Baseline blood count levels increase odds of cytopenia among CML patients in Kenya: a case control study

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Abstract

Background

Imatinib is the gold standard for the treatment of all phases of Philadelphia positive Chronic Myeloid Leukemia (CML). During treatment, patients may develop cytopenia. We aimed to study the baseline characteristics and factors associated with cytopenia at a Nairobi Hospital.

Methods

This was a retrospective case-control study of patients aged ≥ 18 years on follow-up at the Glivec International Patient Access Program (GIPAP) clinic from 2007–2015. The cases consisted of CML patients on imatinib who developed cytopenia. The controls were CML patients on imatinib who did not develop cytopenia. Baseline socio – demographic, clinical, hematologic, and molecular data were retrieved from patients' files. Chi square or fishers' exact tests were used to analyze for differences between cytopenia and no cytopenia. Binary logistic regressions were employed to identify relationships. Univariate and multivariate analyses were done to identify independent predictors of cytopenia. Odds ratios (OR) were presented including the 95% confidence intervals and respective p values.

Results

A total of 201 patients were studied. Males were 52%, 42% were aged 36–50 years, 70% had symptoms for > 12 months before diagnosis, 78.6% had B symptoms at baseline, 80% had a moderate splenomegaly at baseline, 40% and 37.4% developed cytopenia within 3 months and 3–6 months respectively after imatinib initiation. Baseline neutrophilia, neutropenia, anaemia, thrombocytosis, thrombocytopenia was found in 68%, 11%, 11%, 23.5% and 11% respectively. Baseline hemoglobin, neutrophil and platelet level were significantly different between the cytopenia and the no cytopenia group. On univariable analysis, baseline anemia with hb < 7.9g/dL (p = 0.002), neutropenia (p = 0.001), neutrophilia > 100,000/mm^3 (p = 0.002) and thrombocytopenia (p = 0.001) increased the odds of developing cytopenia. On multivariable analysis, baseline anaemia (p value < 0.002), neutropenia (p value < 0.001), thrombocytopenia (p value, < 0.001) and thrombocytosis (p value, 0.033) increased the odds of developing cytopenia.

Conclusion

Odds of cytopenia were higher in presence of baseline cytopenia and thrombocytosis. Clinicians should have a high index of suspicion for these patients.

Introduction

Chronic myeloid leukaemia (CML) is due to a clonal disorder that cause granulocyte cell line proliferation (1). It develops following a translocation that occurs reciprocally between two somatic chromosomes, t (9:22) (2).

The fusion protein resulting from this translocation, the BCR-ABL1, is a tyrosine kinase which acts independently of any stimulation and results in the development of CML (3). Tyrosine kinase inhibitors (TKI) block this kinase and in turn block signaling pathways involved in myeloid proliferation while stimulating apoptosis and cellular adhesion(4, 5). CML is more common in adults than in children and has an excellent five year overall survival (6, 7). The disease is also common in the elderly and in men in the developed world (6). Myelosuppression may develop during treatment of CML with imatinib, a TKI, especially in the setting of advanced disease (8).

Available data reported that longer time from diagnosis to treatment, prior interferon or imatinib therapy, and a lower white blood cell count at the initiation of TKI therapy were associated with an increased risk of grade II to IV cytopenia (9). Guillot et al also reported that advanced disease, baseline low hemoglobin, history of interferon induced cytopenia and previous busulphan therapy were risk factors for cytopenia (10). Mauro et al found that increased percentage of bone marrow blasts, low hemoglobin level, a longer time from diagnosis to treatment and a history of cytopenia were risk factors for cytopenia (11).

Cytopenia is a recognized problem at the Glivec International Patients' Assistance Program (GIPAP) clinic in Nairobi. Its presence may be associated with poorer response to treatment (12). Understanding the factors associated with its development during imatinib therapy will enable clinicians to plan for its prevention and management. We aimed to study the sociodemographic as well as the clinical and laboratory characteristics associated with increased odds of development of cytopenia among CML patients on imatinib at the GIPAP clinic.

Methods

Study Design, Aim and Setting

This was a retrospective case-control study of patients, ≥ 18 years of age, on imatinib, enrolled between 2007 and 2015. It aimed to analyze the sociodemographic as well as the clinical and laboratory characteristics associated with increased odds of development of cytopenia among CML patients on imatinib. The Max access program provides imatinib therapy for patients enrolled in the GIPAP (CML) clinic at the Nairobi Hospital. Cumulatively, the clinic has 1200 patients. An average of 150 patients attend the clinic bi-weekly. The age range of patients seen in the clinic is six years to 75 years. Males in the clinic are in similar proportion to females and almost 90% present in chronic phase. Patients who initiate treatment are compliant with treatment with adherence rates of approximately 80% (13).

Study population and sample size

The estimated required sample size for cases and controls was 76 each using a simple approximation for calculating sample sizes for comparing independent proportions by Fleiss (1980) (14). Consecutive sampling was used. The cases were patients with cytopenia matched for age, sex and calendar year of enrolment with the controls, who had no cytopenia. A control was sampled each time a case was found. Data on sociodemographic, clinical and laboratory characteristics were extracted using a coded questionnaire, which in turn was entered into an excel sheet.

Variables

Sociodemographic variables included age, sex, marital status, level of education and occupation.

Clinical variables included symptom duration prior to diagnosis, determined by diagnosis of CML less than or more than 12 months after onset of symptoms. Presence of B symptoms was defined as unintentional weight loss of $\geq$ 10 kg in the preceding 6 months, fevers, and night sweats. Spleen size was categorized as normal spleen size (< 11cm), moderately enlarged spleen (11-20 cm), or a massively enlarged spleen (>20 cm) as documented in patient files from clinical examination or imaging. Time to development of cytopenia was defined as less than 3 months, 3-6 months and 6-12 months after imatinib initiation. Laboratory characteristics included the CBC with grade of cytopenia determined as per National Cancer Institute Common Terminology Criteria for Adverse Events v.3 (15). Baseline BCR-ABL1 from RT-PCR was collected.

Data Management

Data from excel was imported into the statistical analysis software for data management and analysis. Continuous data was presented using means and respective standard deviations (SD). Counts and corresponding percentages were used for categorical variables such as gender of participants and cytopenia group. Bivariate comparisons such as comparisons of cytopenia versus no cytopenia was done using chi square or fishers' exact tests for categorical variables as deemed appropriate. Univariable logistic regression analysis was employed for demographic, clinical and laboratory variables associated with cytopenia. The odds ratio (OR) and 95% Confidence Intervals was also reported. Stata package, version 15.1 was used during statistical analysis. There were some (50 out of 201 records) BCR-ABL1 reports that were missing. To mitigate for this during the regression modeling, a category for missing data was created to ensure that the multivariable model included all the observations as available for all the covariates. Tables were used to display results. All methods were carried out in accordance with relevant guidelines and regulations.

Results

Baseline Characteristics

Ninety four (94) patients with cytopenia and 107 controls were included. Females were 97 and males were 104, 42% (85) of the 211 were aged 36–50 years, 30% (61) between 18–35 years and 27% (55) > 50

years, 73.1% (147) were married, 75.6% (152) were employed and 47.8% (96) and 46.8% (94) had secondary and tertiary education respectively. Clinically, 70% (142) had symptoms for ≥ 12 months before diagnosis, 78.6% (152) had B symptoms at diagnosis, and 80% (161) and 2.5% (5) had a baseline moderate and massive splenomegaly respectively. BCR-ABL was 0–25% for 35.8% (72), 26–75% for 27.9% (56) and > 75% for 11.5% (23) from 151 results available, baseline Hb was < 8 g/dl in 11% (22), 8–10 g/dl in 36.7% (73) and > 10 g /dl in 52.3% (104). Baseline neutrophil was > 7.5 to > 100 x 10^9/L in 68% (134) and < 1.5 x 10^9/L in 22 patients while the rest had normal levels. Baseline platelets count > 450 x 10^9/L was found in 23.5% (47) and < 150 x 10^9/L in 11% (22). There was similar distribution among cytopenia and no cytopenia groups.

Bivariate Analysis

Sex, age, marital status, occupation and education level were similar between the cytopenia and no cytopenia groups, p values > 0.05 (Table1).

Table 1
Bivariate Analysis of Sociodemographic Characteristics

Variable	No Cytopenia n (%)	Cytopenia n (%)	P value
Gender			
Female	54 (50.5)	43 (45.7)	0.504
Male	53 (49.5)	51 (54.3)	
Age category			
17–35 years	31 (29)	30 (31.9)	0.498
36–50 years	43 (40.2)	42 (44.7)	
> 50 years	33 (30.8)	22 (23.4)	
Marital status			
Divorced	2 (1.9)	0 (0)	0.321
Married	80 (74.8)	67 (71.3)	
Single	24 (22.4)	27 (28.7)	
Widowed	1 (0.9)	0 (0)	
Occupation			
Employed	34 (31.8)	43 (45.7)	0.069
Retired	3 (2.8)	6 (6.4)	
Self-employed	49 (45.8)	26 (27.7)	
Student	4 (3.7)	5 (5.3)	
Unemployed	17 (15.9)	14 (14.9)	
Education			
Primary	7 (6.5)	4 (4.3)	0.333
Secondary	55 (51.4)	41 (43.6)	
Tertiary	45 (42.1)	49 (52.1)	

Time duration to diagnosis, spleen size and positive B symptoms were similar between the cytopenia and the no cytopenia groups (Table 2).

Table 2
Bivariate analysis of time duration to diagnosis

Time duration to diagnosis	Cytopenia	No cytopenia	P value
Bivariate Analysis	**36 (33.6)**	**23 (24.5)**	**0.154**
Early (< 12 months)			
Late (> 12 months	**71 (66.4)**	**71 (75.5)**	
Spleen size			
11–20 cm	83 (77.6)	78 (83)	0.632
> 20 cm	3 (2.8)	2 (2.1)	
Normal	21 (19.6)	14 (14.9)	
B symptoms present at diagnosis			
No	26 (24.3)	17 (18.1)	0.284
Yes	81 (75.7)	77 (81.9)	

There was a significant difference in baseline Hb, baseline neutrophils, and baseline platelets among the cytopenia and no cytopenia groups, all p values < 0.001 (Table 3).

Table 3
Bivariate Analysis of Laboratory Characteristics

Variable	No Cytopenia n (%)	Cytopenia n (%)	P value
BCR-ABL at baseline (%)			
0–25%	37 (34.6)	35 (37.2)	0.034*
26–75%	25 (23.4)	31 (33)	
76–125%	13 (12.1)	6 (6.4)	
> 125%	0 (0)	4 (4.3)	
Missing	32 (29.9)	18 (19.1)	
Baseline platelets (x 10^9)			
< 150	4 (3.8)	18 (19.1)	< 0.001*
150–450	80 (75.5)	51 (54.3)	
451–999	22 (20.8)	20 (21.3)	
1000+	0 (0)	5 (5.3)	
Baseline neutrophils (x 10^9)			
< 1.5	4 (3.9)	18 (19.1)	< 0.001*
1.5–7.5	27 (26.2)	14 (14.9)	
7.6–100	58 (56.3)	32 (34)	
> 100	14 (13.6)	30 (31.9)	
Baseline HB (g/dL)			
< 6.5	1 (1)	2 (2.1)	< 0.001*
6.5–7.9	0 (0)	19 (20.2)	
8–10	47 (44.8)	26 (27.7)	
> 10	57 54.3)	47 (50)	

There was a significantly lower proportion of the participants with 0–25% baseline BCR-ABL1 among the no cytopenia than the cytopenia group, p = 0.034.

Logistic regression Analysis

Demographic characteristics were not significantly associated with cytopenia (Table 4).

Table 4: Logistic Regression Analysis, Socio-Demographic Characteristics

	Univariable OR (95% CI)	P value	Multivariable OR (95% CI)	P value
Age Category				
17-35 years	0.991 (0.513-1.913)	0.978	1.153 (0.507-2.62)	0.734
36-50 years	Reference		Reference	
>50 years	0.683 (0.343-1.357)	0.276	0.815 (0.308-2.15)	0.681
Gender				
Female	0.828 (0.475-1.442)	0.504	1.468 (0.589-3.65)	0.41
Male	Reference		Reference	
Marital Status				
Married	Reference		Reference	
Single/divorced/widow	1.194 (0.639-2.229)	0.578	0.965 (0.39-2.385)	0.938
Employment Status				
Not Employed	0.824 (0.402-1.689)	0.597	0.56 (0.195-1.611)	0.282
Employed	Reference		Reference	
Self Employed	0.42 (0.218-0.807)	0.009	0.36 (0.13-1.003)	0.051
Education Level				
Primary/Secondary	0.667 (0.382-1.164)	0.154	0.615 (0.25-1.511)	0.289
Tertiary	Reference		Reference	

Clinical characteristics were not significantly associated with the development of cytopenia (table 5).

Table 5: Logistic Regression Analysis, Clinical Characteristics

	Univariable		Multivariable	
	Odds Ratio (95% CI)	P value	Odds Ratio (95% CI)	P value
Time duration to diagnosis				
Early	0.639 (0.344-1.185)	0.155	0.681 (0.154-3.016)	0.613
Late	Reference		Reference	
Spleen size				
Abnormal	Reference		Reference	
Normal	0.717 (0.341-1.505)	0.379	0.469 (0.122-1.794)	0.268
B symptoms				
No	0.688 (0.346-1.366)	0.285	1.368 (0.328-5.707)	0.667
Yes	Reference		Reference	

A baseline Hb < 7.9g/dL, a baseline neutropenia <1.5 x 10^9/L and baseline platelet count > 450 x 10^9/L or less than 150 x 10^9/L were associated with increased odds of cytopenia in both univariable and multivariable analysis. Neutrophil counts above 100 x 10^9/L increased the odds of cytopenia in the univariable analysis (table 6).

Table 6: Logistic Regression Analysis, Baseline Laboratory Characteristics

	Univariable		Multivariable	
	OR (95% CI)	P value	OR (95% CI)	P value
Baseline BCR-ABL1 (%)				
0-25	Reference		Reference	
26-75	1.311 (0.65-2.642)	0.449	1.059 (0.421-2.662)	0.904
>75	0.813 (0.316-2.092)	0.668	0.688 (0.192-2.463)	0.565
Missing	0.595 (0.284-1.246)	0.168	0.316 (0.111-0.905)	0.032
Baseline Neutrophils x10^9				
<1.5	8.679 (2.459-30.63)	0.001	17.571 (3.909-78.987)	<0.001
1.5-7.5	Reference		Reference	
7.6-100	1.064 (0.489-2.313)	0.875	1.087 (0.398-2.971)	0.87
>100	4.133 (1.672-10.22)	0.002	2.776 (0.798-9.653)	0.108
Baseline Hb (g/dL)				
<7.9	25.47 (3.302-196.4)	0.002	32.231 (3.502-296.653)	0.002
8-10	0.671 (0.363-1.241)	0.204	0.598 (0.269-1.327)	0.206
>10	Reference		Reference	
Baseline platelets x 10^9				
<150	7.059 (2.26-22.05)	0.001	17.036 (4.079-71.157)	<0.001
150-450	Reference		Reference	
451+	1.783 (0.91-3.491)	0.092	2.771 (1.083-7.088)	0.033

Discussion

This was a study of 201 patients, 94 with cytopenia and 107 with no cytopenia. The number of females and males enrolled in the study was similar at 97 and 104 respectively with good gender distribution between the cytopenia and the no cytopenia groups. Data from the USA have reported that more males than females are affected and more females survive the disease in comparison to males (6). Forty two percent (42%) of the patients were aged between 36–50 years, 73% were married, 75% were employed and literacy levels were high. These statistics are in keeping with the Kenya Demographic Health Survey (KDHS) data that reported that the country has a predominantly young population, 54.6% are married, and employment levels are 60% and 80% for males and females respectively. In addition, levels of literacy were high at > 80% among participants (16). In contrast, and with respect to age, data from the developed countries have reported that CML is a disease of the older population, with the SEER database reporting a median age of 66 years (6).

Clinically, 70% of the patients had symptoms for ≥ 12 months before diagnosis, 78.6% had positive B symptoms, 80% had a moderate splenomegaly and 40 % had used imatinib for ≤ 3 months and 34.7% for 3–6 months respectively before the cytopenia developed. The delay in diagnosis as evidenced by time to diagnosis and presence of B symptoms could be a result of weak health systems in Low and Middle Income Countries (LMIC) (17). Likewise the findings of baseline neutrophilia in majority of our patients is a reflection of diagnosis of CML at an advanced stage. In contrast, in the developed countries, up to 50% are asymptomatic at diagnosis and when symptoms are present, splenomegaly is seen in 46–76% (18, 19).

Sex, age, marital status, occupation and education level were similar between the cytopenia and no cytopenia groups and they did not increase the odds of developing cytopenia. A study carried out in Iraqi reported that females on imatinib had a predilection for anemia compared to males (20). This higher likelihood is probably due to the lower level of hemoglobin found in females at baseline compared to males (21). Anemia may also be related to other comorbidities which might be confounding factors in the analysis (22).

Clinical symptoms such as time duration to diagnosis, spleen size and positive B symptoms are markers of advanced disease and were similar between the cytopenia group and the no cytopenia group. These factors did not however, increase the odds of cytopenia. Splenomegaly is a marker of advanced disease and is known to be significantly linked to poor outcomes (23). Cytopenia has been reported to be more common in patients with advanced disease (12).

Blood counts and BCR-ABL1 differed significantly between the cytopenia and no cytopenia groups with more anemia, neutrophilia, thrombocytosis and thrombocytopenia in the cytopenia than the no cytopenia groups. Baseline anemia is known to accompany a higher baseline white blood cell counts, more frequent

splenomegaly, and more CML related deaths (24). Further, the anemia, neutropenia, thrombocytosis and thrombocytopenia increased the odds of cytopenia. Myelosuppression has been reported to contribute to poor response to treatment and to poor survival (25). A study among 527 patients in Nigeria reported that baseline anemia was an independent prognostic factor for poor overall survival (26). This is in contrast to a study conducted in Germany among CML patients that reported that hemoglobin level had no significant influence on overall survival (27). The baseline cytopenia may be due to bone marrow dysfunction or fibrosis with fibrosis developing due to late presentation of CML (28). Cytopenia persisting during treatment may also reflect disease progression or persistent disease (29). Such patients should be closely monitored with additional bone marrow and molecular assays to assess response. A few studies have reported that higher BCR-ABL1 levels are associated with poor outcomes. One study demonstrated that patients who experienced very severe myelotoxicity had a significantly higher BCR-ABL1 value after conducting FISH studies (30). In our study, level of baseline BCR-ABL1 did not have any impact on hematological toxicity.

The study had a few limitations. Being retrospective, there was missing data that could have affected the outcomes of our study. Further, the study results can only be applied to patients with grade 2–4 cytopenia. It was not possible to risk score the patients fully and correlate prognostic score with cytopenia development due to inadequate numbers of bone marrow aspirate and trephine results.

Conclusions

Our findings are similar to those of studies conducted both in sub-Saharan Africa and in the developed world. We recommend that physicians should have a high index of suspicion to recognize patients at risk of developing cytopenia. This includes patients with low baseline cytopenia as well as patients with baseline thrombocytosis.

List Of Abbreviations

CML - Chronic Myeloid Leukemia

GIPAP - Glivec International Patient Access Program

KNH/UON - Kenyatta National Hospital/University of Nairobi

KDHS - Kenya Demographic Health Survey

LMIC - Lower- and Middle-Income Countries

TKI - Tyrosine Kinase Inhibitor

Declarations

Ethics approval and consent to participate

Ethical approval was obtained from the Kenyatta National Hospital/University of Nairobi (KNH/UON) Ethics and Research Committee. Patient identifiers such as names were not collected, instead patients were given a numerical identifier. Data was stored in a password protected computer. Informed consent was obtained from all participants and for those under 18 years, from a parent or legal guardian. For confidentiality, the patients' charts were used only within the confines of the records department and only the investigators and study assistant had access to the files.

Consent for publication

Not applicable

Availability of data and materials

The dataset(s) supporting the conclusions of this article is(are) included within the article (and its additional file(s) which can be provided)

Competing interests

The authors declare that they have no competing interests

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Authors' Contributions

All authors contributed to the development of this manuscript (AM, JR, PO, ME, YB, MO, AO, SM, NAOA). AM and NAOA developed the idea and were in charge of study implementation including data collection. AM, JR, PO and ME were involved in data management, analysis and results writeup. AM, PO, YB and MO contributed in drafting and revision of the manuscript with considerable guidance and intellectual input from co-authors; ME and JR . AM has access to the data and take responsibility for the integrity and accuracy of the data. All authors (AM, JR, PO, ME, YB, MO, AO, SM, NAOA) contributed substantially to the interpretation of the data and gave approval for the final manuscript version.

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- CMLdata010918.xlsx