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Chronic lymphocytic leukaemia (CLL) in Central Africans

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Abstract

Objective: To document the clinical and haematological features of chronic lymphocytic leukaemia (CLL) in Central Africans.
Design : Prospective descriptive analysis.
Setting : Tertiary referral teaching hospitals.
Subjects: 48 Zimbabweans and 27 Malawians formed the basis of this analysis.
Results : There were 75 patients (40 males and 35 females) studied and their ages ranged from 32 to 78 years with a mean ± s.d. of 56.8 ±10.1 years. The peak age incidence of 26.7% occurred between 60 to 64 year old and 21.3% were below 50 years. The major clinical findings included: splenomegaly (68%); hepatomegaly (37.3%); anaemia (34.7%); lymphadenopathy (33.3%) and nine (12%) patients were diagnosed incidentally. The majority of patients (78.7%) had Rai stage III and IV and only seven (9.3%) patients were in stage 0. Of the 32 patients treated with chemotherapy, 25.9% and 59.3% achieved complete or partial remissions respectively. Six patients were still alive after a follow up period of a mean ± s.d of 39.3 ± 24.4 months; five were lost to follow up after a mean ± s.d period of 28.6 ± 18.8 months and 16 were dead after a mean ± s.d. period of 25.7 ± 19.1 months. The main causes of death in the treated group were septicaemia in six, pneumonia in four and tuberculosis in three. In the untreated group of 43 patients, two refused therapy, four died shortly after diagnosis and 37 were lost to follow up.
Conclusions and recommendations : Although the study has disclosed that CLL is not rare in central Africans and its presentations are similar to cases reported in the literature, the majority of patients seek medical treatment late. Optimal therapy is impossible due to lack of chemotherapy and supportive services. Therefore, it is recommended that tertiary referral centers in African health systems should be equipped for better management of CLL patients.

Cent Afr J Med 2004;50(11/12):111-15

Introduction

Chronic lymphocytic leukaemia (CLL) is a haematological malignancy characterized by monoclonal proliferation and accumulation of mature looking small lymphocytes particularly in the marrow, blood, lymph nodes and spleen.[1-3] In 90 to 95% of cases, the cells are monoclonal B lymphocytes.[3] Although in Europe and America CLL of B-cell origin is the commonest type of leukaemia, it is extremely rare before the age of 50 years, after which its incidence increases progressively with age. The male to female (M:F) ratio is 2:1.[2,3] In contradistinction to these findings, CLL is rare throughout Southern, South Eastern and Eastern Asia as well as in Asians who migrated to North America and Europe. This suggests genetic determinants as they usually suffer from the CLL of T-cell origin.

Reports from sub-Saharan Africa[4] show that CLL occurs from the age of 17 years with the overall M:F ratio of 1:1. There is a bimodal distribution so that about half of the patients are aged 45 years or less with a M:F ratio of 1:2. Over 45 years the M:F ratio is 2:1, as in the developed western world. Frequency rises in women towards the end of their reproductive life. CLL is associated with upper socio-economic status and with rural habitation.[4,5]

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Previous studies from Zimbabwe[6] and Malawi[7] show that CLL is not rare in indigenous Central Africans. However, these studies were not detailed with respect to CLL and cell marker studies were not attempted. This study presents a detailed description of the clinical, haematological, immunophenotyping, treatment and follow up results and compares with experience from Africa and elsewhere in the world.

Materials and Methods

The study comprised 48 Zimbabweans and 27 Malawians who were consecutively seen and prospectively documented by the authors at the Departments of Haematology of the University of Zimbabwe Medical School, Harare, Zimbabwe, from January 1986 to June 1989 and at the University of Malawi, College of Medicine, Blantyre, Malawi between January 1997 to December 2002 respectively. For each patient, clinical details were recorded after a history and a physical examination had been performed.

In Harare, full blood counts (FBCs) were determined using Coulter Counter Models S and JS and in Blantyre, FBCs were analyzed using the Coulter Counter Onyx. Other diagnostic tests done were peripheral blood films and bone marrow aspirations which were stained according to standard techniques.[8] Other relevant tests which were carried out on some of the patients in order to conserve expensive reagents included antiglobulin (Coombs) test; serum protein electrophoresis and estimation of gamma globulins; immunophenotyping using Flow cytometer Model FACScan, Becton Dickinson, USA. The diagnosis of CLL was based on clinical and haematological findings *viz*: persistent lymphocytosis ≥ 10.0 x 10^9/l with or without bone marrow lymphocyte count ≥ 30% of marrow cells.[2,9] The clinical staging was according to Rai, *et al.*[10] The indications for therapy were Rai stages III, IV or bulky and symptomatic stages I or II disease.[9]

Chlorambucil 0.1 to 0.2 mgs/kg/day or cyclophosphamide 2 to 3 mgs/kg/day with or without prednisolone 40 to 60 mgs/m^2/day were administered and treatment was given for at least five months before evaluating response. Response criteria were as described by Sawitsky, *et al.*[11] These were complete remission (CR) = normalization of all clinical and haematological parameters; partial remission (PR) = reduction in the size of organomegaly to 50% of that at diagnosis and lymphocyte count less than 15.0 x 10^9/l; no response (NR) = no change in the clinical or lymphocyte count; progression (Pg) = worsening over 28 days with increase in size of organs and lymphocyte count. Due to scarcity of chemotherapeutic agents, the majority of patients were treated conservatively and followed up in the clinic with observation only. The results were analyzed using the desk-top Scientific Calculator Model HP48GX, Texas Instruments, USA. The student's t-test and Chi squared tests were used to determine statistical significance between groups. A p value of less than 0.05 was considered significant.

Results

Of the 75 patients studied, 40 were males and 35 females, giving an overall M:F ratio of 1.1:1. Their ages ranged from 32 to 78 years with a mean ± s.d. of 56.8 ± 10.1 years. Table I shows the age and sex distribution of the CLL patients in the study. In 16 (21.3%) patients, CLL occurred below the age of 50 years. Of these 16 patients, 10 (62.5%) were women of a relatively younger age. The clinical presentation at diagnosis is shown in Table II.

Table I: Age and sex distribution of 75 CLL patients.

Age group (yrs)	Sex		Total	
	Male	Female	No.	%
30-34	—	2	2	2.7
35-39	3	1	4	5.3
40-44	—	4	4	5.3
45-49	3	3	6	8.0
50-54	10	1	11	14.7
55-59	3	7	10	13.3
60-64	12	8	20	26.7
65-69	6	7	13	17.3
70-74	1	2	3	4.0
≥ 75	2	-	2	2.7
Total	40	35	75	100.0

Table II: Presenting clinical features in 75 CLL patients.

Clinical feature	No. (n = 75)	%
Symptoms:		
Splenic discomfort/pain	33	44.0
Weakness/fatigue/malaise/syndrome	25	33.3
Abdominal fullness or mass	18	24.0
Weight loss	16	21.3
Fevers on and off	8	10.7
Bleeding tendency	2	2.7
Headaches	2	2.7
Excessive sweating	2	2.7
Signs:		
Spleen palpable	51	68.0
1-9cms (mild to moderate splenomegaly)	30	40.0
10–19.9 cms (severe splenomegaly)	19	25.3
≥ 20cms (gross splenomegaly)	2	2.7
Spleen not palpable	7	9.3
Hepatomegaly	28	37.3
Anaemia/pallor	26	34.7
Lymphadenopathy (cervical/axillary/inguinal)	25	33.3
Pyrexia	8	10.7
Cardiac failure	3	4.0
Respiratory tract infections	2	2.7
Incidental diagnosis	9	12.0

Clinical features: Complaints attributable to splenomegaly (68%) and constitutional symptoms were the dominant clinical features and accounted for 68% and 65.3% respectively, followed by hepatomegaly 37.3%, anaemia 34.7%, lymphadenopathy in 33.3%, pyrexia 10.7%, cardiac failure 4% and other features 10.8%. In nine (12%) patients, the diagnosis was incidental, i.e.

patients were being investigated for unrelated complaints, blood donation or for employment purposes.

Table III : Haematological findings at diagnosis in 75 CLL patients.

Blood count index	No.	%	Mean ± s.d.	Range
Wbc (x 10^9/1)	75	100.0	127.0 ± 128.0	15.2–675.0
Hb (g/dl)	75	100.0	9.5 ± 2.5	3.3–15.2
Platelets (x 10^9/1)	75	100.0	165.2 ± 81.3	32.0–480.0
Absolute lymphoctye count (x 10^9/1)	75	100.0	115.8 ± 122.2	11.6–648.0
10–29	10	13.3	18.5 ± 6.4	11.6–28.5
30–49	11	14.7	40.5 ± 5.4	30.1–46.9
50–100	26	34.7	67.7 ± 11.9	52.0–93.7
Over 100	28	37.3	224.7 ± 143.1	101.9–648.0
Hb (g/dl):				
< 10	44	58.6	7.8 ± 1.5	3.3–9.9
10 to 12	17	22.7	10.8 ± 0.5	10.0–12.0
Over 12	14	18.7	13.2 ± 1.0	12.1–15.2
Platelet count				
< 100	17	22.7	72.6 ± 20.2	32–98
100 to 150	20	26.7	130.8 ± 15.6	100–150
Over 150	38	50.6	224.7 ± 68.6	152–480

Haematological findings : Haematological features at diagnosis are shown in Table III. There was no statistically significant difference in the haematological values between the Zimbabwean and Malawian groups ($p>0.05$). The overall absolute lymphocyte count ranged from 11.6 to 648.0 x10^9/l with a mean ± s.d. of 115.8 ± 122.2 x 10^9/l. Seventy two percent had a lymphocyte count equal to or greater than 50 x 10^9/l and in 28% the lymphocyte count was between 10 to 49 x 10^9/l. The overall haemoglobin (Hb) level showed a mean ± s.d. of 9.5 ± 2.5 g/dl with a range of 3.3 to 15.2 g/dl. Of the patients 58.6% had an Hb of less than 10.0g/dl. The platelet count ranged from 32 to 480 x 10^9/l with a mean ± s.d platelet count of 165.2 ± 81.3 x 10^9/l and thrombocytopenia (platelet count <100 x 10^9/l) was found in 17 (22.7%) patients with a mean ± s.d platelet count of 72.6 ± 20.2 x 10^9/l; range 32 to 98 x 10^9/l. Immunophenotyping revealed that all the 19 (25.3%) patients were of the B-CLL type. Fifty six (74.7%) patients were not typed due to lack of reagents. The antiglobulin (Coomb's) test performed in 36 patients was positive in five(13.9%) patients but none of these had evidence of auto immune haemolytic anaemia. Serum protein electrophoresis performed in 24 patients showed depressed gamma globulins in eight (33.3%) patients.

Table IV: Rai clinical stages in 75 CLL patients.

Stage	No.	%
0	7	9.3
1	2	2.7
11	7	9.3
111	42	56.0
IV	17	22.7
Total	**75**	**100.0**

Table IV shows the clinical stages of CLL patients at diagnosis according to Rai, *et al.*[10] The majority (78.7%) presented with stages III and IV disease. Stages 0, I and II accounted for 9.3%, 2.7% and 9.3% respectively.

Therapy, response and outcome: Thirty two (42.7%) patients were treated with chemotherapy that was available at the time of diagnosis. Seventeen received chlorambucil and 15 cyclophosphamide with or without prednisolone. Chlorambucil produced complete or partial remissions in 28.6% and 57.1% respectively and in 14.3% there was no remission. Cyclophosphamide produced complete or partial responses in 23.1% and 61.5% respectively. No response was seen in 15.4%. Three patients in the chlorambucil group and two in the cyclophosphamide group were not evaluated as they absconded soon after therapy was started. At the time of this presentation, of the remaining evaluable 27 patients in the group treated with chemotherapy, six patients are still alive and on follow up with a mean ± s.d. survival duration of 39.9 ± 24.4 months; median 41 months and range eight to 76 months since diagnosis.

Five patients were lost to follow up after a follow up period of a mean ± s.d. of 28.6 ± 18.8 months; median 27 months, range seven to 57 months from the time of diagnosis. Sixteen are known to have died and the duration of survival for this group was a mean ± s.d. of 25.7 ± 19.1 months; median 19.5 months and range five to 60 months after diagnosis. The causes of death were: septicaemia in six, pneumonia in four, pulmonary tuberculosis in three and unknown causes in three. Forty three (57.3%) patients were not treated due to lack of cytotoxic drugs. Of these seven had early disease, 30 were lost to follow up and are presumed dead, four died shortly after the diagnosis of CLL was made but post mortems were refused and two refused therapy on religious grounds.

Discussion

Chronic lymphocytic leukaemia (CLL) is the most common form of leukaemia in North America and Europe accounting for one third of all leukaemias in humans. It is extremely rare in Orientals and their descendants who migrated to America and Europe.[2,3] In the western countries, the disease typically occurs in older patients, with the highest incidence being in those aged 50 to 60 years. It affects men twice as often as women.[3] However, in sub-Saharan Africa CLL rates range from 12 to 40%.[4-7,12] It has been reported to occur from the teens to the elderly and the overall M:F ratio is 1:1 as was found in this study.[4]

But there is a bimodal distribution; about half of the patients being aged 45 years or less and in them the M:F ratio is 1:2. Over the age of 45 the M:F ratio is 2:1 as in developed western countries.[4]

In this study in 16 (21.3%) patients CLL occurred below the age of 50 years and of those 16 patients, 10 (62.5%) were women of a relatively younger age just as it was found by Fleming, *et al.* in neighbouring Zambia[5] and Kulkarni in Nigeria.[12]

It has been postulated that CLL occurring in younger adults in Africa is a consequence of recurrent malaria and other infections, resulting in a polyclonal B-cell proliferation which in an extreme form is hyper reactive malarial splenomegaly (HMS).[5] B-cell proliferation is greatest with the more frequent exposure to infection associated with rural poverty and with recurrent depression of cell mediated immunity during the pregnancy of the grand multiparae.[4,5]

A second event that has been hypothesized as leading to transformation to a monoclonal B-cell proliferation could be an infection by an unidentified virus whose transmission is more frequent in impoverished rural communities and whose impact is enhanced by the depression of immunity by malaria and pregnancy.[4,5]

The main clinical presentation in this series were symptoms attributable to splenomegaly and hepatomegaly that caused the patients to seek medical attention, unlike in the western hemisphere where lymphadenopathy is the dominant presenting clinical feature.[2,3,9] Splenomegaly and hepatomegaly accounted for 68% and 37.3% respectively, figures which are comparable to the Ethiopian[13] figures of 55.9% and 32.4%, unlike in Kenyans where figures of 80.9% and 76.5% were found.[14] Significant pallor, which is rare in Caucasians,[2] was noted in 34.7%, but Shamebo, *et al.*[13] and Oloo, *et al.*[14] found figures of 37.3% and 59.5% in their series. In western developed nations,[2,9] with the use of routine blood testing, the number of CLL patients diagnosed incidentally is around 40 to 60%, unlike in Ethiopians[13] and this series where respective figures of 4.9% and 12.0% accounted for incidental diagnoses of CLL. In this study, only seven (9.3%) patients were in stage 0. Stages I and II, III and IV accounted for 12.0% and 78.7% respectively in contrast to the study by Gale, *et al.*[15] who reported 25% in stage 0, 50% in stage I and II and 25% in stage III and IV. The findings in this study, therefore, show that most of our patients seek medical attention in late stages of the disease as in the Ethiopian[13] and Kenyan[14] studies.

There is controversy as to at what degree of lymphocytosis should the diagnosis of CLL be considered. A level above five to 10 x 10^9/l has been established in most commonly accepted staging systems.[9]

In our patients the overall absolute lymphocyte count was mean ± s.d. of 115.8 ± 122.2 x 10^9/l; range 11.6 to 648.0 x 10^9/l; and in 72% of the patients the absolute lymphocyte count was above 50x10^9/l; a figure which is in agreement with a figure of 70% reported in Kenyans.[14] Platelet counts of 100 to 150 x 10^9/l and <100 x 10^9/l were recorded in 26.7% and 22.7% respectively. Two patients with platelet counts of 32.0 x 10^9/l and 48.0 x 10^9/l presented with bleeding tendencies especially from mucus membranes. The overall mean ±s.d. haemoglobin was 9.5 ± 2.5 g/dl; range 3.3 to 15.2g/dl with 81.3% having less than 12.0g/dl and 58.6% less than 10.0g/dl. In the Ethiopian[13] study mean haemoglobin was found to be 10.77g/dl with 62.7% having less than 12.0g/dl and 37.3% less than 10.0g/dl; whereas in Kenyans,[14] anaemia was even more marked; Hb less than 8.0g/dl was reported in 66.7%.

In western countries, patients rarely present with pallor or other features of anaemia.[2] About 20% of CLL patients have a positive Coombs' test at some time in their illness but only about 8% develop an auto-immune haemolytic anaemia.[15] In this series Coombs test, performed only in 36 (48%) patients, was positive in five (13.9%) patients but none of the patients had evidence of auto-immune haemolytic anaemia. It is also interesting to note that immunophenotyping done in 19 (25.3%) patients revealed that all of them were of the B-CLL origin, which is in total agreement with the western pattern.[2,3] In the western hemisphere responses to chlorambucil and cyclophosphamide with or without prednisolone have ranged from 38% to 100% but the interpretation of these data is difficult because of the lack of homogeneity in the groups of patients studied.[1-3]

In our patients that could be evaluated for outcome of treatment, overall responses of 85.7% and 84.6% which were found for chlorambucil and cyclophosphamide are similar to those reported in the literature.[1-3,11,16] However, most patients in tropical Africa do not benefit from the advances in leukaemia therapy and other malignancies in general. Besides, there are other constraints which are related to CLL management *viz*: limited laboratory diagnostic facilities like immunophenotyping, lack of chemotherapy agents, lack of support services, poor patient compliance and a high default rate. Consequently, lack of accurate diagnosis results in inappropriate staging and therapy. Therefore, establishment of multicentre studies and a major investment into haemato-oncology in tropical Africa twinning with centres in industrialized countries are required and should be followed by commensurate humanitarian benefit.

Acknowledgements

To the various colleagues under whom some of the patients included in this study were admitted and looked after. To Mrs MT Bwanali, Secretary, Department of Haematology, College of Medicine, University of Malawi, for word-processing of the manuscript and above all, to the Secretaries for Health, Ministries of Health, Zimbabwe and Malawi Governments, for permission to publish.

References

1. O'Brien S, del Giglio A, Keating M. Advances in the biology and treatment of B-cell chronic lymphocytic leukaemia. *Blood* 1995;85(2):307-18.
2. Johnston JB. Chronic lymphocytic leukaemia. In: Lee GR, Foerster J, Lukens J, *et al.*, editors. Wintrobe's clinical haematology. 9th ed. Vol. 2, Philadelphia: Lippincott Williams and Wilkins, 1993;2405-27.
3. Dighiero G, Travade P, Chevret S, *et al.* B-cell chronic lymphocytic leukemia: present status and future directions. *Blood* 1991;78(8):1901-14.

4. Fleming AF. Chronic lymphocytic leukaemia in tropical Africa: a review. *Leuk Lymphoma* 1990;1:169-73.
5. Fleming AF, Terunuma H, Tembo C, *et al.* Leukaemias in Zambia. Leukaemia 1999;13:1292-3.
6. Levy LM. The pattern of leukaemia in adult Zimbabweans. *Cent Afr J Med* 1984;30(4):57-63.
7. Mukiibi JM, Nyirenda CM, Adewuyi JO, *et al.* Leukaemia at Queen Elizabeth Central Hospital in Blantyre, Malawi. *E Afr Med J* 2001;78(7):349-54.
8. Dacie JV, Lewis SM. Practical haematology. 7th ed. London: J and A Churchill Livingstone, 1991;75-85.
9. International workshop on chronic lymphocytic leukaemia. Chronic lymphocytic leukaemia: recommendations for diagnosis, staging and response criteria. *Ann Inter Med* 1989;10:236-8.
10. Rai KR, Sawitsky A, Cronkite EP, Chanena AD, Levy RN, Pasternack BS. Clinical staging of chronic lymphocytic leukemia. *Blood* 1975;46:219-34.
11. Sawitsky A, Rai KR Glidewell O, Silver RT. Comparison of daily versus intermittent chlorambucil plus prednisolone therapy in the treatment of patients with chronic lymphocytic leukaemia. *Blood* 1977;50:1049-59.
12. Kulkarni AG. Leukaemias in the Guinea Savanna area of north of Nigeria. *EAfr Med J* 1986;63(10):660-5.
13. Shamebo M, Gebremedhin A. Chronic lymphocytic leukaemia in Ethiopians. *E Afr Med J* 1996;73(10):643-6.
14. Oloo AJ, Ogada TA. Chronic lymphocytic leukaemia (CLL): clinical study at Kenyatta National Hospital (KNH). *E Afr Med J* 1984; 61(11):797-810.
15. Hamblin TJ, Oscier DG, Young BJ. Auto-immunity in chronic lymphocytic leukaemia. *J Clin Pathol* 1986;39:713-6.
16. Boggs DR, Sofferman SA, Wintrobe MM, Cartwright G.E. Factors influencing the duration of survival of patients with chronic lymphocytic leukaemia. *Am J Med* 1966;40:243-54.