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ORIGINAL ARTICLE

Determinants of Remission in Acute Lymphoblastic Leukaemia in a Tertiary Health Facility in Southwestern Nigeria

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ABSTRACT

Background: The clinical outcome of Acute Lymphoblastic leukaemia (ALL) is still poor in Nigeria despite advances in treatment options available. This study therefore seeks to identify the predictors of remission in patients with ALL in Ibadan, Southwestern Nigeria.

Methods: This was a retrospective study of all patients diagnosed of ALL between January 2021 and December 2022 at the University College Hospital, Ibadan. Data on socio-demographic: age, gender and clinical features, full blood count, chemotherapy regimen and remission status were collected from the treatment records of the patients and analyzed using SPSS Version 23.0. A *p*-value of < 0.05 was considered significant.

Results: Thirty cases of ALL were diagnosed over the study period. The median age was 15years (IQR:6.6, 20.0). The most common clinical presentation was lymphadenopathy (73.3%), fever (63.3%), and mucocutaneous bleeds (33.3%). All the patients presented with anaemia [packed cell volume (mean±SD) 23.3± 8.2%)], thrombocytopenia [median (IQR)40.0 (15.0,130.0)] and leukocytosis [17.0(4.9, 80.0) c/mm^3]. Induction chemotherapy used were cyclophosphamide, vincristine, cytosine arabinoside and prednisolone (COAP) (83.3%) and Vincristine and prednisolone (V+ P) (16.7%) with a mean of 4 cycles of administration. The remission rate was low (26.7%). Neutrophil and lymphocyte counts at presentation were the only factors associated with remission (*p*=0.016 and 0.010 respectively). Male gender, higher neutrophil count, lower lymphocyte count and V + P chemotherapy though positively predicted remission, did not reach statistical significance(*p*>0.05).

Conclusion: Remission status in ALL patients is still abysmally poor in our setting and neutropenia is an important independent negative predictor.

Keywords: Acute lymphoblastic leukaemia; Determinants; Remission status; Africa

INTRODUCTION

Acute lymphoblastic leukaemia (ALL) is a biologically heterogenous malignant disease of early lymphoid precursors characterized by arrest of maturation, proliferation of blasts in the marrow leading to replacement of normal haemopoietic cells and eventual spillage into peripheral blood. ALL is the most common childhood leukaemia diagnosed in children aged 2 to 5 years as well as in young adults.[1-3] with an estimated 5-year survival of about 72% in the United States.[4] ALL treatment outcome has improved significantly in developed countries with remission rate reaching up to 80% [5] unlike in resource constraint nations like Nigeria where rates are mostly less than 50%. The improved outcome witnessed results from better understanding of the disease pathogenesis arising from advances in molecular methodology, development of targeted therapy with less toxicity protocols, as well as availability of other supportive interventions.

The prognostic factors affecting clinical outcome in ALL patients include age, leukocytes count, tumour genetic factors and response to chemo-therapy. Cytogenetic characteristic of patients in Nigeria is still not available due to dearth of infrastructure. Several studies have been done and documented the dismal survival rate of ALL patients, but a few have looked at the clinical and laboratory predictors of outcome in these patients in Nigeria.[6,7] This study was undertaken to determine the factors associated with remission following induction chemo-therapy in a tertiary hospital in Nigeria.

MATERIALS AND METHODS

This was a retrospective study of children and adults managed at the haematology department of the University College Hospital, Ibadan. Physicians at haematology department make diagnosis of acute lymphoblastic leukaemia for all patients who presented to this hospital following review of clinical presentation,

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peripheral and marrow slides of all suspected acute lymphoblastic leukaemia in the hospital. They are also involved in prescription of chemotherapy and monitoring of Paediatric patients who are under the primary care of Paediatric haemato-oncologists of the hospital. The patients were diagnosed between January 2021 and December 2022 in the hospital.

The patient's clinical information was obtained from the pink forms. The pink form contains succinct summary of all patients on treatment for haematological conditions in the hospital. The pink forms are securely kept by the physicians and serves as alternative medical records. The information retrieved included age, gender, clinical features at presentation, full blood count parameters, chemotherapy administered and how many cycles and clinical and haematological remission status. Clinical remission status was defined as resolution of signs and symptoms related to the ALL at presentation while haematological remission status was defined as normalization of full blood count parameters and absence of peripheral blood lymphoblasts as well as less than five percent lymphoblast on marrow examination.[8]

The data obtained for each patient were entered into SPSS version 23 (SPSS, Inc., Chicago, IL, USA). The data was explored for normal distribution using the Kolmogorov-Smirnov and Shapiro-Wilk. Packed cell volume (PCV) was normally distributed and was summarized as mean and standard deviation while age and other FBC parameters were summarized as median and interquartile range. Gender, clinical features, chemotherapy type and remission status were presented as frequency and percentage. Comparison between continuous variables were tested using either independent *t* test or Mann-Whitney U. Predictors for remission were assessed for using binary logistic regression. Statistical significance was set at *p*-value <0.05. Ethical approval was obtained from the institutional review board.

RESULTS

A total of 30 patients diagnosed with ALL within the period under review were analyzed. The median age of all the participants was 15.0 years (IQR, 6.6-20.0). The highest proportion [9/30, 30.0%] were between 15-19 years. A male preponderance 23 (76.7%) was observed [M: F, 3.3: 1]. Females were significantly older [Med=23.0, n=7) compared to males [Med=12.7, n=7], U=37.5, *p*=0.044, with a negligible effect size, r=0.1 (Table 1). The clinical presentation pattern of the patients is shown in Figure 1. The most common symptoms were lymph node enlargement 22 (73.3%) followed by fever 19 (63.3%) and bleeding 10 (33.3%).

Table 2 shows the laboratory parameters of the participants. All the patients presented with anaemia (PCV<30%) and only 8 (26.7%) attained normal PCV without transfusion, Leukocytosis was present in all the patients at diagnosis (WBC> 11000c/mm3) however the counts became normalized with treatment. Thrombocytopaenia was present in all cases at diagnosis and remained suboptimal throughout the period of treatment (platelets: 45.0-50.0 x 10^3 c/mm^3). The patients were all neutropenic at presentation and remained so all through the period of review in majority 22 (73.33%) (ANC: 0.7-1.0 c/mm^3). Cyclophosphamide, Oncovin, Cytosine Arabinoside and Prednisolone (COAP) chemotherapy was the most used combination (10, 83.3%) followed by Vincristine and Prednisolone (VP) (2, 16.7%). Majority of the patients had IT therapy and COAP in the first induction. The patients had induction chemotherapy for an average of 4 times which indicated a high rate of induction failure. The data also show that only a minority (8, 26.7%) achieved clinical remission on first, 2(20%) on second and 1(33%) on third induction respectively (Table 3). It was noted that the PCV, neutrophil and platelet counts though increased with administration of chemotherapy they were never normalized. On the other hand, the total white cell and lymphocytes counts reduced with each induction therapy. However, when Friedman test was used to compare the haematological parameters measured at the three different times, there were no significant difference in all the parameters (p>0.05). The treatment outcome shows that only 8 (27%) achieved haematological remission at first induction, and of the remainder 10, 2 achieved remission on second induction while only 1 of 3 achieved remission at third induction. The rest of the patients were either lost to follow up or succumbed to the disease.

The factors associated with remission were sought for and there was no significant difference in age(years) in those that achieved remission and those that did not (p=0.961). Also, gender and type of treatment modality were not associated with remission status (p=0.896 and 0.671 respectively). The patents who had higher neutrophils count were more likely to achieve remission [34.0 vs 9.5, p=0.045] The patients that achieved remission had higher PCV and platelets count than those that did not [27.5% vs 21.55 and 99.0 vs 35.5 x 10^3 c/mm^3], although these were not statically significant [*p*=0.081 and 0.115 respectively]. The patients that did not achieve remission had higher WBC and lymphocyte count at presentation, but these did not reach statistical significance (p=0.401 and 0.057 respectively. (Table 4). However, on further multivariate analysis using

Table 1: Age and gender characteristics of the ALL patients seen over a period of two years (January 2021 to December 2022)

Variable	Frequency (n=30)	Percent
Age (years) (Med, IQR)	15.0 (6.0, 20.0)	
Age group (years)		
≤ 5	6	20.0
6 - 9	4	13.3
10 - 14	4	13.3
15 - 19	9	30.0
≥20.0	7	23.3
Gender		
Male	23	76.7
Female	7	23.3

Med -median, IQR -Interquartile range

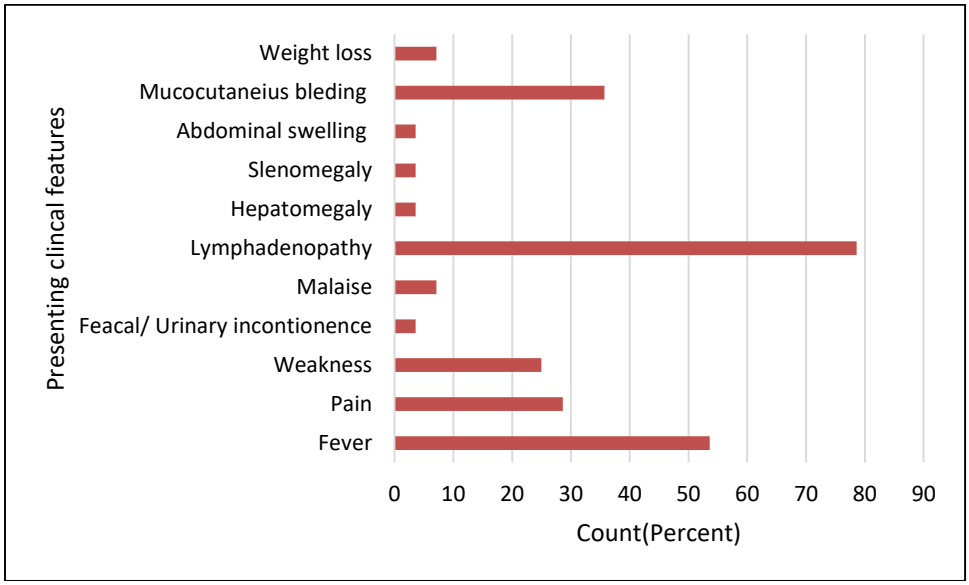

Figure 1: Bar chart of presenting complaints of ALL patients

Table 2: Full blood count parameters of the ALL at diagnosis, days 15, and 28 of treatment

FBC parameters	First FBC (Day 0)	Second FBC (Day15)	Third FBC (Day 28)	p value
*PCV %	23.0 ± 8.2	27.0 ±6.8	27.0 ±6.8	0.183*
**WBC x 10 ^{3} c/mm^3	17.0(4.9, 80.0)	4.7 (3.0,9.8)	3.3 (3.0, 8.11)	0.665**
**Platelets x 10 ^{3} c/mm^3	40.0 (15.0,130.0)	35.0 (20.0,50.0)	55.5(18.0, 233.0)	0.905**
**Neutrophil %	26.0 (9.0,65.0)	18.0 (11.0, 49.0)	20.0 (13.4,48.3)	0.446**
**Lymphocytes %	61.0 (32.0,82.0)	57.0 (38.0, 94.0)	57.0 (22.5, 80.8)	0.118**
**Monocytes %	4.0 (2.0,12.0)	8.0 (5.0,20.0)	5.50 (3.5, 10.3)	0.348 **

**Mean ± sd, **Median (interquartile range) *Independent t test, ** Mann Whitney U, p value <05. FBC-Full blood count, PCV-packed cell volume, WBC-White cell count*

Table 3: Chemotherapy regimen administered to the patients during three different admission periods

Treatment / Chemotherapy	Treatment on 1st Admission n (%)	Treatment on 2nd Admission n (%)	Treatment on 3rd admission n (%)
IT	8 (57.1)	3 (66.7)	0
COAP	10 (83.3)	1 (33.3)	1
V+P	2 (16.7)	1 (33.3)	
Number of cycles (Mean, SD)	3.71 (2.79)	3 (1.41)	9

IT-Intrathecal therapy, CAOP- Cyclophosphamide, vincristine, cytarabine, prednisolone, V+ P- Vincristine, prednisolone, SD- standard deviation

Table 4: Association between sociodemographic characteristic, laboratory findings at presentation and remission status

Variable	Remission status		Test statistics	*P* value
	Yes	No		
Age (years, n=30)	15.0	15.0	083.0***	0.961
Gender (n=30)				
Male	6 (26.1%)	7 (73.9%)	0.017*	0.896
Female	2 (28.6%)	5 (71.4%)		
Type of treatment				
COAP	2 (28.6%)	5 (71.4%)	0.171*	0.679
V+P	2 (40.0%)	3 (60.0%)		
PCV%1(n=29)	26.5 ±7.9	21.5±7.9	1.815**	0.081
WBC1 $X10^3c/mm^3$	5.2	7.9	39.0***	0.401
Platelets $X10^3c/mm^3$	99.0	35.5	11.0***	0.115
Neut $X10^3c/mm^3$ [Med (IQR)]	1768.0 (3404.0)	711(2862.0)		**0.016*** **
Lymph $X10^3c/mm^3$ [Med (IQR)]	2912.0 (30672.0)	6241.0(33206.3)		0.010***

Chi-square **Independent t test, * Mann Whitney U, ® Significant p< 0.05. COAP -Cyclophosphamide, vincristine, cytarabine, prednisolone; V+ P- Vincristine, prednisolone, Neut-Neutrophil, Lymph-Lymphocytes; Med-median, IQR-Interquartile range, FBC-Full blood count, PCV-packed cell volume, WBC-White cell count*

Table 5: Binary Logistic regression of factors influencing remission

Variable	Adjusted OR	P-value	95% Confidence Interval	
			Lower	Upper
Gender				
Male	1.133	0.896	0.172	7.469
Female (Ref)				
Type of treatment				
COAP (Ref)				
V+P	1.667	0.680	0.147	18.874
Wbc	1.000	0.347	1.000	1.000
Platelet	1.000	0.330	1.000	1.000
Neutrophil	1.024	0.347	0.974	1.077
Lymphocyte	0.967	0.746	0.842	1.131

COAP -Cyclophosphamide, vincristine, cytarabine, prednisolone; V+ P- Vincristine, prednisolone

binary logistic regression, no predictor was identified for achievement remission (Table 5).

DISCUSSION

The poor clinical outcome of patients with acute lymphoblastic leukaemia in Nigeria is in sharp contrast with those in developed countries. The factors associated with the poor clinical outcome were sought for in this study. Majority of ALL patients were males who were also younger than the females with a male to female ratio of 3.3: 1 which is similar a range of 2:1 to 3.7: 1 by others.[9-15] Globally, the prevalence of ALL also has a male preponderance of M: F, 1. 4: 1. The reason for this male preponderance has remained largely unexplained [16-17] though a protective sex-responsive gene near to the ABO gene locus on chromosome 9 in female has been suggested.[18]

A median age prevalence of 15 years was found in this study. The median age of 15 years found in this study is like age range of 13.5 -19 years reported by other studies.[4,12,19,20] The exact reason for predominance of ALL among children is not clear. Olaniyi et al [12] proposed that the reason for high incidence of ALL in children may be due to genetic rather than environmental factors. It therefore appears that the reason for this high incidence in childhood may both be due to environmental and genetic factors. Genetic characterization of acute lymphoblastic leukaemia, if routinely made available may help resolve the enigma of factors responsible for this high incidence in this environment.

Peripheral lymphadenopathy, fever and muco-cutaneous bleeding were the commonest clinical presentation in this study. This finding is similar to Oyesakin et al [13] who reported fever, hepatomegaly and abnormal bleeding as the commonest clinical futures. All the patients presented with anaemia, thrombocytopaenia and lymphocytosis with only a few normalizing with treatment. This is similar to finding by other studies in Nigeria.[6,9] Bone marrow failure is a cardinal feature of acute leukaemia which is a result of accumulation of malignant blasts in the marrow and suppression of normal hae-mopoiesis. This underscores the prevalent deficiency related to supportive management of patients with acute leukaemia our setting due to short supply of blood products by the blood

transfusion facilities and lack of funds to procure these products because payment of services for treatment is mostly out of pocket expenditure.[6,9,12,21]

The aim of definitive treatment in ALL is to eradicate the malignant blasts in the bone marrow to restore normal haemopoiesis and this is achieved with the use of combination chemotherapy. The ALL patients in this study received either COAP or V+ P chemotherapy as opposed to novel and more effective chemotherapy regimens in developed nations like HyerCyclophosphamide, Vincristine, Adriamycin, and Dexamethasone (Hyer-CVAD). Vincristine plus prednisolone (V+P) was used as a pre-induction therapy. There is therefore urgent need in this regard to include more effective drugs in the essential drug list of the country and to liaise with pharmaceutical industries to make available in the country these new drugs in form of clinical trials or otherwise.

The remission rate of 27% at first induction in this study is poor. This was similar to finding of other studies in Africa with rate between 5-33% [9,10,13,22] and Latin America[23] compared to rate as high as 90% in developed countries.[24] As previously alluded to, poor blood products support, lack of funds to procure medications and other supportive care contributed to delay in commencement of chemotherapy and underdosing instances may indirectly be responsible for the reported low reemission rate. Furthermore, lack of facility for the detection of cytogenetic and immunophenotypic abnormalities associated with malignancy blasts affected proper prognostication of the patients.[12] Remission attainment was found to be significantly associated with increased neutrophil count but not with Packed cell volume (PCV), White blood cell count (WBC), platelet and lymphocyte counts as well as choice of chemotherapy whether COAP or V+P. Togo et al attributed cause of death in Mali to infections and this has also been observed in our setting.[9] Acute lymphoblastic leukaemia patients who present-ed with neutropenia must be aggressively treated by prompt identification of the offending microbes through cultures and use of appro-priate antimicrobials according to sensitivity pattern. This fact also underscores the need to allocate more resources to pathology labor-atories in the country to scale up diagnostic capacity of our hospitals. The small sample size and retrospective nature of this study might have affected the outcome as some data were not available for analysis. A longitudinal study design with more participants may shed more light on the factors associated with poor remission status in ALL patients in this environment.

Conclusion: The commonest clinical features of ALL patients in this study are lymphadenopathy, fever and thrombocytopaenic bleeds. Remission rate is low in the patients and identified contributors included neutropenia, high relapse rate following induction chemotherapy using COAP and V+ P regimens.

Recommendations: There is need for emphasis to be placed on control of infections in the management of ALL patients. A multi-centre study to determine the factors associated with clinical outcomes in ALL patients is also recommended with a view to improving the clinical outcomes.

Clinical Practice Points: This manuscript was set out to determine the determinants of remission outcome in ALL patients who received care at the University College Hospital, Ibadan which is the premier teaching hospital in Nigeria. We observed that neutropenia is the single most important negative predictor of remission in our setting. Male gender, higher neutrophil count, lower lymphocyte count and V + P chemotherapy though positively predicted remission, did not reach statistical significance(p>0.05). We posited therefore that treatment of neutropenia and its resolution would improve the outcomes of ALL patients in our setting.

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Authors' contributions: WAS conceived the research idea and reviewed the draft manuscript, SPO analyzed the data, wrote the draft manuscript while OA collected the data.

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