Clinico-Pathologic Features and Outcome of Chronic Lymphocytic Leukemia In Ilorin, North Central Nigeria.

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Abstract

A retrospective analysis of all patients that were diagnosed and managed for Chronic lymphocytic Leukemia(CLL) in the Department of Haematology of University of Ilorin Teaching Hospital, Ilorin between 1st January 2005 and 31st December 2018 was carried out with the aim of characterizing the clinical, haematological and prognostic features as well as outcome in the patients. A total of 39 patients were reviewed consisting 25(64.1%) males and 14(35.9%) females giving a M:F ratio of 1.6:1. The median age of patients at diagnosis was 65.5 years and the highest prevalence was found in the 60 – 69 years age group. The commonest symptoms at presentation were night sweats (59.0%), Body weakness (51.3%), fever (41.0%), and weight loss (41.0%) while the commonest signs included lymphadenopathy in all patients (100%), splenomegaly (87.2%), pallor (53.9%) and hepatomegaly (46.2%). The mean values of haematological parameters were: Packed cell volume (28.6%), Haemoglobin concentration (9.4g/dL), Total white blood cell count (87.6 x 10^9/L), Absolute lymphocyte count (55.8 x 10^9/L) and platelet count (134.8 x 10^9/L). The majority of the patients (94.9%) were diagnosed with advanced disease (Rai stage III and IV) while only 2(5.1%) had Rai stage II and none in Rai stage 0 – I. Chlorambucil-based regimen was used in 71.8% of patients, and only 2 patients had Rituximab as part of their treatment regimen. The clinical presentation, haematological features and disease outcome observed in our study was similar to what had been reported in Nigeria and other parts of the world.

Keywords: Clinical, Haematological, Features, Chronic lymphocytic leukemia, Ilorin

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Introduction

Chronic lymphocytic leukemia is an acquired low-grade B lineage lymphoproliferative disorder characterized by slow but progressive accumulation of matured-appearing immunologically incompetent lymphocytes in peripheral blood, bone marrow and lymphatic tissues[1]. The lymphocytes in CLL are monoclonal B cells that express biological markers such as cluster of differentiation (CD) antigens CD5, CD19, CD20, CD23, CD79b, surface immunoglobulins (Ig) and FMC7 [2,3].

Chronic lymphocytic leukemia has an annual incidence of 3.4 to 3.7 per 100,000 population in males and 1.6 to 1.9 per 100,000 population in females with a male to female (M:F) ratio of 1.5 -2.5:1 and has been reported to account for 20-30% of all leukemia cases in the United States of America [4,5]. " Benin City, Nigeria CLL was reported as the second commonest leukemia, next to Chronic myeloid leukemia and constituted 21.3% of all leukemia[6].

CLL is an indolent disease and about 50% of patients are usually diagnosed by chance following routine full blood count examination, and constitutional symptoms (B symptoms) such as fever, night sweats, body weakness and weight loss are present in about 15% of patients at diagnosis. The clinical presentation of CLL is highly variable and ranged from little or no symptoms at all to a rapidly progressive features of high risk disease and immunoblastic transformation (Richter's syndrome)[7]. The commonest clinical features include painless, non-tender lymphadenopathy of one or more lymph node groups in the neck, axillae and groins, splenomegaly and/or hepatomegaly. Bone marrow involvement is manifested as anaemia (haemoglobin concentration <10g/dl), thrombocytopaenia (platelet count <100 X 10^9/L) and bone marrow infiltration by the malignant lymphocytes [5,7].

Diagnosis of CLL is established by presence of mature-appearing lymphocytes $\geqslant$ 5 X 10^9/L in peripheral blood, $\geqslant$30% lymphocytes on bone marrow aspirate examination; and depending on the disease stage, presence of anaemia, thrombocytopaenia, lymphadenopathy, splenomegaly and/or hepatomegaly[5].

Rai and Binet classifications are commonly used to classify patients into different prognostic groups based on absolute lymphocyte count in

peripheral blood, presence of anaemia and/or thrombocytopenia, lymphadenopathy, splenomegaly and/or hepatomegaly[8,9].

The management of patients with CLL involves a "wait and see" approach in the early stable phase of the disease while intermediate and late stages require treatment with a combination of chemotherapeutic agents+/- immunotherapy .Chlorambucilalone or in combination with steroid (predisolone) has been used over the years as the drug of choice until recently when newer drugs like Fludarabine, Cladribine, Alemtuzimab and Rituximab were introduced for treatment of individuals with CLL. However, due to non-availability or high cost of these newer agents, Chlorambucil in combination with Prednisolone or Cyclophosphamide-based regimen still remain the first line drugs in many economically disadvantaged and resource-limited countries like Nigeria[10,11,12].

Also, in most tertiary hospitals in Nigeria and other resource-limited countries, the newer diagnostic toolslike immunophenotyping and molecular markers may not be readily available, or the high costs make them unaffordable even when they are available. is imperative, therefore, to be conversant with the basic clinical and haematological characteristics of Chronic lymphocytic leukemia especially in our environment and many other resource-limited societies where diagnosis and management of the disease still depend largely on clinical features and routine haematological investigations.

The main objectives of this study was to characterize the clinical and haematological features, treatment response and survival outcome of CLL patients diagnosed and managed at the University of Ilorin Teaching Hospital, Ilorin, North central Nigeria and compare our results with studies from within and outside Nigeria.

Materials and Methods

This study was a retrospective review of all cases of Chronic lymphocytic leukemia which were diagnosed and managed at the Haematology department of University of Ilorin Teaching Hospital (U.I.T.H), Ilorin between 1st January 2005 and 31st December 2018.

The study tools included case folders of all CLL patients diagnosed and managed during the study period. Relevant data extracted from the folders included demographic parameters, clinical features at presentation, haematological profile, Bone marrow aspiration report, Full blood count, Urea, Electrolytes & Creatinine, Liver function test results among others, spleen size, liver size, Binet or Rai stage at diagnosis, chemotherapeutic regimen used for treatment, time interval between diagnosis and when patient was last seen and outcome of therapy. Diagnosis of CLL was made using either the Rai or Binet classification methods[8,9] based on presence of peripheral lymphadenopathy, splenomegaly and/or hepatomegaly on clinical examination, peripheral blood findings of anaemia and/or thrombocytopenia and blood and bone marrow lymphocytosis. tients were also sub-classified into CLL, CLL/PL (Chronic lymphocytic/ Prolymphocytic Leukemia) and PLL(Prolymphocytic leukemia) based on the percentage of prolymphocytes in peripheral circulation (CLL $\leqslant$10%prolymphocytes, CLL/PL $\geqslant$10% but$\leqslant$50%prolymphocytesand PLL $\geqslant$ 50% prolymphocytes)[13].

Data generated from above sources were entered into Excel data sheet, and data analysis was done using the Statistical Package for the Social Sciences SPSS v.21. Data presentation was in the form of frequency tables.

Results

A total of 39 patients were diagnosed and managed for Chronic lymphocytic leukemia at the Haematology department of the U.I.T.H within the study period. There were 25 males and 16 females giving a male to female (M:F) ratio of 1.6:1.

The median age of patients at diagnosis was 65.5 years (range 45 – 90 years), and the disease was found to have the highest prevalence in the 60 – 69 years age group (n = 15, 38.5%), and only 3 patients (7.7%) were below the age of 50 years. Table I shows the age and sex distribution of CLL patients in our study.

Table I: showingAge and Sex distribution of CLL patients in UITH Ilorin

Age group (years)	Sex Distribution		Total number (%)
	Male (n)	Female (n)	
= 49	3`	0	3 (7.7)
50 – 59	4	1	5 (12.8)
60 – 69	9	6	15 (38.5)
70 – 79	6	5	11 (28.2)
= 80	3	2	5 (12.8)
Total	25	16	39 (100)

Table II: showing signs and symptoms of CLL patients at presentation

Clinical Features	Frequency (n)	Percentage (%)
SYMPTOMS		
Fever	16	41.0
Night sweats	23	59.0
Anorexia	19	48.7
Body weakness	20	51.3
Cough	12	30.8
Weight loss	16	41.0
Abdominal pain/discomfort	18	46.2
Abdominal mass	13	33.3
Cervical, axillary, inguinal mass	30	76.9
SIGNS		
Anaemia (Pallor)	21	53.9
Thrombocytopenic bleeding	7	18.0
Lymphadenopathy (Cervical,Axillary&Inguinal)	39	100.0
Splenomegaly		
Mild/Moderate		
Massive	20	51.3
Hepatomegaly	5	12.8
	18	46.2

Table IV: showing the distribution of CLL patients according to Rai And Binet Staging Methods at diagnosis

RAI CLINICAL STAGING	Number of Patients (%)
0	0 (0)
I	0 (0)
II	2 (5.1)
III	11 (28.2)
IV	26 (66.7)
TOTAL	39 (100)
BINET CLINICAL STAGING	Number of Patients (%)
A	2 (5.1)
B	20 (51.3)
C	17 (43.6)
TOTAL	39 (100)

Table V: showing the drugs used for treatment of CLL patients in Ilorin

Type of Drug Used for Treatment	Number of patients (%)
Chlorambucil only	3 (7.7)
Chlorambucil + Prednisolone	24 (61.5)
Chlorambucil + Rituximab	1 (2.6)
COP	3 (7.7)
CHOP	2 (5.1)
COP + Rituximab	0 (0)
CHOP + Rituximab	1 (2.6)
Rituximab only	0 (0)
Treatment	5 (12.8)
Total	39 (100)

COP = Cyclophosphamide, Oncovin, Prednisolone

CHOP = Cyclophosphamide,Hydroxodaunorubicin, Oncovin, Prednisolone

Table III: showing the haematological profile of CLL patients at Diagnosis

Parameter	Mean ± SD	Range	Normal Range
Packed Cell Volume (%)	28.6 ± 7.88	11 – 44	42 – 54 (M) 38 – 48 (F)
Haemoglobin Concentration (g/dL)	9.4 ± 2.30	3.2 – 13.9	13.5 – 17.5(M) 11.5 – 15.5(F)
White Blood Cell Count (x 10^9/L)	89.6 ± 70.94	9.7 – 284	4 - 11
Absolute Lymphocyte Count (x 10^9/L)	55.8 ± 49.83	5.2 – 198.6	1.0 – 4.8
Platelet Count (x 10^9/L)	134.8 ± 80.76	9.0 -371	100 - 400

SD= StandardDeviation, M = Male, F= Female

There were 35 (89.7%) patients with CLL, 3 (7.7%) patients were CLL/PL, while only one patient (2.6%) was diagnosed with PL. The commonest symptoms in the patients at presentation included cervical, axillary or inguinal swellings in 76.9% of cases, abdominal pain or discomfort (46.2%), abdominal mass (33.3%).Anaemia (pallor) was seen in 21 (53.9%) patients and bleeding due to severe thrombocytopenia was found in 7 (18.0%) patients. Mild to moderate splenomegaly (spleen size< 10cm) was observed in 20 (51.3%) of patients while massive splenomegaly (spleen size> 10cm) was present in 5 (12.8%) patients. Hepatomegaly was also observed in 18 (46.2%) patients (Table II).

The mean values of haematological parameters of patients in our study were as follows: Packed cell volume (28.6%), Haemoglobin concentration (9.4g/dL), Total white blood cell count (87.6 x 10^9/L), Absolute lymphocyte count (55.8 x 10^9/L) and Platelet count (134.8 x 10^9/L). The mean values of packed cell volume (PCV) and Haemoglobin concentration (Hb) were reduced below the normal range while the mean values of Total white blood cell count (WBC) and Absolute lymphocyte count (ALC)

were higher than the normal range.(Table III).

Majority of patients, 37 (94.9%) were diagnosed with advanced (high risk) disease at presentation (Rai stage III & IV/Binet stage B & C), and only 2 (5.1%) patients had early or intermediate disease at diagnosis (Rai stage 0-II/Binet stage A). Table IV.

" the management of our patients, treatment was done using cytotoxic drugs either as single agent or combination of drugs. Majority of our patients had Chlorambucil and Prednisolone (61.5%), 3 patients (7.7%) were treated with Chlorambucil alone while other patients had Cyclophosphamide or Rituximab - based regimens (Table V).

The median duration of treatment from diagnosis to last clinic contact for our CLL patients was 6 months (range 1 – 96 months), and at the time of our study 18 (46.2%) are alive and still being followed up, 13 (33.3%) were dead while 8 (20.5%) had been lost to follow-up.

Discussion and Conclusion

Chronic lymphocytic leukemia is an indolent disease characterized by a slow but progressive accumulation of malignant mature-appearing B lymphocytes in blood, bone marrow and lymphoid tissues[14]. The disease has variable presentation and outcome; the prognosis being determined by the presence of certain factors at diagnosis such as age and sex of patients, pattern of marrow infiltration by malignant cells, laboratory profile, presence or absence of genetic abnormalities and response to treatment among others.

CLL is reported to be the commonest leukemia encountered in adults in Western countries occurring more in the seventh decade of life [15,16]. Previous studies on the prevalence of leukemia in Nigeria had reported CLL as the second most common leukemia in adults after Chronic myeloid leukemia[6,17], and many studies from Nigeria and other African or Asian countries have reported the highest prevalence of CLL in adults aged 55- 65 years[3,5,11,12,13,18]." this study, the median age in our CLL patients at diagnosis was 65.5 years (range 45 – 90 years), and the highest prevalence was observed in the 60 – 69 years age group. This finding was in agreement with previous studies by Omoti*et al*, Madu*et al* and Salawu *et al* in Nigeria[11,12,13], Ahmed *et al* in Sudan[3] and Agrawal *et al* in India[5], but at variance with the reports of Sant*et al*, Halleck M *et al*, and Pfell AM *et al* [18,19,20]. While it is generally believed that CLL is rare below age 50 years [21], this study recorded 3(7.7%) patients below age 50 years, and this finding corroborates some other studies which also found CLL in patients below age of 50 years[19,21].

The most common symptoms which our patients presented with included cervical, axillary, and inguinal masses(79.6%), abdominal pain/discomfort (46.2%), abdominal mass (33.3%), fever (41%), night sweats (59%) and body weakness (51.3%). Similar observations were reported by other authors in their studies[3,5,10,11,12,13,19]. The commonest physical sign elicited in our CLL patients was lymphadenopathy which was found in all patients (100%) in our study. This finding was in agreement with many studies which also found lymphadenopathy as the commonest clinical sign of CLL in their patients[10,11,20,21]. Splenomegaly and hepatomegaly were also found in 51.3% and 46.2% of our patients respectively. This finding was consistent with the report of Agrawal *et al* in India[5], Madu*et al* and Salawu*et al* in Nigeria[12,13] and Mukiibi JM *et al* in Central Africa[22].

The mean haemoglobin concentration of CLL patients in this study was 9.4 g/dL. Anaemia (Hb< 10 g/dL) was recorded in 53.9% of patients. This finding was in agreement with previous studies by Madu *et al*[12]in Nigeria and Ahmed and Ousman[3] in Sudan which also reported anaemia in a large proportion of their patients. Presence of anaemia is indicative of advanced or high-risk disease.

One of the major criteria to establish the diagnosis of CLL by World Health ganization (WHO) recommendation is the presence of Absolute lymphocyte count (ALC) > 5 x 10^9/L on peripheral blood examination [23]. The mean values of WBC and ALC in our study were 87.6 x 10^9/L (range 9.7 - 284 x109/L) and 55.8 x 10^9/L (range 5.2 – 198.6 x 10^9/L) respectively. Very high ALC at diagnosis is associated with advanced disease and poor prognosis in CLL patients [16.]" our study, majority of the patients (96.4%) had high ALC at diagnosis. This finding was in agreement with other previous studies from Nigeria and other parts of the world [3,11,12,20,22,24].

" our study, we found advanced disease (Rai stage III and IV) in majority of our patients (94.6%). Higher proportion of CLL patients diagnosed with advanced disease was also reported by Agrawal *et al* in India and Hassan KM in Iraq[5,10].

The finding of advanced disease (Rai Stage III and IV) in majority of patients in our study could be due to the high number of diffuse bone marrow involvement recorded in our patients.

The commonest form of treatment received by patients in this study was Chlorambucil-based regimens. Chlorambucil alone was used in 3(7.7%) patients, Chlorambucil and Prednisolone in 24 patients (61.5%) and Chlorambucil and Rituximabin 1 patient (2.6%). This finding was similar to the reports of Agrawal *et al* andMadu *et al*[5,12]which reported that all their patients were treated with Chlorambucil and Prednisolone. This finding was at variance with reports from Western and other developed countries where patients were treated with Fludarabine-based regimen with or without Rituximab[25].

" our study, the median duration of follow-up

of CLL patients was 6 months (range 1 – 96 months). This finding was in agreement with the study of Madu *et al* which reported median follow-up duration of 4 months in their patients[12]. õ the time of writing this report, 46.2% of our patients are alive and being followed up in the Haematology clinic while 33.3% had been lost to follow-up. Salawu *et al* in Ile-ife, Nigeria also reported that a high proportion of their patients (> 50%) being lost to follow-up[13].

CLL is not a rare disease in our environment, and the clinical and laboratory features in our patients were similar to what had been reported from different populations all over the world. " resource-limited settings such as ours, diagnosis and monitoring of patients with CLL still rely on the clinical and laboratory features of the disease to a large extent, hence the need for Haemato-oncologists and Physicians to be conversant with these features as much as possible, more so, in view of non-availability or high cost of the newer diagnostic tools in such environments.

References

1. Thomas JK. Chronic lymphocytic leukaemia and related disorders. In: Lichtman MA, Beutler E, Kipps TJ, Seligsohn U, Kaushansky K, Prchal JT [eds] Williams Haematology. 髓 Edition. New York. McGraw-Hill. 2006, pp1343 . 1383.
2. Yee KWL, O'Brien SM. Chronic lymphocytic leukemia: Diagnosis and treatment. Mayo Clin Proc. 2006; 81:1105-29.
3. Ahmed RAEM, Osman IM. Clinical and haematological pattern of chronic lymphocytic leukaemia in sudanese patients. Int Blood Res Rev. 2017;7(1):1–10.
4. Dighiero G, Hamblin T J. Chronic Lymphocytic Leukemia. Lancet, 2008; 371: 1017-1029.
5. Agrawal N, Naithani R, Mahapatra M, Panigrahi I, Kumar R, Pati HP, Saxena R, Choudhary VP. Chronic lymphocytic leukemia in India--a clinico-hematological profile. Hematology. 2007;12(3):229-33.
6. Omoti CE, Imiere EO. Trends in the Pattern of Leukemia Incidence in a Tertiary Health Centre in Nigeria: 1990-2004. J. Med. Biomed. Res., 2006; 5(2): 44-49.
7. Abbott BL. Chronic lymphocytic leukemia: Recent advances in diagnosis and treatment. The Oncologist, 2006; 11:21-30.
8. Rai KR. A critical analysis of staging in chronic lymphocytic leukaemia: Recent progress and future Directions. Gale RP, Rai KR (eds). Liss AR, New York, 1987; 253-254
9. Binet JL, Auquire A, Dighiero G, Chastang C, Piguet H, Goasguen J, et al. A new prognostic classification of Chronic lymphocytic leukaemia derived from a multivariate survival analysis. Cancer. 1981 Jul 1;48(1):198-206.
10. Hassan KM. Clinical Aspects, Immunophenotypic Analysis and Survival Rate of chronic lymphocytic leukemia patients in Erbil City, Iraq. Sultan Qaboos Univ Med J., 2018; 18(4): e461-467.
11. Omoti CE, Awodu OA, Bazuaye GN. Chronic lymphoid leukaemia: Clinicohaematological correlation and outcome in a single institution in Niger Delta region of Nigeria. International Journal of Laboratory Hematology. 2007;29(6):426-32.
12. Madu AJ, Korubo K, Okoye A, Ajuba I, Duru AN, Ugwu AO et al .Presenting features and treatment outcomes chronic lymphocytic leukemia in a resource poor Southern Nigeria. Malawi Med J., 2019; 31(2): 144- 149.
13. Salawu L, Bolarinwa RA, Durosinmi MA. Chronic lymphocytic leukaemia: a-twenty-years experience and problems in Ile-Ife, South-Western Nigeria. Afr Health Sci. 2010;10(2):187–192.
14. Montserrat E, Hillmen P. Chronic lymphocytic leukaemia and other chronic B-cell disorders .In: Hoffbrand A V, Higgs DR, Keeling DM, Mehta AB (eds.)*Postgraduate Haematology*, 7th Edition, JohnWiley& Sons, Ltd, 2016, pp 5001-523.
15. Sall A, Touré AO, Sall FB, Ndour M, Fall S, Sène A, et al. Characteristics of chronic lymphocytic leukemia in Senegal. BMC Hematol. 2016;16:10.
16. Sant M, Allemani C, Tereanu C, ♀ Angelis R, Capocaccia R, Visser O, et al. Incidence of hematologic malignancies in Europe by morphologic subtype: results of the HAEMACARE project. Blood. 2010;116(19):3724–34
17. Babatude A, Amiwero C, Olatunji P, Durotoye I. Pattern of Haematological Malignancies in Ilorin Nigeria: A Ten year review. The internet J of Haemat. 2009; 5 (2).
18. Mulwa-Babu E, Paresh D, Riyat M. Chronic lymphocytic leukemia in Kenya: an immunophenotypic and clinicopathologic study. J. Afr. Cancer, 2013;5: 192-197.
19. Hallek M. Chronic lymphocytic leukemia: 2015 Update on diagnosis, risk stratification, and treatment. ¨ J Hematol. 2015;90(5):446–60.
20. Pfeil AM, Imfeld P, Pettengell R, Jick SS, Szucs TD, Meier CR, Schwenkglenks M. Trends in incidence and medical resource utilisation in patients with chronic lymphocytic leukaemia: insights from the UK Clinical Practice Research Datalink (CPRD) Ann Hematol. 2015;94(3):421–429.
21. Basabaeen AA, Abdelgader EA, Babekir EA, et al. Clinical presentation and hematological profile among young and old chronic lymphocytic leukemia patients

in Sudan. *BMC Res Notes*. 2019;12(1):202.
22. Mukiibi JM, Paul B, Nyirenda CM, Adewuyi JO, Gwanzura C, Mzulu E, et al. Chronic lymphocytic leukaemia (CLL) in Central Africans. *Cent Afr J Med*, 2004; 50: 111-115.
23. Swerdlow SH, Campo E, Harris NL, Jaffee ES, Pileri SA, Stein H, et al. eds. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues,* 叅 ed. Geneva, Switzerland: WHO Press, 2008.
24. Tsimberidou AM, Wen S, O'Brien S, McLaughlin P, Wierda WG, Fardel S, et al. Assessment of chronic lymphocytic leukemia and small lymphocytic lymphoma by absolute lymphocyte counts in 2,126 patients: 20 years of experience at the University of Texas M.D. Anderson Cancer Center. J ClinOncol. 2007; 25:4648 – 4656.
25. Elchhorst BF, Busch R, Stilgenbauer S, et a l. First-line therapy with fludarabine compared with chlorambucil does not result in a major benefit for elderly patients with advanced chronic lymphocytic leukemia. Blood 2009;114:3382 – 3391