PATTERN OF PRESENTATION OF CHRONIC MYELOID LEUKAEMIA IN PORT HARCOURT, NIGERIA: AN EIGHT YEAR STUDY

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ABSTRACT

Background:

Chronic Myeloid Leukaemia (CML) is a relatively common leukaemia that has been extensively studied and was the first malignancy identified to have specific mutation present.

Aim:

The aim was to study the presentation of CML in our centre. Data was extracted from case folders of already diagnosed CML patients. Results were analyzed using SPSS.

Subjects and Methods:

This was a hospital based retrospective study for an eight year period.

Results:

CML accounted for 34 out of 105 (32.4%) haematological cancers seen in the 8 year period with 18 males and 16 females and median age at presentation of 36.5 years. No patient was asymptomatic at presentation, common findings were abdominal swelling 27 (79.4%), symptoms of anaemia 21 (61.8%). Complications of CML were seen in 7 (20.6%). The mean haemoglobin concentration was

8.5g/dl while the mean WBC was 293 X10^9/L and majority (n=27, 79.4%) had a WBC >100 X 10^9/L. No one had thrombocytopenia but 9 (26.5%) had thrombocytosis. Majority (n=30, 88.2%) presented in chronic phase, 3 (8.8%) in the accelerated phase and 1(2.9%) in the blastic phase. Karyotyping for the Philadelphia chromosome was done for 12(35.3%) where it was positive in all cases.

Conclusion:

CML presented at a lower median age. Although facilities for karyotyping and molecular studies are not readily available, the Philadelphia chromosome was positive in all tested cases. Regular health checks are essential in early identification of the disease as all our patients were symptomatic at presentation.

Keywords: Chronic Myeloid Leukaemia, CML in Nigeria, Philadelphia chromosome

INTRODUCTION

Chronic Myeloid Leukaemia (CML) is a haematological malignancy that arises due to a molecular lesion in a single pluripotent haematopoietic stem cell resulting in uncontrolled proliferation of the myeloid progeny.[1] It has been extensively studied, making it the first malignancy to have a constant identified mutation present which is relevant for diagnosis. Following the groundbreaking discovery by Nowell and Hungerford in 1960, CML was the first malignancy to be associated with a specific chromosomal abnormality- the Philadelphia chromosome- which is shortened chromosome 22 resulting from balanced translocation between chromosome 9 and 22.[2,3] This translocation involves the breakpoint cluster region (BCR) of chromosome 22 and the Abelson (ABL) oncogene on chromosome 9. The BCR-ABL mutation creates a fusion gene which produces a protein with increased tyrosine kinase activity.[4] In recent times CML should not be diagnosed without molecular studies as defined by the 2008 World Health Organization classification of myeloid malignancies.[5,6]

Patients with CML have a median age of 50 - 65 years with males slightly more affected than females.[7] [8] The patients may be asymptomatic at presentation where CML is discovered following an abnormal full blood count. CML is a tri-phasic or bi-phasic disease with most symptomatic patients presenting in the chronic phase. Common clinical features include fatigue, anorexia, weight loss, anaemia, splenomegaly, easy satiety, excessive sweating and fever. Less commonly, features of hyperviscosity, spontaneous bruising or bleeding and rarely gout, priapism, vertigo and hearing loss may be present[9,10,11] .The natural course of the disease has been altered in this imatinib era. Initially patients with CML had a median survival of about 5 years, however with the use of tyrosine kinase inhibitors survival has increased profoundly.[12] In the absence of therapy progression from the chronic phase into the accelerated or blastic phase occurs and the stages are distinguished by several clinical and laboratory parameters including the spleen size, percentage blasts and basophils, platelet count and cytogenetics. The accelerated phase is characterized by increasing maturation arrest ultimately leading to the blastic phase of >20% blasts.[6,13]

Diagnostic criteria for CML include leucocytosis which may be severe with counts ranging from 100-1,000 X 10^9/L. Examination of the blood film shows neutrophilia, a left shift with presence of all stages of maturation of the granulocytic series and usually eosinophilia and basophilia. Cytogenetic studies reveal the Philadelphia chromosome in up to 90 – 95% of cases and in up to half of the Philadelphia chromosome negative cases, the BCR-ABL mutation (which can be major, minor or micro depending on the breakpoint on BCR) can still be demonstrated using molecular techniques.[14]

CML was the first malignancy for which targeted therapy was developed. The drug of choice, Imatinib, acts by competitively inhibiting the ATP binding site to the catalytic domain of the abnormal BCR-ABL tyrosine kinase.[15]

The presentation of CML in our center has not been reported and may be different from that reported in other geographical zones and the western world. The aim of this study is to determine the pattern of presentation of CML based on clinical and laboratory features in a tertiary center in a metropolitan city in southern Nigeria.

Subjects and Methods

This is a retrospective study of all CML cases who presented from January 2004 to December 2012. The materials used were data collected from the patients' case folders retrieved from the medical

records department of the hospital. The age, sex, presenting symptoms, and laboratory investigations were retrieved from the case folders.

The criteria for diagnosis of CML[8] in our cohort was based on clinical features of asymptomatic or symptomatic splenomegaly, abnormal laboratory features such as, raised white cell count with sequential maturation of granulocytes, thrombocytosis, high uric acid level, bone marrow aspirate and karyotyping for Philadelphia chromosome (where available). Other investigations done included the erythrocyte sedimentation rate and uric acid. All the peripheral blood films of the patients were prepared using Leishman's stain following standard haematological methods as described by Dacie and Lewis.[16]

The data generated from the above information were analyzed using SPSS version 20 statistical package software with results expressed in statistical tables.

Results

A total of 105 haematological cancers were seen at the University of Port Harcourt Teaching Hospital between July 2004 and June 2012 of which 34 (32.4%) were chronic myeloid leukaemia (CML) who were diagnosed by full blood count, peripheral blood cytology and karyotyping (where available in 50% of the cases). The age range of presentation was 19 to 75 years, with median age of presentation of 36.5 years and mean age of 32.4 (± 16.2) years. The mean age of the males was 37.3 (± 13.8) years, median age 36 years; while the mean age of females was 40.4 (± 18.9) years, median age 36.5 years; however this was not statistically significant (p= 0.58). There were 10 patients (29.4%) who presented at age >50 years; 6 females (37.5%) and 4 males (22.2%). Of the 34 cases, there were 18 males (52.9%) and 16 females (47.1%) giving a male, female ratio of 1.1 : 1.

No patient was asymptomatic at presentation while 6 (17.6%) presented as incidental findings on investigations for other medical reasons. The common presenting clinical symptoms were abdominal swelling 27 (79.4%), symptoms of anaemia 21 (61.8%), fever 17 (50%), weight loss 17 (50%) and malaise 14 (41.2%) [Table 2]. Less commonly they presented with infections 3 (8.8%) while complications of CML were seen in 7 (20.6%) [Table 3]. Thirty-one (91.2%) patients had splenomegaly, with a mean spleen size of 25.5cm (range 10cm – 39cm). Nineteen (55.9%) had splenic size between 10-20cm while 12(35.3%) had splenic size >20cm. Hepatomegaly was seen in 13(8.2%) of cases with an average size of 7.6cm (range 2 – 16cm) below the coastal margin.

There was a low mean haemoglobin concentration of 8.5g/dl (±2.5), and majority (n=26, 76.5%) had anaemia at presentation. Those with anaemia had a mean haemoglobin concentration of 7.5g/dl (range 4.7 – 10g/dl). All of the patients presented with leucocytosis (mean WBC of 293 $X10^9$/L, range 72 – 1343 $X10^9$/L) and majority (n=27, 79.4%) had a WBC >100 X 10^9/L *(normal WBC 4 – 11 X 10^9/L)*. Thrombocytopenia was not found in any of the patients but 9 (26.5%) had thrombocytosis with platelet count >450 X 10^9/L, *(normal 150 – 450 x 10^9/L)*. Nineteen (55.9%) had a raised erythrocyte sedimentation rate (ESR) while 9 (26.9%) of them had a markedly raised ESR of >100mm/hr.

Of the total 34 patients, 30 (88.2%) presented in chronic phase, while 3 (8.8%) presented in the accelerated phase and only 1(2.9%) in the blastic phase. Karyotyping for the Philadelphia chromosome was done for 12(35.3%) of which, all were positive.

Discussion

CML represented about a third of the haematological cancers seen at our center. Unlike Caucasian median age presentation usually after the 5th decade of life,[7] we had a lower median age of presentation of 36.5 ±16.2 years. This is similar to that seen in other African literature and studies from Pakistan and West Indies and Asia[17,18,19,20,21] and may be due to a younger population in these countries[8.] Although the males presented at an earlier age than the women, this was not statistically significant. The patients commonly presented with splenomegaly and anaemia as reported in other literature.[17,22,23]

In our centre, none of the patients were asymptomatic at presentation compared to the western literature where up to 50% of patients present asymptomatic and are discovered by routine full blood count.[7,14] This may due to poor health seeking behavior of Nigerians.[24,25,26,27] As expected, splenomegaly was the commonest clinical feature and those with splenomegaly all had spleen size >10cm below the costal margin. Over a third of the patients had spleen size >20cm and CML is a known cause of massive splenomegaly.[28, 29]

Some of our patients were diagnosed as incidental findings during investigations for other reasons of presentation in the hospital. These findings included double malignancy (CML co-existing with breast cancer) and complications such as priapism, deafness and hyperviscosity. Patients who presented with these complications had very high total WBC counts (Table 3).

Before the development of molecular techniques in diagnosis of CML, the clinical and laboratory parameters which include spleen size, total white blood cell count, peripheral and bone marrow smears were essential in making a diagnosis of CML. In a developing country with less availability of molecular techniques of diagnosis, these parameters are still invaluable. Karyotyping facilities for Philadelphia chromosome were initially unavailable in our environment and therefore diagnoses from 2004 to 2008 were made without Karyotype and relied upon the clinical features and laboratory investigations especially the characteristic morphology of the blood film. However the Philadelphia chromosome was positive in all the cases where it was done, in keeping with over 90% cases of CML being Philadelphia chromosome positive.[14]

Conclusion

The cases of CML who presented in our department generally had the usual features of CML, however our patients presented at a younger median age and higher WBC count. None of the cases were asymptomatic at presentation.

We therefore recommend that awareness level of this disease should be increased, since preliminary diagnosis can be made from basic laboratory tests such as full blood count and peripheral blood film.

Individuals should be educated to have routine medical evaluation frequently, as this will ensure early diagnosis and prompt management of CML.

Table 1: Summary of Features of CML Cases

Variable	Mean Value (SD)
Age	38.8 years (±16.2)
Spleen Size*	17.5cm (±7.5)
Liver Size**	7.6cm (± 4.6)
Haemoglobin	8.5g/dL (± 2.5)
Total WBC	293 $X10^9$/L (± 273)
Blast Count	4.4% (± 5.1)
Basophil	6.1% (± 7.7)
Platelets	356.7 $X10^9$/L (±222)
ESR	68.4 mm/Hr (± 59.8)
Uric Acid	634.6 (± 241)

*Below the left costal margin

**below the right costal margin

Table 2: Clinical presentation of cases

Features	Total = 34	Percentage (%)
Splenomegaly	31	91.2
Abdominal swelling	27	79.4
symptoms of Anaemia	21	61.8
Fever	17	50
Weight loss	17	50
Malaise	14	41.2
Infections	3	8.8
Hepatomegaly	13	38.2

Table 3: Patients who presented with complications

Age (yrs)	Sex	WBC (X 10^9/L)	Complications
61	M	96	Renal Complication
22	M	99.3	ARF
55	M	360	Priapism
22	F	367.3	Renal Complication
22	F	652	Blurred Vision, Tinitus
50	M	832	Renal Complication
24	F	1343	Hearing Loss

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