

Clinical and Laboratory Features of Nigerian Patients with Chronic Myeloid Leukaemia: A Cohort Study

Osho P. O¹, Aneke J. C², Ojo M. A¹, Onoja A. M³, Oni T.I¹.

¹Department of Haematology and Virology, University of medical sciences, Ondo state, Nigeria.

²Department of Haematology and Blood transfusion, Nnamdi Azikiwe University, Anambra state, Nigeria

³Department of Haematology and Blood transfusion, Federal University of Health Sciences, Otukop (FUHSO), Benue State, Nigeria

*Correspondence: Dr Patrick O. Osho. Department of Hematology and Virology, University of Medical Sciences, Ondo State, Nigeria. Email: droshopo@unimed.edu.ng.

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ABSTRACT

Introduction: Chronic myeloid leukaemia (CML) is a clonal haematological condition characterized by marked leukocytosis, with preponderance of leucocyte series at different levels of maturation. Bone marrow suppression with symptomatic cytopenias and end organ dysfunction have been reported in patients with CML, particularly in those with hyperleucocytosis or advanced disease. **Objectives:** This study aimed to highlight the spectrum of laboratory and clinical features of Nigerian patients with chronic myeloid leukaemia, at presentation. **Methodology:** This is a retrospective study which involved patients with CML seen in our facility over a six (6) year period between 2004-2010. The study was registered and approved by our institutional review board. The case records of all confirmed, Ph/BCR-ABL1-positive CML cases were retrieved from the departmental archives and information such as age, gender, degree of organomegaly, full blood count, results of biochemical parameters (liver and renal function tests, uric acid) and disease stage were extracted and recorded in a case proforma. **Results:** A total of 266 patients' case records; 157 males and 109 females (M:F = 1.4) was reviewed. In this study. Patients in the 21-40 years age group had the highest representation. More study patients had massive splenomegaly, compared with those with massive hepatomegaly; 62.7% vs. 14.1%. The proportion of study patients with chronic, accelerated and blastic phases of CML were 86.7%, 12.7% and 0.6%, respectively. **Conclusion:** The age at presentation of CML in our patients was earlier than previously reported among Caucasians. Majority of our patients presented in chronic phase had hyperleucocytosis with very few biochemical evidence of hepatic and renal impairment.

Key words: Chronic myeloid leukemia, Cytopenias, Hyperleucocytosis.



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INTRODUCTION

Chronic myeloid leukaemia (CML) is a clonal haematological condition characterized by marked leukocytosis, with preponderance of leucocyte series at different levels of maturation¹

It originates following a malignant transformation of a pluripotent stem cell which arises in majority of cases from a reciprocal translocation between chromosomes 9 and 22 t(9;22)(q34;q11), forming a fusion gene, which encodes the 210 kDa BCR-ABL oncoprotein.² The BCR-ABL oncoprotein is central in driving the massive expansion of myeloid elements in CML because of its constitutive tyrosine kinase activity, devoid of any regulation.³

In the evolution of CML, three (3) classical phases are recognized; chronic, accelerated and blastic phases. The chronic phase has the best overall survival, the blastic phase has the worst while the accelerated phase occupies an intermediate position⁴

The disease could be discovered incidentally, particularly in the chronic phase, when a high white blood cell count is discovered during routine blood count or an enlarged spleen is found on medical examination for an unrelated condition⁵ Among the common clinical features reported in symptomatic patients included, fatigue/lethargy, bleeding diathesis from platelet dysfunction, weight loss, anorexia, excessive sweating, abdominal fullness (usually due to massive splenomegaly) and malaise.⁶ Extra medullary involvement of the skin/soft tissues and lymph nodes have also been reported and could follow disease progression.⁷ In addition to these common presentations, a number of atypical presentations have been described even in the Nigerian cohort. Aneke et al and Joseph et al independently described cases of CML with digital gangrene and osteonecrosis in Nnewi, South East Nigeria and Jos, North Central Nigeria, respectively^{8,9} Bone marrow suppression with symptomatic cytopaenias and end organ dysfunction have been reported in patients with CML, particularly

in those with hyperleucocytosis or advanced disease.¹⁰

¹¹ This study was aimed at highlighting the spectrum of laboratory and clinical features of Nigerian patients with chronic myeloid leukaemia, at presentation.

MATERIALS AND METHODS

This is a retrospective study which involved patients with CML seen in our facility over a six (6) year period between 2004-2010. The study was registered and approved by our institutional review board. The case records of all confirmed, Ph/BCR-ABL1-positive CML cases were retrieved from the departmental archives and information such as age, gender, degree of organomegaly, full blood count, results of biochemical parameters (liver and renal function tests, uric acid) and disease stage were extracted and recorded in a case proforma.

Laboratory analysis

Full blood count (FBC), including white cell differential count was performed for all patients following standard protocols while serum transaminases were measured by the continuous monitoring method as described by Henderson and Moss.^{12,13} Serum total protein and albumin were analysed by the Biuret and automated dye binding methods, respectively.¹⁴ The phosphotungstic acid (PTA) method was used to measure serum uric acid levels, while the Fearon and Jaffe's methods were used to assay for urea and creatinine, respectively.¹⁵ The absolute neutrophil count (ANC) was calculated using the standard formula while the stratification of patients into chronic, accelerated and blastic phases was based on the WHO staging of CML^{12,16}

All clinical and laboratory information were those at presentation to our facility, patients whose details were completely lacking in the case notes were excluded from the study.

Statistical analysis:

All data analysis was performed with SPSS version 20 software (SPSS Inc., Chicago, IL, USA); laboratory and clinical variables of patients were expressed using descriptive statistics such as percentages, means and standard deviations.

This study was approved by the ethics and research committee of our hospital.

RESULTS

A total of 266 patients; 157 males and 109 females (M:F = 1.4) participated in this study. Patients in the 21-40 years age group had the highest representation (50.0%, Table 1). More study patients had massive splenomegaly, compared with those with massive hepatomegaly; 62.7% vs. 14.1%, Table 1. The proportion of study patients with chronic, accelerated and blastic phases of CML were 86.7%, 12.7% and 0.6%, respectively, Table 1.

A larger proportion of study patients had mild anaemia (Haematocrit 30-35.9 L/L) and normal platelet counts; 98/255 (38.4%) and 212/230 (92.2%), respectively, while 52/230 (22.6%) had elevated platelet count ($>450 \times 10^9/L$), Table 2. Hyperleucocytosis (white cell count $\geq 100 \times 10^9/L$) was observed in 121/253 (47.8%) of study patients while 25/253 (9.9%) presented with a normal white cell count (white cell count $< 12 \times 10^9/L$), Table 2. None of the study patients had severe neutropaenia (ANC $< 0.5 \times 10^9/L$) while 2/237 (0.8%) presented with moderate neutropaenia (ANC 1.0 - $1.5 \times 10^9/L$). Majority of study patients, 234/237 (98.7%) had normal absolute neutrophil count (ANC $\geq 1.5 \times 10^9/L$), Table 2.

Serum creatinine and urea were not higher than the upper limit of normal ($\geq 127 \mu\text{mol/L}$ and $\geq 9.1 \text{mmol/L}$, respectively) while serum albumin was not lower than the lower limit of normal ($< 28 \text{g/L}$) in a larger proportion of study patients; 152/165 (92.1%), 162/166 (97.6% and 157/161 (95.7%), respectively, Table 3. Serum transaminases, SGOT and SGPT levels were

Table 1: Socio-demographic and clinical information of study patients.

Parameters	Frequency	Percent (%)
Age (years):		
≤20	20	7.5
21-40	133	50.0
41-60	94	35.3
>60	19	7.1
Gender:		
Male	157	59.0
Female	109	41.0
Weight (kg):		
≤60	118	50.2
>60	117	49.8
Splenomegaly (cm):		
<10	90	37.3
≥10	151	62.7
Hepatomegaly (cm):		
<10	176	85.9
≥10	29	14.1
Disease phase:		
Chronic	222	86.7
Accelerated	30	12.7
Blastic	2	0.6

Table 2: Blood counts of study patients

Parameters	Frequency	Percent (%)
Haematocrit(L/L)		
≤21	76	29.8
21-29.9	66	25.9
30-35.9	98	38.4
>36	15	5.9
Platelet count (x 10⁹/L)		
<20	1	0.4
20-49.9	3	1.3
50-99.9	14	6.1
100-450	212	92.2
>450	52	22.6
WBC (x 10⁹/L)		
≤12	25	9.9
13-99.9	107	42.3
≥100	121	47.8
ANC (x 10⁹/L)		
0.5-0.99	1	0.4
1.0-1.5	2	0.8
>1.5	234	98.7

Key:

WBC- White blood cell count.

ANC- Absolute neutrophil count.

within normal limits (<18 IU/L and <25 UI/L, respectively) in a larger proportion of our patients, 114/151 (75.5%) and 114/153 (94.1%), respectively, Table 3. Serum uric acid was normal (≤ 0.36 mmol/L) in 84/135 (62.2%) of study patients while 88/134 (65.7%) had normal albumin to globulin ratio (Table 3).

Table 3: Biochemical parameters in study patients

Parameters	Frequency	Percent (%)
Creatinine ($\mu\text{mol/L}$)		
<127	152	92.1
≥ 127	13	7.9
Urea (mmol/L)		
<9.1	162	97.6
≥ 9.1	4	2.4
Albumin(g/L)		
<28	7	4.3
≥ 28	157	95.7
SGOT (IU/L)		
<18	114	75.5
≥ 18	37	24.4
SGPT (IU/L)		
<25	114	94.1
≥ 25	9	5.9
Uric acid (mmol/L)		
≤ 0.36	84	62.2
> 0.36	51	37.8
AGR (g/L)		
<1.1	46	34.3
≥ 1.1	88	65.7

Key: SGOT- Serum glutamic oxaloacetic transaminase;
SGPT- Serum glutamic pyruvic transaminases;
AGR- Albumin globulin ratio

DISCUSSION

A larger proportion of our study population were young adults as patients in the age range of 21-40 years predominated ((133/266 (50 %), Table 1). This is in keeping with earlier reports in Nigeria but much lower than that observed among Caucasians.^{17,18} Even though the reason(s) for the age discrepancy at presentation between Nigerian and Caucasian cohorts is not entirely clear, it has however been observed that lower age of

disease presentation tends to occur in countries with relatively younger populations.¹⁸

The gender distribution of CML has been differently reported; while Hoglund et al observed a female predominance at presentation in a study that involved several European CML registries, Cortes et al documented a slight male excess.^{19,20} Another study observed a female predominance in early adulthood and a subsequent male excess in the elderly.²¹ Our finding in this study re-iterated the observation of Cortes et al; we noted a slight male predominance in disease distribution (male to female ratio of 1.4:1, Table 1). While the cause of the gender difference in the distribution of most haematological cancers remains the subject of ongoing research, it has been postulated that differential occupational exposure coupled with possible genetic polymorphic variability in genes that detoxify potential carcinogens may be contributory.²¹ Splenomegaly is predominantly seen in patients with CML. More 50% of patients were reported to have splenomegaly at presentation in the European Society for Medical Oncology (ESMO) working group report.¹⁸ In general, organomegaly, particularly splenomegaly, in patients with CML is thought to result from venous congestion due to infiltration by malignant myeloid cells.²² The finding from this study emphasized the above observation as 151/241 (62.7%) of our study population presented with massive splenomegaly (Table 1). Massive hepatomegaly was observed in fewer of our patients at presentation, 29/205 (14.1%); this is in agreement with an earlier observation.²⁰ Chronic myeloid leukaemia typically presents in either chronic, accelerated or blastic phases, based on the WHO disease staging.¹⁶ The prognosis for patients tend to progressively worsen from chronic through the blastic phase. Consequently, different manifestations of disease severity such as cytopenias, bone marrow fibrosis and organ/tissue dysfunction tend to aggregate in patients with more advanced disease.^{10,11} A higher percentage of the patients in this study were in chronic phase at presentation, 222/256 (86.7%), Table 1.

In keeping with the observation that peripheral blood cytopaenias occur more in patients with more advanced disease, very few patients in this study presented with severe thrombocytopaenia and neutropaenia [1/230 (0.4%) and 1/237 (0.4%)] while a significant proportion [160/230 (69.6%) and 234/237 (98.7%)] had normal platelet and neutrophil counts, respectively, Table 2. Even though Baccarani *et al* [18] had earlier alluded to the rarity of severe anaemia in Caucasian CML patients, this does not appear to completely mirror our observation in this study; only 15/255 (5.9%) of our study patients had normal haematocrit at presentation (Haematocrit of $\geq 36\%$), Table 2. It may thus appear that anaemia in our patients may reflect other causes in our general population, such as nutritional deficiencies. Indeed nutritional anaemias are quite common in our environment due to the high burden of intestinal helminthiasis and under nutrition.²³ In any case, it will be interesting to subsequently evaluate the determinants of anaemia in our CML patients to enable a better understanding of this observation. Increased white cell count is a consistent laboratory feature of CML and is believed to be a direct consequence of excessive cell proliferation from the aberrant tyrosine kinase activity of the BCR-ABL oncoprotein.³ Only 25/253 (9.9%) of our patients had normal white cell count ($\leq 12 \times 10^9/L$), while 121/253 (47.8%) had hyperleucocytosis ($\geq 100 \times 10^9/L$), Table 2. Hyperleucocytosis is common in patients with CML and could predispose to tumour lysis syndrome.¹

Only a minority of our patients had evidence of renal or hepatic impairment at presentation, as shown in table 3. This is not unexpected, as significant end organ dysfunction tends to be associated with more advanced disease.^{10,11} Majority of our patients were in chronic phase at presentation (Table 1).

Increased serum uric acid level is commonly encountered in haematological malignancies, particularly those with a high tumour burden.¹ In this study, 51/135 (37.8%) had hyperuricaemia (>0.36 mmol/L, Table 3), this is an important observation and

underscores the need for tumour lysis syndrome prophylaxis in CML patients at presentation, particularly those with hyperleucocytosis.

CONCLUSION

The age at presentation of CML in our patients was earlier than previously reported among Caucasians. Majority of our patients presented in chronic phase had hyperleucocytosis with very few biochemical evidence of hepatic and renal impairment. Tumor lysis syndrome prophylaxis continues to be encouraged as a good proportion of our patients had elevated serum uric acid levels.

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