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## Determinants of survival in Nigerians with Burkitt's Lymphoma

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### Summary

There is paucity of information on the factors influencing survival of patients with Burkitt's lymphoma (BL) in Nigeria. This work was undertaken to examine the roles of presenting clinical and laboratory features in the survival of a number of Nigerian patients with BL. Confirmed cases of BL diagnosed in the hospital between January 1986 and December 1999 were studied. Diagnosis of the tumour was based on fine needle aspiration cytology of easily accessible mass in a large majority of patients. Median survival was calculated for all the dead patients using Kaplan-Meier technique. SPSS 10 statistical software and EPI 6.04b were used for all statistical calculations. A total of 213 patients were recruited over the 13-year period; with ages ranging from 3-45 years (median = 9) at diagnosis. The male-female ratio was 1.8:1. At the time of analysis in December 2001, 166 (77.9%) of patients had defaulted, 44 were known to have died and 3 were still alive. Only 81 (38%) of the patients had adequate chemotherapy (4-6 cycles). Fifty one (23.9%) patients had an initial complete remission. The mean survival of the 44 patients that died was 10.5 weeks (95% CI = 3.9-17.1). It is concluded that survival in Burkitt's lymphoma was significantly better in patients who had adequate therapy, mean  $40.8 \pm 12.2$  (SE) weeks compared to those who had less than adequate cycles of chemotherapy, mean  $3.7 \pm 1.0$  (SE) weeks ( $p = 0.0000$ ). Inadequate therapy and high default rate were partly responsible for the poor survival results obtained in this study.

### Résumé

Il y a un manque d'information sur les facteurs influençant la survie des patients ayant le lymphome Burkitt au Nigéria. Ce projet examinait les symptômes cliniques et les caractéristiques des échantillons au laboratoire dans la survie d'un tel patient. Les cas de BL diagnostiqués et étudiés à l'hôpital de Janvier 1986- décembre 1999. le diagnostic des tumeurs était basé sur l'analyse de la masse cytologique chez la majorité des patients aspirée à l'aide d'une aiguille. La survie médiane était calculée pour les décès par la technique de Kaplan-Meier. Un total de 213 patients étaient recrutés pendant cette période, âgés de 3-45 ans (médiane=9). La proportion male/femelle était de 1.8:1. En décembre 2001, 166 patients abandonnaient la survie, 44 étaient décédés et 3 étaient vivants. 81 (38%) des patients avaient une chimiothérapie adéquate (4-6 cycles)

51(23.9%) des patients avaient une remission complète adéquate. La moyenne de suivi de 44 patients décédés était 10.5 semaines (95%CI=3.9-17.1) Il était conclu que la survie de ces cas était significativement mieux aux patients qui avaient une thérapie adéquate de  $40.8 \pm 12.2$  (SE) semaines comparé à ceux qui avaient une chimiothérapie moins adéquate de  $3.7 \pm 1.0$  (SE) semaines ( $P=0.0000$ ) La thérapie inadéquate et le taux de perte de vie étaient partiellement responsables des faibles résultats de suivi obtenus dans cette étude.

### Introduction

Burkitt's lymphoma (BL) is a highly aggressive non-Hodgkin's lymphoma (NHL) characterised by a diffuse proliferation of an undifferentiated malignant clone of B-lymphocytes. The neoplastic Burkitt's lymphoma cells are monomorphic, small non-cleaved cells that produce a diffuse pattern of tissue involvement [1]. This variant of lymphoma is the fastest growing neoplastic tumour in man, with a doubling time of about 24 hours and a growth fraction of nearly 100% [2] The tumour is the commonest childhood malignancy in Nigeria [3] and most other countries falling within the same climatic belt [4]. The peak age incidence varies from 3 to 14 years (median, 7 years), with a male to female ratio of 2:1 [5].

Epstein-Barr virus (EBV) and malaria are very important in the aetiopathogenesis of African Burkitt's lymphoma [4, 6], but play little role in sporadic (non-endemic) cases outside Africa [7]. Although endemic and sporadic Burkitt's lymphoma are very dissimilar aetiologically [4,6], the major cytogenetic aberration seen in this tumour, translocation of *c-myc* oncogene from chromosome 8 to the immunoglobulin (Ig) heavy-chain region on chromosome 14 (t(8;14), is seen in over 90% of cases; the less common variants involving translocations of the *c-myc* gene to the kappa or lambda light chain regions on chromosomes 2 (t(2;8)) or 22 (t(8;22)), respectively occur in the rest [6-8].

In endemic (African) Burkitt's lymphoma, the commonest sites of tumour growth are the face (jaw tumours), abdomen or both [5,9]. The third most frequent site is the central nervous system, where cranial nerve palsies and flaccid paraplegia, as well as malignant pleocytosis are notable abnormalities [5,9-10]. The abdomen is the principal site of disease in adult patients

and in the sporadic (non-endemic) disease, irrespective of age of the patient at diagnosis [11-12].

Long-term survival for patients with Burkitt's lymphoma is a major problem in Nigeria, with a majority of the patients dying within 12 months of diagnosis [9,13]. In East Africa, however, up to 50% of the patients were reportedly cured of the disease [14], with about 25% enjoying 5-year disease free survival [15]. The major factors influencing remission duration and survival in Burkitt's lymphoma are disease stage at diagnosis and quality of treatment. Others include patient surveillance, sanctuary effect of the CNS disease, bone marrow involvement, pattern of relapse and resistance to chemotherapy [13-16].

This study was carried out at the Obafemi Awolowo University Teaching Hospitals Complex (OAUTHC), Ile-Ife, Nigeria. Ile-Ife, which lies between latitude 7°N and 7° 35' N and longitudes 4° 20' E and 4° 45' E, is within the BL endemic zone of equatorial rain forest of South West Nigeria. There is paucity of data on prognostic indices and survival in patients with BL in this environment. The aim of this study therefore was to identify prognostic factors influencing survival in a population of patients managed for Burkitt's lymphoma in Ile-Ife, Nigeria.

#### Patients and methods

Cytologically and/or histologically confirmed cases of Burkitt's lymphoma managed between January 1986 and December 1999 were studied retrospectively; patients recruited in the previous 2 years before 1999 were followed prospectively until they died or were lost to follow up. The patients were jointly managed at the Haematology and Paediatric Departments of the Obafemi Awolowo University Teaching Hospitals Complex (O.A.U.T.H.C), Ile-Ife, Nigeria. The diagnosis of BL was based on fine needle aspiration of easily accessible tumour for cytological examination. Surgical biopsy was obtained for histological diagnosis in doubtful cases. Bone marrow aspiration and lumbar puncture were carried out as part of the staging procedure in 57 (26.8%) and 100% of patients, respectively. The following were documented in each patient at presentation: age, sex, domicile or state of origin, date of diagnosis, duration of symptoms and site(s) of tumour. Others include, stage of the disease at diagnosis (17), full haematological and biochemical parameters. The nature of chemotherapy given, cycles of chemotherapy given and dates of remission/relapse, dates of induction, dates of last follow-up and dates of death were recorded.

Data are presented as medians, means  $\pm$  standard deviations (SD) or standard errors (SE) of means. Chi-squared ( $\chi^2$ ) analyses were used for comparison of distribution. Two-sided probability (p) values of less than 0.05 were taken as significant. Living patients were censored on the date they last visited the hospital. Survival analysis was done for all the patients whose dates of diagnosis and dates of last follow up or deaths were known. Median survival was calculated for all the patients that

were known to have died with Kaplan-Meier technique. Log rank test was used for comparison of survival determinants within groups. Regression analysis was carried out between survival and some variables such as age at presentation, cycles of chemotherapy given, haematocrit and total white blood cell counts at diagnosis, amongst others. The last case was recruited on the 10<sup>th</sup> December 1999. Analysis was carried at the end of December 2001. SPSS 10 statistical software (SPSS INC; 1989-1999) and EPI6.04b (CDC, USA & WHO, Geneva, 1997) were used for all statistical calculations.

#### Results

Two hundred and thirteen cases of Burkitt's lymphoma were managed over the 13-year period, giving an annual incidence of 16.4 cases per year. The ages of the patients ranged from 3 to 45 (median = 9) years. There were 136 males (63.8%) and 77 (36.2%) females, with a male: female ratio of 1.8:1. One hundred and eighty four (86.4%) of the patients were children under age 15 years and 29 (13.6%) were adults aged 15 and above (Fig. 1).

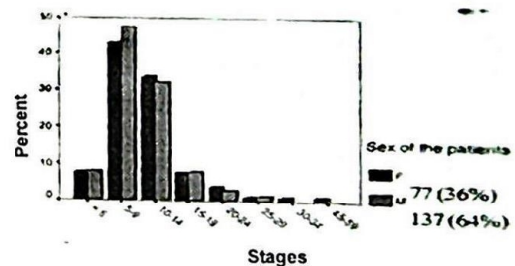


Fig. 1: Age-sex specific incidence rate of burkitt's lymphoma in Ile-Ife, Nigeria.

#### Clinical manifestations at presentation:

The median duration of symptoms before presentation was 4 weeks with a range of 1-28 weeks. One hundred and sixty (75.1%) patients presented in stages C and D (Table 1) (Fig. 2). Frequency of abdominal tumour was significantly higher in adults (65.5%) compared to children (40.2%),  $\chi^2 = 6.52$ ,  $p = 0.011$ . Stages A and B (jaw masses only) were significantly higher in children (38.6%) than they were in adults (13.8%),  $\chi^2 = 6.75$ ,  $p = 0.009$  (Table 2). Fifty nine (27.7%) patients had primary involvement of the central nervous system (CNS); the majority of whom (61%) had cranial nerve palsy (Table 3). Burkitt's cells were confirmed in the bone marrow of 11 (19.3%) of 57 patients (7 of 45 children and 4 of the 12 adults) who underwent the procedure as part of the staging work up; the difference was not statistically significant ( $\chi^2 = 1.92$ ,  $p = 0.219$ ). The

Table 1: Staging System for Burkitt's Lymphoma

Stages	Findings
A	Single extra abdominal tumour
AR	Intra abdominal tumour with > 90% surgically resected
B	Multiple extra abdominal tumour [excluding bone marrow (BM) and central nervous system (CNS)]
C	Unresectable abdominal tumour without BM and/or CNS disease
D	Tumour cells in the BM and/or CNS at diagnosis

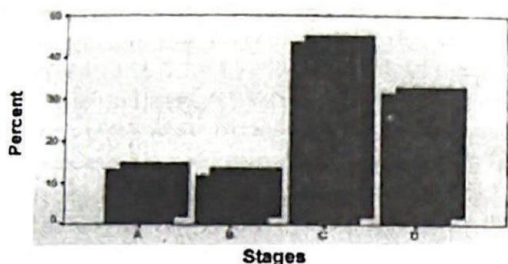


Fig. 2: Disease stage of the 213 Burkitt's lymphoma patients at diagnosis

Table 2: Cross tabulation of abdominal and jaw tumours in Nigerians with Burkitt's lymphoma against ages at diagnosis

Tumour Location	Age subgroup in years		Total (%) n (%)
	<15 (yrs) n (%)	≥ 15 (Years) n (%)	
Abdomen	74 (40.2)	19 (65.5)	93 (43.5)
Jaw	71 (38.6)	4 (13.8)	76 (35.5)
Abdomen+jaw	38 (20.7)	4 (13.8)	42 (19.6)
Others	1 (0.5)	2 (6.9)	3 (1.4)
Total	184 (100)	29 (100)	213 (100)

$\chi^2 = 16.0$ ,  $df = 3$ ,  $p = 0.001$

incidence of abdominal disease was significantly higher in females (53.2%) than it was in males (36.9%),  $\chi^2 = 5.46$ ,  $p = 0.019$ . Similarly, more males (30.4%) presented with jaw tumour compared to females (16.5%), the difference was also statistically significant ( $p = 0.033$ ). Some unusual sites of disease at presentation included the kidneys, thyroid, peripheral nodes, orbit, pelvic bone, tibia, skull, femur and humerus. Breast and ovarian tumours were seen in 1.3% and 13% of the female patients, respectively and testicular disease in 5.9% of males at diagnosis (Table 3).

Table 3: Sites of tumour at presentation in 213 Nigerians with Burkitt's lymphoma

Sites	No. of patients	% of cases
Abdominal mass	135	63.4
Jaw mass	95	44.6
Maxilla	57	60
Mandible	26	27.4
Maxilla + mandible	6	6.3
Maxilla + proptosis	4	4.2
Proptosis	2	2.1
Abdomen + jaw	42	19.7
Central nervous system	59	27.7
Cranial nerves (CRnn)	35	61
Paraplegia (Pplg)	12	20.3
CRnn + Pplg	11	18.6
Malignant pliocytosis	1	1.7
Breast tumour	1 (of 77)	1.3
Thyroid tumour	2	0.9
Testis	8 (of 136)	5.9
Peripheral nodes	8	3.8
Kidney	25	11.7
Ovary	12 (of 79)	15.2
Bone marrow	11 (57)	19.3
Pelvic bone	1	0.5
Skull	1	0.5
Spleen	1	0.5
Subcutaneous nodules	3	1.4
Long bones	3	1.4
Tibia	1	0.5
Tibia + humerus	1	0.5
Femur + tibia + humerus	1	0.5

The haematological parameters at presentation were not significantly deranged; the median haematocrit was 30% (range = 15–45%). The mean serum albumin (g/l) in all the patients was  $32.2 \pm 7.8$  (SD), range 4 to 49.

### Management:

Cyclical administration of combination chemotherapy was the only definitive treatment given to the patients. The chemotherapy comprised of cyclophosphamide, oncovin and methotrexate (or cytosine arabinoside, ara-C) with or without prednisolone (COM (P)). Prophylactic intrathecal methotrexate and/or ara-C were routinely administered. Eighty-one (38%) of the 213 patients had adequate treatment (i.e., 4–6 cycles), 93 (44.6%) had less than 4 cycles of chemotherapy, while 39 (17.8%) had no chemotherapy (Table 4). Administration of subsequent cycles of chemotherapy was delayed in some of the patients as a result of therapy-related myelosuppression and/or inability to purchase drugs as at when due.

### Outcome of treatment and analysis of prognostic factors:

#### Disease remission:

Fifty one (23.9%) of the 213 patients had an initial complete remission and 14 (6.6%) had partial remission, in which

greater than 50% tumour size reduction was recorded after therapy (18). There was no remission in 148 (69.5%) of the patients, including all the patients that had no therapy and a majority of those that had less than 4 cycles of chemotherapy (Table 4). Twenty (24.7%) of the adequately treated patients did not achieve any remission (Table 4). Of the 80 patients who had not less than 4 cycles of chemotherapy (Table 5), complete remission rates were higher for stages B (87.5%) and A (70.6%), compared to C (65.5%) and D (43.5%); however the differences were not statistically significant ( $p = 0.174$ ).

**Table 4:** Outcome of therapy in 213 patients with Burkitt's lymphoma, Ile-Ife, Nigeria.

No of cycles	No (%)	CE (%)	PR (%)	NR (%)
>4 cycles	81 (38%)	50 (61.7)	11 (13.6)	20 (24.70)
<4 cycles	93 (43.7%)	1 (1.1)	3 (3.2)	89 (95.7)
None	39 (17.8)	0	0	39 (100)
Total	213 (100)	51 (23.9)	14(6.6)	148 (69.5)

$\chi^2 = 125.8$ ,  $df = 4$   $p$ -value = 0.000

Keys: CR = complete remission  
PR = partial remission  
NR = no remission

**Table 5:** Remission types and stages at presentation of patients with Burkitt's lymphoma who had not less than 4 cycles of chemotherapy, Ile-Ife, Nigeria.

Remission Type	Disease stage at diagnosis				Total
	A %	B %	C %	D %	
CR	12 (70.6)	7 (87.5)	21 (65.6)	10(43.5)	50
PR	3 (17.6)	-	2 (6.3)	5(21.7)	10
NR	2 (11.8)	1 (12.5)		8(34.8)	20
Total	17	8	32	23	80

$\chi^2 = 8.987$ ,  $df = 6$ ,  $p$ -value = 0.174

Keys: CR = complete remission  
PR = partial remission  
NR = no remission

### Default rate

At the time of analysis, 166 (77.9%) of the 213 patients were lost to follow-up, 44 (20.7%) were known to have died and only 3 (1.4%) were still alive. The defaulters include all of the 14 partial remitters and 37 (72.4%) of the complete remitters (Table 4). Fourteen (27.5%) of the 51 patients that had CR came back in relapse after a period of between 2.1 and 224.3 weeks (median = 11). Three of the relapsed patients later died in the hospital. The median duration of follow-up of all the 166 patients who voluntarily withdrew from hospital care was 2.3 months; 135 (81.3%) had defaulted before 6 months and only 2 (1.2%) were seen for up to 60 months. The 3 confirmed living patients have been followed up for a median period of 69.2 months (range = 51.2-164.7); the longest survivor of the patients was a

nursing sister with a stage C disease confirmed at age 45 years (19).

### Survival estimates

The overall mean ( $\pm$  SE) survival calculated for the 44 (20.7%) patients known to have died was  $10.5 \pm 3.4$  weeks (95% CI = 3.9-17.1). Forty one (93.1%) of the dead patients presented in stages C and D; the other 3 had stage B disease. Only two (4.5%) patients survived beyond 12 months. Mean survival in the 9 patients that had adequate number of chemotherapy was  $40.8 \pm 12.8$  (CI =  $16.9 \pm 64.7$ ) weeks compared to  $2.7 \pm 0.7$  (CI =  $1.4 \pm 4.1$ ) weeks in the 35 patients that had less than 4 cycles of chemotherapy; the difference was statistically significant (log rank = 23.4,  $p = 0.000$ ).

Survival was slightly better in adults, mean  $23.2 \pm 11.9$  (SE) weeks than it was in children, mean  $6.3 \pm 1.9$  (SE) the difference was not statistically significant (log rank = 3.14;  $p$ -value = 0.076). Survival was slightly better in females, mean 17.4 weeks (95% CI = 1.2-33.6) than it was in males, mean 6.1 (95% CI = 3.0-9.2) weeks, but the difference was not statistically significant (log rank = 0.96,  $p$ -value = 0.323). Patients who had corticosteroid-based therapy survived longer with a mean of  $20.2 \pm 11.1$  (SE) weeks compared to the  $10.5 \pm 2.8$  (SE) weeks in those who had no corticosteroid, the difference was not statistically significant, log rank = 0.07,  $p = 0.793$ . Survival was also similar between stages B and D patients (means of 6.7 and 5.2, respectively; log rank of 0.02 and a  $p$ -value of 0.894) and stages C and D individuals, with means of 14.7 and 5.21 weeks, respectively, log rank of 0.75,  $p$ -value of 0.387.

Multiple regression analyses also confirmed the cycles of chemotherapy given to be the most positive prognostic factor in BL, with a  $\beta$ -coefficient of 0.335 ( $p = 0.01$ ). Urea, creatinine and serum potassium levels all showed negative regression coefficients that were not statistically significant. Haematocrit, platelet counts, total white cell count, absolute neutrophil and lymphocyte values at presentation did not appear to have any prognostic significance.

### Discussion

The predominance of younger age incidence of disease onset (median age of 9 years), jaw manifestations in the younger patients, dominance of abdominal disease in the older age group and higher incidence in males (M: F ratio of 1.8:1) are similar to previous publications from different populations [11-12], particularly in Africa [5-8].

Twenty (24.7%) of the adequately treated patients did not achieve any remission (Table 4), probably because of long delay in-between therapy, with consequent induction of chemotherapy resistant clone of cells. Although rather lower complete remission rates were obtained for stages C and D, compared to stages A and B (Table 5), the differences were not statistically significant ( $p = 0.174$ ). The very poor outcome of treatment obtained

in this study as compared to reports from East Africa [5, 14] and USA [15] was due largely to inadequate treatment (Table 4). Regression analysis confirmed the cycles of chemotherapy given to be the most important positive prognostic factor in this study ( $\hat{\alpha}$ -value = 0.537,  $P = 0.001$ ). The findings are consistent with previous reports [13-15]. As many as 132 (61.9%) of the patients had less than adequate cycles of chemotherapy, nearly a third of these had no single dose of chemotherapy (Table 4)! It is therefore not surprising to note that only 51 (23.9%) of the patients achieved complete remission, which itself is related to cycles of chemotherapy administered. The median remission duration of 6.7 months was rather poor.

The overall mean survival of 10.50 weeks obtained for the 44 confirmed dead patients is abysmally low. It is also disturbing that the mean survival among 9 of the dead patients was only 40.8 weeks, in spite of adequate therapy. The reasons for this might be due to failure to give drugs as at when due to financial constraints and/or therapy-related myelosuppression, both of which enhance development of resistant clones. We can not completely rule out the possibility of fake cytotoxic drugs and/or 'sterile' drugs due to improper storage as the causes of poor outcome of therapy among the adequately treated patients (Table 4). Only two (4.5%) patients survived beyond 12 months. It appears adult patients survived longer than the younger patients, the difference was not statistically different ( $P = 0.076$ ). The overall 5-year survival rate for all the 213 patients was only 1.9%. This is far lower than the 25% 5-year disease free survival recorded by Olweny, *et al* [5]. Although very poor survival is characteristic of this disease in Nigeria [9, 13], the current report is most disappointing in this era of modern chemotherapy.

This study was undertaken during the period of the IMF/World Bank Structural Adjustment Programme (SAP), which was introduced to Nigeria about 1986. The severe economic effects of SAP, especially on the poor (the majority of Burkitt's sufferers) continue to adversely affect social services, such as health care and education in Nigeria and most other African countries with similar experience [16, 20]. This explains the very high default rate of 77.9% among the patients and the inability of a majority to pay for treatment [20-21].

### Conclusion

Declining Health facilities consequent on the national economic adversity are strong limiting factors to effective cancer management in Nigeria. The study also shows that survival of patients with the lymphoma is adversely affected by the quality of treatment offered and availability of chemotherapeutic agents. Since Burkitt's lymphoma is a potentially curable cancer, we strongly recommend that heavily subsidised cytotoxic drugs should be readily available in cancer treatment centres across the country. Efforts should also be made to limit default rate among

patients through introduction of home visitation to confirm the status of defaulting patients. We also believe that the disease can be effectively controlled through provision of funds for research into the aetiology and management of the tumour.

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