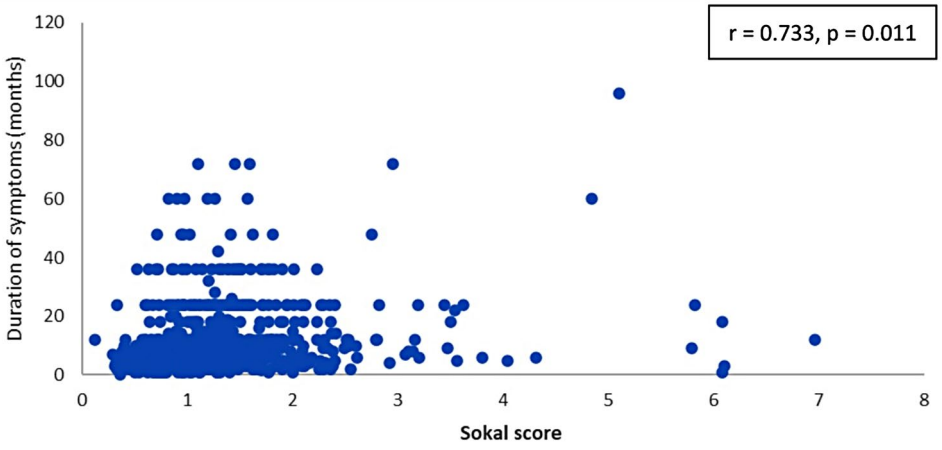

Fig. 1 Scatter plots showing the relationship between the duration of symptoms (months) and baseline Sokal scores. N=889

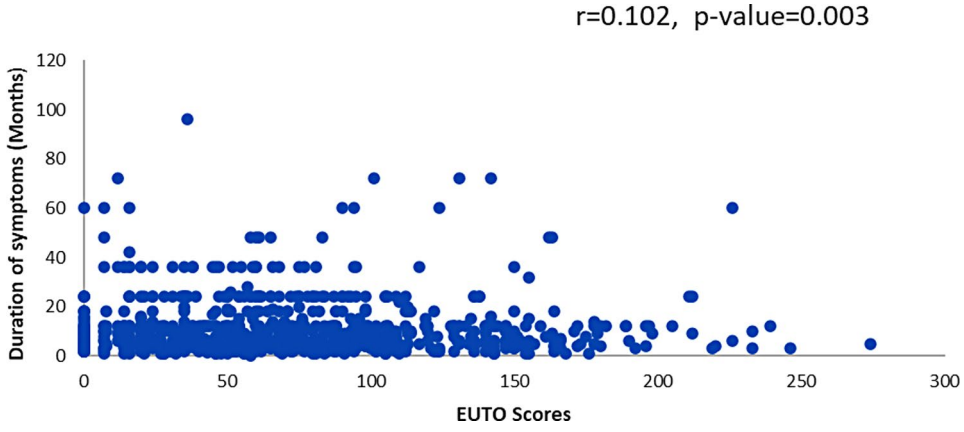

Fig. 2 Scatter plots showing the relationship between the duration of symptoms (months) and baseline EUTOS scores. N=889

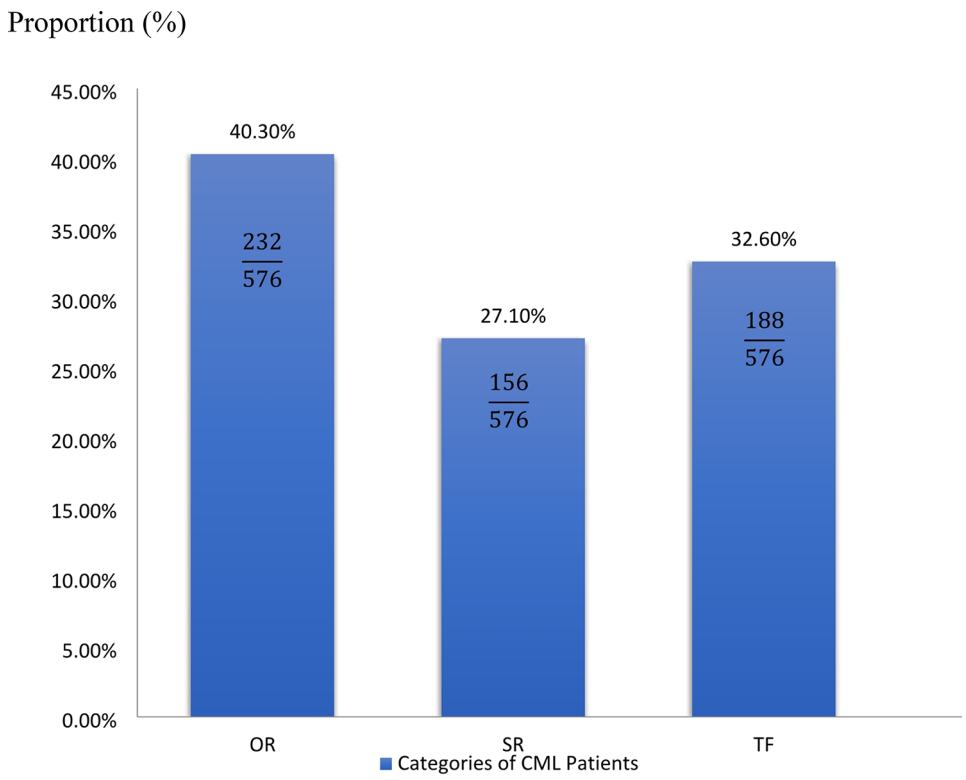

Fig. 3 Categorization and Proportion of 576 CML patients with Optimal response (OR), Suboptimal response (SR), and Treatment failure (TF)

on CML in other parts of the world [15–18]. The male predominance in the incidence of CML has shown in this study is more likely to result from the difference in risk than in latency because it seems males have more target cells and are at risk of developing CML than females [18].

The mean duration of symptoms at presentation in this study was 12±10.6 months. A similar longer mean duration of 18 months at diagnosis was reported by Koffi et al. among CML patients in Cote d'Ivoire [15]. The long duration of symptoms before diagnosis reported in our cohort is incomparable to what has been reported from centres in developed countries where the majority of patients are diagnosed asymptomatically during routine medical screening. This has been attributed to the availability of specialized healthcare that is accessible to patients [19, 20]. The reason for this late presentation of our CML cohort as reported is probably due to ignorance and poor healthcare-seeking habits by the patients [21]. In underdeveloped and developing nations, people usually attribute their sickness to a spiritual attack that can only be cured through divine interventions thereby resorting to prayers or consulting the traditional healers before going to the hospital. Moreover, access to specialist care where prompt and accurate diagnosis of CML would be made may be a challenge and this is unconnected to difficult access to a tertiary health care facility, lack of robust health insurance scheme, poverty and low socioeconomic level, recurrent civil unrest, political crisis and high level of illiteracy among the populace [22].

Reports have shown that in developed countries, up to 50% of CML patients were diagnosed at the asymptomatic stage during routine medical checkups or investigations for other illnesses [2, 19]. Conversely, in this study, only 3.2% of the patients were diagnosed asymptomatically. A low proportion of asymptomatic presentation of 3.9% was also reported by Bhatti et al. [23] in Pakistan which is also a developing country like Nigeria where the accessibility to timely specialized medical care is also limited, and medical checkups are not routinely done until there are obvious clinical signs of disease.

This study showed a mean Sokal score of 1.3±0.8 at presentation, with almost half (49%) presenting with high-risk scores. This finding is similar to what was obtained from an earlier study on the survival of CML in Nigeria where the majority (64%) of the patients were diagnosed with intermediate, and high-risk Sokal scores [24]. Similarly, in Cote d'Ivoire, Koffi et al. [15] reported a high Sokal score in 39% of the CML patients. In contrast, Hoffman et al. [17] and Lee et al. [5] reported a greater proportion of CML patients that presented with lower Sokal scores in Europe and the United States respectively. Further risk categorization of the BCR::ABL1 positive CML patients was done based on the European Treatment and Outcome Study Score (EUTOS) score [13]. The EUTOS score, a more recent risk stratification score

was described by Hasford et al. 2011 to predict complete cytogenetic response and subsequently progression free survival in patients with CML on imatinib. Two risk groups were identified as proposed by EUTOS and used to categorize the patients into low-risk (score of less than 87) and high-risk (score of greater than or equal to 87) [13]. This index study revealed that a sizeable number (47%) of patients presented with high-risk scores. This contradicts the findings from a study on the risk classification of 618 CML patients in Southern India using the EUTOS risk score. Findings from the latter study categorized 64% of the patients into low risk and 35.9% into high risk [25]. It is important to state that since India and Nigeria have a similar socioeconomic characteristic, [26] this disparity may not be unconnected to the fact that all their patients were enrolled in the chronic phase of CML. However, access to imatinib and other TKIs remains a challenge in Nigeria, it is made available freely only at one centre via the Glivec International Patient Assistance Program (GIPAP), now the Max Solution (MAS), fronted by Novartis pharmaceutical company and the Max Foundation, it will be important to compare this with the situation in India.

The factors responsible for the high proportion of patients presenting with high-risk prognostic scores compared with the Caucasians, cannot be far-fetched. It is probably connected to socioeconomic factors such as poverty, poor access to health care, poor health-seeking behaviours, paucity of specialist physicians, and scarcity of specialized health care. All these factors delay the presentation to the hospital and therefore delay the diagnosis.

As seen in this study, there was a statistically significant positive correlation between the Sokal and EUTOS scores and the duration of symptoms at presentation). Although, a study done by Usman et al. [4] revealed that variables such as age, and disease duration at the time of starting imatinib did not show any significant influence on response to imatinib, however, long duration of symptoms before the commencement of treatment in CML patients have been said to predict poor prognosis [27, 28].

Though the Sokal score was developed in the pre-imatinib era, it still retains prognostic significance in imatinib-treated patients [4]. Thompson et al. [19] reported a high Sokal score as a predictor of increased relapse while Jabbour et al. [29] reported a better response rate in patients with a low baseline Sokal score. Moreover, a recent study in Nigeria also highlighted the importance of the Sokal score in imatinib-treated CML patients, Sokal score was identified as a predictor of imatinib-induced thyroid dysfunction [30].

Furthermore, when we evaluated the treatment outcome of the patients using the European leukaemia Network (ELN) criteria, 40.3% of the patients had an optimal response (OR), while 27.1% and 32.6% had suboptimal and treatment failure respectively. The 40.3% of optimal responders reported in this study is lower when compared with what was reported by Palandri et al. [6], in Italy, Preetesh et al. [7] in the United States, and Jabbour et al. [8] in the IRIS study. This lower overall response rate is related to multiple factors including late diagnosis, delayed access to TKIs, and poor adherence rate [31]. Patients with suboptimal and treatment failure are managed following the NCCN and ELN guidelines. Their recommendations include; evaluation of the patient's compliance and the possibility of drug interaction, and mutational analysis. Physicians can consider increasing the dose of imatinib to a maximum dose of 800 mg or switching to alternate TKI. In addition to the earlier mentioned, allogeneic stem cell transplantation (ASCT) is recommended for patients with treatment failure [12, 13]. Though second and third-line TKIs are available free courtesy of MAS but to a limited number of patients in Nigeria, management of patients with suboptimal and treatment failure in Nigeria is a herculean task. This is mainly due to the limited access to facilities for mutational analysis which is often unaffordable by most patients and the unavailability of facilities for ASCT. Undoubtedly, late presentation as a result of poor socioeconomic status is a major factor responsible for the poor response of patients to imatinib in Nigeria.

Conclusion

This study reported a low optimal response rate of 40.3% and a high treatment failure rate of 32.6% in Nigerian CML patients while on first-line Imatinib therapy. This observation is strongly attributable to the long duration of symptoms of ≥12 months before diagnosis and a resultant high risk categorisation score at presentation. Timely, accessible and affordable specialized care is strongly advocated to reverse the trend.

Acknowledgements

We like to appreciate the management of the Obafemi Awolowo University and Obafemi Awolowo University Teaching Hospitals Complex, Ile-Ife, Nigeria for providing the enabling environment for research.

Author contributions

NEA, BRA, SL and DMA contributed to conception and design of the study. NEA, AIO, BRA, ABA and AAJ obtained the data, NEA, AIO, BRA, AAJ, ABA, SL, BOO and DMA analysed and interpreted the data. NEA, AIO, BRA, ABA, AAJ, SL, BOO and DMA drafted the original manuscript. NEA AIO, BRA, ABA, AAJ, SL, BOO and DMA critically revised the manuscript. All authors read and approved the final manuscript.

Funding

No fund was received for carrying out this research.

Data availability

The data sets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethical approval and consent to participate

Ethical approval was obtained from the Ethics and Research Committee of the Obafemi Awolowo University Teaching Hospitals Complex, Ile-Ife, Nigeria. Consent to participate did not apply to this study due to its retrospective nature.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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Received: 18 June 2024 / Accepted: 22 August 2024
Published online: 03 September 2024

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