ORIGINAL RESEARCH

Presenting features and treatment outcomes of chronic lymphocytic leukaemia in a resource poor Southern Nigeria

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Abstract

Background

Chronic lymphocytic leukaemia is a relatively common haematological malignancy affecting older adults, accounting for about 20% of haematological malignancies in Nigeria. Diagnosis of this disease depends on the demonstration of clonal lymphocytosis > 5 x 109/L with a characteristic immunophenotypic pattern amidst other clinical and laboratory features.

Objectives

To determine the predominant clinical and laboratory features of CLL at presentation and their relationship with patient survival. This study also aims at examining the relationship between treatment protocol and outcome.

Methods: This is a retrospective study with 8 years data (2010-2018)collected from four different centers. Data was analyzed using SPSS 20.0.

Results

There were a total of 97 cases, with a male: female ratio of 1.1:1. The median age at presentation was 59 years. Approximately 55% of the patients presented at Binet stage C, with splenomegaly in 93.2% and 78% were anaemic. The mean white cell count was 137.9 ± 14.7 x 109/L, with a median absolute lymphocyte count of 86 x 109/L. The commonest treatment regimen was chlorambucil and prednisolone and males had a superior response. The number of chemotherapy cycles, serum alkaline phosphatase and aspartate transaminase correlated positively with duration of survival. Mortality rate over the five year period was 14.3%.

Conclusion

CLL was found to present in younger patients when compared to previous studies with a median age of 57 years at diagnosis. Our study showed a slight female preponderance and better response to therapy in males. Majority of the patients presented in Binet stage C and were treated with chlorambucil-based drug combinations compared to more current treatment with Fludarabine-based combinations. A high serum alanine transaminase and alkaline phosphatase was found to positively correlate with survival amongst this patient population

Introduction

Chronic lymphocytic leukaemia (CLL) is a monoclonal proliferation of mature-looking B lymphoid cells with attendant peripheral lymphocytosis. This malignancy accounts for 17 – 20% of all haematological malignancies in Nigeria. It is the second most common haematological malignancy after diffuse large B-cell lymphoma, with 2 – 6 per 100,000 new cases diagnosed annually[4]. The prevalence of CLL has been found to be 18.2% of all lymphoid malignancies.[5] In other studies done in some countries with low socio-economic status there has been an observed paucity of diagnostic capacity and lack of novel treatment options. The incidence varies widely across geographical locations, with Asia having a 5-10 fold lower prevalence. [6] This indicates the possible role of genetic factors offering a protective role in Asians, as migrated Asians in western countries also have a reduced incidence of CLL. [7] The higher prevalence in the resource limited countries, not withstanding their lower diagnostic capacity is more in support of a possible genetic aetiopathogenesis.

The malignancy is commoner in males, mostly seen in the elderly (age > 65 years) with some familial tendency being alleged.[d,8] Clinical presentation varies widely with some patients being diagnosed incidentally during a routine full blood count check. Staging of the tumor is usually done at diagnosis, using the system described by Rai et al or Binet et al, [9] both of which are used for prognosis and decision on the commencement of therapy. Bone marrow trephine biopsy is also done to obtain a higher cell yield for cytogenetic studies and recently is being proposed for monitoring of minimal residual disease.[10,11] Immuno-phenotyping is important to ascertain the monoclonality of the malignant cells as well as differentiate the T from the B cell malignancies. The malignant cells in CLL show co-expression of CD5, a T cell marker and CD 19 [12,13] and levels of monoclonal B cell above 5 x 10^9/L is considered diagnostic[10,14].

The malignant cells in CLL have been found to have undergone somatic hypermutation (antigenic stimulation in the germinal centers) and include both the memory and marginal zone B cells. [15] CLL cells over-express Bcl-2, an anti-apoptotic protein which is thought to immortalize the malignant clone. There appears to be a dependence of CLL

cells on the bone marrow microenvironment because CLL cells in suspension culture undergo spontaneous apoptosis in vitro, except when co-cultured with bone marrow stromal cells[16]. These cells also express (immunoglobulin heavy chain variable region genes) IGHV as well as restricted subsets of B cell receptors to a larger extent than the normal mature B cells. These findings suggest that antigenic stimulation plays an important role in the pathogenesis of CLL. DNA sequencing studies have also detected mutated genes; MYD88, NOTCH1, SF3B1 and XPO1, all of which are thought to be of prognostic importance[17]. Other important biological markers include, lymphocyte doubling time, ZAP70[18,19], CD38[20], serum β-2 microglobulin[21], thymidine kinase as well as presence of other cytogenetic abnormalities. There exists a remarkable paucity of investigative facilities to attain this depth of investigation for most patients in resource poor settings.

Management protocol for treatment of CLL includes combination of immunotherapy and standard chemotherapy for patients with symptomatic, advanced or progressive disease. While for patients with stable disease the "watch and wait" algorithm is usually deployed. In the past chlorambucil with or without steroids was the gold standard for management of CLL[9]. This was been replaced by more efficient combinations involving the use of bendamustine, fludarabine, cladribine, alemtuzumab (recombinant anti-CD52) and rituximab (anti-CD20 monoclonal antibody)[22]. However, these current first line drugs are quite expensive and not easily available in the economically disadvantaged parts of the world where treatment is largely still chlorambucil/ cyclophosphamide-based. This study is aimed at describing the predominant clinical and laboratory features of CLL and their relationship with patient survival. We also intend to examine the relationship between treatment protocol and outcomes / survival achieved in this milieu of sub-optimal care.

Patients and Methods

Clinical data was obtained from the case notes of 97 patients diagnosed with CLL at the University of Nigeria Teaching Hospital, Ituku-Ozalla, University of Port Harcourt Teaching Hospital, Nnamdi Azikiwe University Teaching Hospital, Nnewi and Federal Medical Center Abakaliki, all in Nigeria. Data obtained were age, sex, Binet stage, spleen size, hepatic and renal function tests, haematological parameters and chemotherapeutic regimen used as well as the duration from the date of diagnosis to when the patient was last seen. This was done for all patients diagnosed between June 2010 and July 2018, using the patients' case notes, in the wards and clinics ,as well as the admission registers from the four different participating hospitals.This was done retrospectively for the patients seen prior to 2015 and prospectively for the patients seen up till July 2018. A pre-designed excel data sheet was used for uniform data collection from the participating centers.

Statistics

Data was analyzed using SPSS20.0 (Illinois, Chicago) and expressed in tables and figures. The Kaplan Meier survival curve and equation was used to assess survival differences between groups. Spearman Rho and Kendaull_taub were employed to assess correlation and the value < 0.05 were assumed to be significant.

Results

Ninety seven patients were diagnosed and treated for CLL in the 4 centers within the 8 year interval. Their ages ranged from 29 to 89 years with a median age of 59 years and a mean age of 60 years. These consisted of 50 (51.5%) males and 47 (48.5%) females, giving a male: female ratio of 1.1:1. Majority, 53 (54.6%) of the patients were of Binet Stage C at diagnosis, while 11.3% and 5.2% of them presented with Binet Stage B and A, respectively. Splenomegaly was observed in 93.2% of the patients and the spleen size ranged from 0 to 36 cm below the left costal margin, with a median value of 14 cm.

Clinical and Laboratory Aspect

The median value of the total white cell count at diagnosis was found to be 93.5 x 10^9/L, while the mean value was 137.9± 17.1 x 10^9/L. The median absolute lymphocyte count was 86 x 10^9/L, with a mean value of 136.5 ± 22.7 x 10^9/L. The mean Hb at diagnosis was 8.5 ± 0.3 g/dL with a median of 8.8g/dL. Seventy-eight percent of the patients were anaemic at diagnosis (Hb < 10g/dL), while 31.5% were thrombocytopaenic (platelet count < 100 x 10^9/L). There was no direct relationship between Hb at presentation and the duration of management/ survival, p = 0.053 (correlation coefficient 0.224). The Binet stage was also found to be associated with the Hb at diagnosis (coefficient 0.359, p=0.001), spleen size (coefficient 0,275, p=0.014), leucocyte count at diagnosis (coefficient 0.215, p=0.032), absolute lymphocyte count (coefficient 0.303, p=0.007), platelet count at diagnosis (coefficient 0.236, p=0.028) and alkaline phosphatase (coefficient 0.312, p=0.019). Coombs test was positive in only 2 patients out of 62 tested while none of the patients were HIV positive. Majority of the patients (93/97) had CLL while only 4 of them had CLL/ PL. The haematological parameters as well as some of the clinical features of the patients on presentation is shown on Table 1.

Table 1.Clinical and laboratory parameters at presentation and their correlation with survival in CLL patients

Parameter	N	Mean	Median	Coefficient (p value)
Age (years)	97	60	59	0.065 (0.547)
Haemoglobin concentration (g/dL)	80	8.5	8.8	0.224(0.053)
Leucocyte count (x 10^9/L)	84	137.9	93.5	-0.079 (0.463)
Spleen size (cm)	59	16	14	_-0.031 (0.813)
Absolute Lymphocyte count (x 10^9/L)	57	136.5	86	-0.139 (0.228)
Platelet count (x 10^9/L)	73	146	132	0.105 (0.391)

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Figure 1a shows a bar chart of the spleen size and Hb in males versus females. Figure1b shows the distribution of absolute lymphocyte count and serum alkaline phophatase amongst the patients in the different Binet stages. This liver enzyme also showed a significant relationship with both the duration of management/ survival and the number of chemotherapy cycles given. (p= 0.003 and 0.041, respectively).

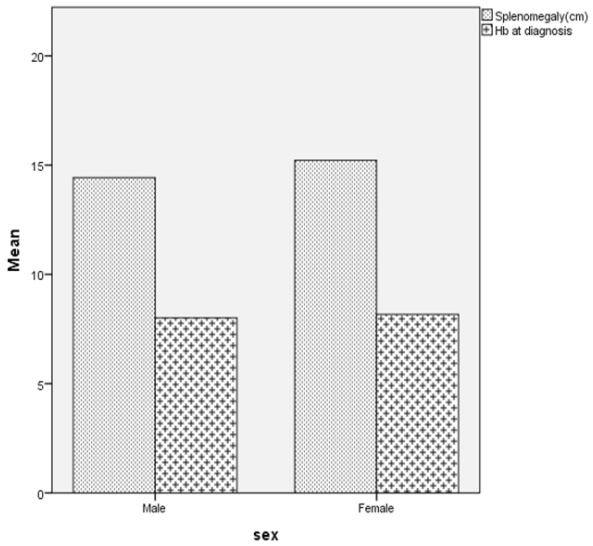

Fig 1a

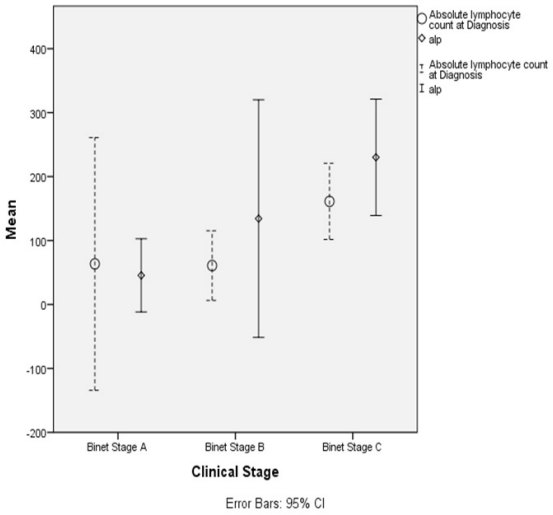

Fig 1b

Treatment Outcomes

Majority of the patients (43.1%) were on chlorambucil and prednisolone (Chl+P), 27.6% on cyclophosphamide/ vincristine/ prednisolone (CVP) and 8.6% cyclophosphamide/ prednisolone (C+P) while 2.1% were placed on cyclophosphamide/ hydroxodaunorubicin/ vincristine/ prednisolone (CHOP). The drug regimen used was switched in 27.2% of the patients and the reason was mainly due to poor response to chemotherapy (non-response, relapse and resistance). The median duration of management was 4 months and ranged from 0 to 72 months, this was found to show a significant positive correlation with the number of cycles of chemotherapy, alanine transaminase and aspartate transaminase levels (p= 0.0001, 0.013 and 0.004, respectively).

Figure 2 (a-d) shows the Kaplan-Meier survival curve for males versus females as well as individuals who received varying chemotherapeutic combinations.

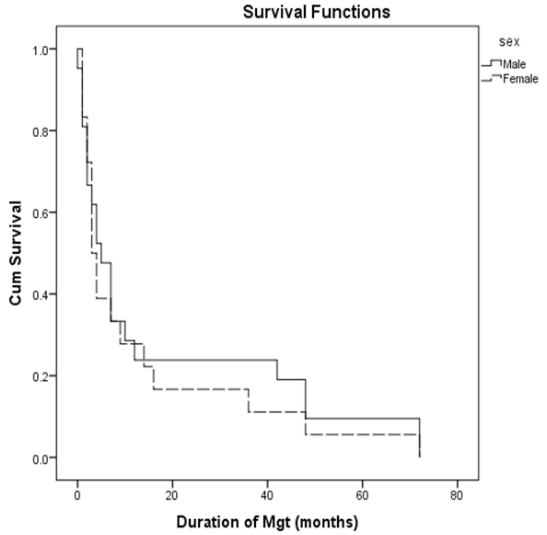

Fig 2a

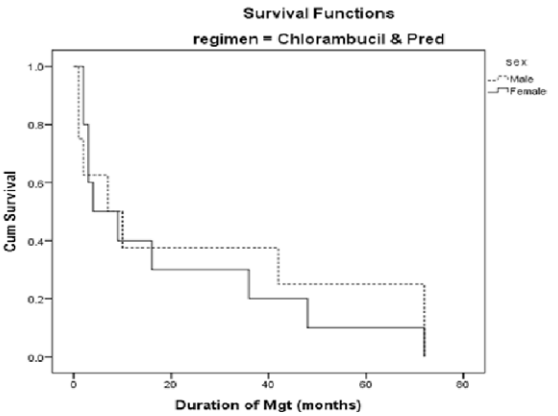

Fig 2b

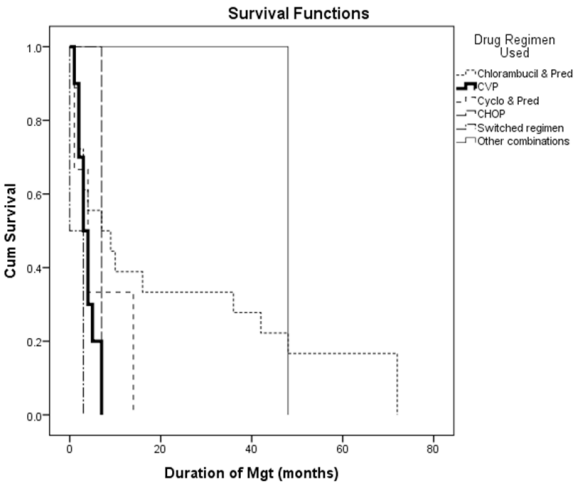

Fig 2c

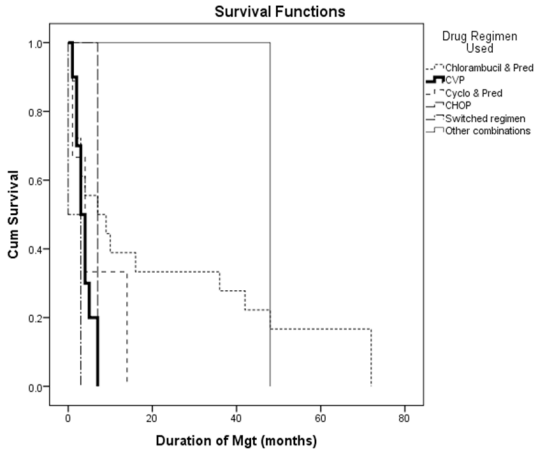

Fig 2d

The most common co-morbidity in these patients was diabetes mellitus which was observed in 28% (5/18) of the patients. This is followed by peptic ulcer disease in 17% (3/18). Complications observed in patients on treatment included; skin eruptions (pemphigus and shingles inclusive) – 12% (3/25), anaemia -20% (5/25), respiratory tract infections (including 2 cases of Tuberculosis) – 16% (4/25). However in the majority (70%) of the patients where these were recorded no complication of the treatment or primary disease was noted. The duration of management/ survival was influenced by neither the total white cell count nor the absolute values. (p=0.463 and p=0.228, respectively). Males showed superior survival rates between the 10th and 48th month post-diagnosis compared to females. At the time of this report 8 (5 females and 3 males) of the patients had been reported dead representing mortality rate of 14.3% and 76.4% 5-year survival.

Discussion

Malignancies are driven by genetic mutations, which confer some variability in clinical presentation as well as response to treatment. Patients in this study presented at a mean age of 59 years and this is similar to what was observed by Salawu et al in Ile-Ife[23] , while older age groups have been predominantly affected in the Europe and United States[24] . This however implies that a younger age group is affected by CLL in Nigeria, thus the need for further investigation into the predominant mutations causing this leukaemia in these patients. This may also be explained by the recent finding of monoclonal B lymphocytosis with increasing age[25], considered against the wide gap in life expectancy across the 2 patient populations. The male: female ratio in our study shows a slight male preponderance although previous studies have shown either a slight male or female predominance. Even though we may not be technologically advanced in terms of diagnostics making for possible misdiagnosis, this may imply that there may not be any actual difference in prevalence across the sexes. Majority of patients presented in Binet stage C, this is understandable, as in most cases lymphocytosis is discovered as an incidental finding from a blood count done for other reasons. However the staging system is dependent on the haemoglobin concentration; a decreasing level of which this study shows to negatively affect survival. In other Nigerian studies higher lymphocyte count was found to favor survival[23]; however this was refuted by our study, where no association was observed. It is known that the degree of splenomegaly, lymphadenopathy as well as lymphocyte counts are indirect measures of tumor bulk and are expected to hamper longevity. However, our study did not reveal this and this may be due the presence or absence of other prognostic markers like ZAP70 and CD38 which are not routinely assessed in CLL patients in low and middle income countries (LMICs). The serum alkaline phophatase at diagnosis showed a positive correlation with the duration of survival. The clinical significance of this finding is currently unknown but requires further investigation as it may provide a future laboratory prognostic marker which can be easily assessed in resource limited settings. Disease presentation at a younger age was found to be associated with progressive disease and by extension, reduced survival. This may be due to the occurrence of a different mutation in the younger CLL patients which may connote more aggressive disease phenotype [6,26]. CLL in the elderly might actually be "genotypically" different from CLL in the younger adults[26,27]. Chlorambucil-based regimen was used for majority of the patients in this study. Recently re-classification of CLL patients has become necessary with the advent of the disease entity – clinical monoclonal B- lymphocytosis, depending on the B cell count[28]. Majority of the centers in LMICs do not further differentiate their CLL patients based on this criterion and might possibly lump both patient groups together. None of the patients were placed on fludarabine or rituximab, both of which, though considered standard of care[22], are quite expensive and cannot be afforded by most patients in LMICs. The median duration of follow-up was 4 months and this portrays the lack of adequate documentation and patient tracking systems. Of the various chemotherapeutic combinations used in the patients in this study, patients on chlorambucil/prednisolone were shown to have longer duration of survival. This indicates that this combination is still the best of what is available although patients are more likely to benefit from using the more standard combinations. Patients treated with fludarabine/ cyclophosphamide/rituximab, (FCR) combination has been known to achieve deeper remission to the extent of eliminating minimal residual disease[10,11]. This treatment target is usually unachievable with the treatment regimen in use in LMICs. Better therapeutic options have to be explored for the CLL patients in resource-limited settings in order to optimize their life expectancy. Unlike other studies[29,30], males were shown to have superior survival rates compared to females. The reason for this variation is not known and will require further research.

Limitations of the study

This being a retrospective study was hampered by poor documentation, and missing data/incomplete data. This has affected the depth of the study.

Conclusion

CLL was found to affect the younger patients in this study with a median age at presentation being of 59 years. There was significant association between the serum alkaline phophatase levels at diagnosis and the duration of management/survival in the CLL patients studied. Majority of the patients received chlorambucil and prednisolone, while none received fludarabine-based treatment, with a median duration of 4 months follow-up. This portrays sub-

optimal treatment response with an underlining poor patient documentation and tracking system.

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Ethical considerations

Ethical approval for this study was obtained from the research and ethics unit of the college of Medicine, University of Nigeria, Enugu campus. Authors declare no conflict of interest

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