

LONG-TERM EXPERIENCE WITH BURKITT'S LYMPHOMA IN UGANDA

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The cumulative results and long-term follow-up of all patients with Burkitt's lymphoma treated at the Uganda cancer Institute Kampala are reported. The annual admission rate is 29. The tumor patients commonly present with jaw swelling (72%), abdominal swelling (56%) and central nervous system involvement (30%). Complete response rate is achieved in a high proportion of patients (81%). About 50% of these relapse, equal numbers relapsing before and after 3 months. The most important factor influencing remission duration and survival is disease stage. Other important factors are treatment protocols and, to a lesser extent, the type of relapse. Central nervous system relapse does not necessarily augur poor prognosis as second remissions and long-term survival can be achieved with appropriate therapy. Presently 25% of all treated patients have survived free of disease well beyond 5 years.

Burkitt's lymphoma (BL) is a malignant lymphoma composed of uniformly undifferentiated lymphoid cells with characteristic histology and cytology (Burkitt, 1959; Berard *et al.*, 1969) and is the commonest malignant tumor affecting children in tropical Africa. Various treatment protocols have been conducted at the Uganda Cancer Institute (UCI) during the past 10 years. We now report the cumulative results and long-term follow-up of all patients treated according to these protocols.

MATERIAL AND METHODS

All patients with a histologic and/or cytologic diagnosis of BL were admitted to the Lymphoma Treatment Centre (LTC) from August 1967 to July 1977. Clinical details were obtained from the case records kept at the UCI and, on the basis of these data, patients were re-staged according to the staging criteria devised by Ziegler and Magrath (1974) (Table I). The five chemotherapy trials used over the 10 years, code names and chronological order are detailed in Table II (Ziegler *et al.*, 1970, 1972). Magrath and Ziegler 1976; (Olweny *et al.*, 1976, 1977). Every effort was made to trace defaulting patients. Those found still alive were re-admitted so that their remission status could be ascertained. For those reported to have died, the date and mode of death were sought.

Pretreatment evaluation

The pre-treatment patient evaluation in every case included: complete blood count; serum urea, uric acid, electrolytes, bilirubin, alkaline phosphatase and transaminases; bone-marrow aspirate, urinalysis, stool examination for occult blood, ova and cysts; intravenous pyelogram and jaw and chest roentgenograms. Cerebrospinal fluid examination

for malignant cells and protein was performed initially as part of the staging work-up and subsequently every 2 weeks up to 6 months and thereafter monthly up to 1 year.

Follow-up

Follow-up visits were made possible in most cases by the issue of bus tickets or taxi fares. Patients were requested to return every 2 weeks for 6 months, then monthly for another 6 months. After 1 year of follow-up, patients were seen every 3 months up to 3 years, then every 6 months up to 5 years, and thereafter yearly provided the patient remained in clinical remission. Relapsing patients (systemic and/or central nervous system) were started on 2-weekly visits as if they were newly admitted. Defaulting patients were sought by medical assistants at their homes.

RESULTS

During the 10 years, 291 patients were admitted with confirmed diagnosis of BL. There were 190 males and 101 females giving a male:female ratio of 1.9:1.

Clinical features and staging

The commonest presenting feature was jaw swelling, observed in 72% of patients. The second commonest presentation was with abdominal swelling, seen in 56% of cases. Central nervous system (CNS) involvement was the third commonest presenting feature, observed in 30% of all patients. The peak age at admission is 5 years (range 2-20 years). No patient was seen below the age of 1 year, and only one patient was less than 2 years old on admission. Five percent were 3 years old when seen. There was then a sudden increase to a peak at 5 years. A sudden drop was observed after 14 years and only 6% were 15 years or over (Fig. 1).

Two hundred and eighty patients had sufficient data for accurate staging, shown in Table III. Over 60% were either stage C or stage D on admission. Eleven patients were excluded from further analysis either because their original case records could not be traced (5) or because their treatment flow-sheets had been inadvertently destroyed (3) or because they had been treated elsewhere and details of pre-treatment status were not given in the referral letter (3).

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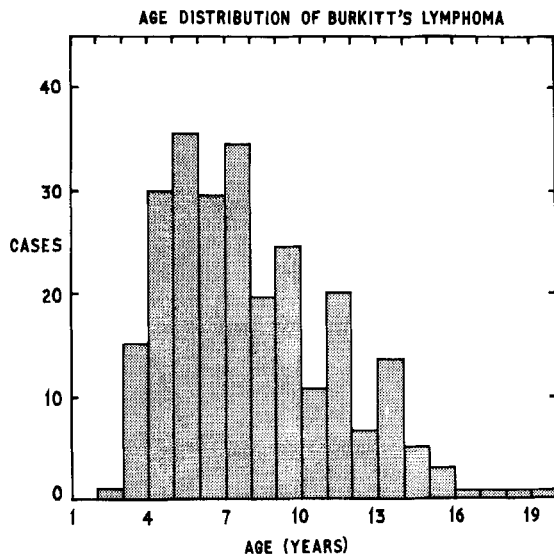


FIGURE 1 — Age distribution of Burkitt's lymphoma.

TABLE I
STAGING SCHEME FOR BURKITT'S LYMPHOMA

Stage	Tumor site
A	Solitary extra-abdominal site
B	Multiple extra-abdominal sites
C	Intra-abdominal tumor with or without facial tumor
D	Intra-abdominal tumor (Stage C) with sites of tumor other than facial
AR	Resected intra-abdominal tumor

Treatment response

Of the 280 patients with adequate staging and treatment data available, 33 died within 4 weeks of admission (early deaths); The mean survival for the 33 early deaths was 7 days (range 1 - 28 days). The causes of death in most cases were fluid and electrolyte imbalance and renal failure following rapid tumor lysis. Sepsis, marrow failure and post-opera-

TABLE II
CLINICAL TRIAL OF BURKITT'S LYMPHOMA LTC 1967-1977

Trial and reference	Stage	Drug ²	Dose	Route ³	Schedule	Duration of trial
I (Ziegler <i>et al.</i> , 1970)	All	CTX vs CTX	40 mg/kg 40 mg/kg	i.v. i.v.	Single dose 6 doses at 2-3-week intervals	1967-1969
II (Ziegler <i>et al.</i> , 1970; Ziegler <i>et al.</i> , 1972)	I ¹ and II ¹ III ¹ and IV ¹	CTX CTX vs Trike (a)CTX (b)VCR + (c)MTX (d)Ara-C	40 mg/kg 40 mg/kg 40 mg/kg 1.4 mg/m ² 15 mg/m ² 250 mg/m ²	i.v. i.v. i.v. i.v. p.o. i.v.	1-2 doses till remission 6 doses at 2-3-week intervals 2 cycles followed 2 weeks later by on day 1 of 4 schedule of oral MTX Days 1-4 followed 2 weeks later by daily for 3 days	1969-1971
III (Magrath and Ziegler, 1976)	All	CTX BCG vs No BCG	40 mg/kg	i.v. Scarification	1-2 doses till remission twice weekly × 6 then weekly up to 12 doses	1971-1973
IVA (Olweny <i>et al.</i> , 1976)	All	CTX vs COM (a)CTX (b)VCR (c)MTX	40 mg/kg 30 mg/kg 2 mg/m ² 15 mg/m ²	i.v. i.v. p.o.	2 doses at 2 weekly intervals repeated 12-14 days later day 1 day 1 days 1-3	1973-1975
IVB (Olweny <i>et al.</i> , 1977)	All in remission	CSIR vs No CSIR	20-24 Gy (total)	Cerebro-spinal	5 days weekly at 0.7-0.75 Gy per fraction	
V (On-going protocol)	All	COM + MTX COM + No IT MIX	As in IVA 15 mg	Above i.t.	Days 1 and 3 of COM	1975

¹ Old staging system. — ² CTX, Cyclophosphamide; VCR, Vincristine; MTX, Methotrexate; CSIR, Cerebrospinal irradiation; Ara-C, Cytosine arabinoside. — ³ i.v., intravenously; p.o., orally; i.t., intrathecally.

TABLE III
BURKITT'S LYMPHOMA CLINICAL STAGING

Stage	No.	Percentage
A	35	12.5
B	69	24.6
C	78	27.9
D	82	29.3
AR	16	5.7
Total	280	100

TABLE IV
TYPE OF RELAPSE AND STAGE

Stage	CNS ¹ only	Systemic only	CNS + systemic	Not recorded	Total
A	1	4	2	-	7
B	11	7	4	2	24
C	8	16	4	-	28
D	7	11	9	4	31
AR	4	5	2	-	11
Total	31	43	21	6	101

¹ Central nervous system.

tive complication accounted for a small fraction of early deaths. The majority of early deaths (88%) were patients in stages C or D and only 12% were in stage B. No stage A patient died early.

Of the remaining 247 surviving patients, 201 (81%) achieved complete responses, 19 (8%) had partial responses and 27(11%) failed to respond to initial therapy. Among the complete responders, 101 (50%) have so far relapsed. The actuarial analysis of remission durations by stage is shown in Figure 2. The long-term (9 years of follow-up) disease-free interval for stage A patients (80.8% with standard error (SE) 7.7% is significantly longer than that of either stage B (50.4%, with SE 7.3%) or stage C (45.1% SE 6.8%) ($Z = 2.871, p < 0.01$). Similarly, stage D patients have a significantly lower long-term disease-free state (22.7%, SE 6.3%) than either stage B or C patients ($Z = 2.881, p < 0.01$). There is no significant difference in the relapse-free intervals between stages B and C. Thirteen of the 16 stage AR patients survived beyond 1 month and of these 11 (85%) have relapsed. The median remission duration for the stage AR patients is 3 months (range 1 - 60 months).

Fifty-three of the 101 patients who relapsed did so within 3 months (early relapse), while the remaining 48 patients relapsed after 3 months (late relapse). There is no significant association between the type of relapse and disease stage (Table IV).

Three patients have relapsed well beyond 5 years of sustained remissions. The relapses occurred after 62, 96 and 102 months of remission, respectively. Two of the patients relapsed with systemic tumor only and the third with malignant pleocytosis and evidence of raised intracranial pressure.

Survival

One hundred and nine of the 280 (39%) are alive and disease-free while 155 (55%) are known to be dead. Sixteen (6%) are lost to follow-up and all attempts to trace them have been unsuccessful because they have crossed the national borders into neighboring Kenya, Rwanda, Sudan, Tanzania or Zaire. Most of these patients are probably still alive judging by remission status in excess of 1 year when last seen. The actuarial survival by stage is shown in Figure 3. Stage A patients have a significantly better long-term (10 years of follow-up) survival (86.9%

DESEASE-FREE STATE (REMISSION) OF BURKITT'S LYMPHOMA

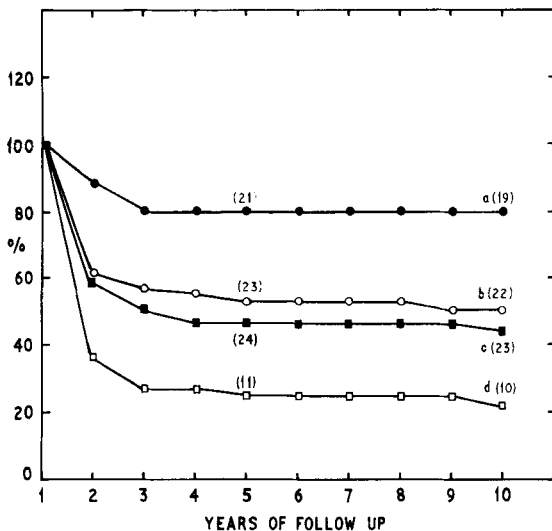


FIGURE 2 - Remission duration of Burkitt's lymphoma by stage. Stage AR not included because of small number.

SURVIVAL OF BURKITT'S LYMPHOMA PATIENTS

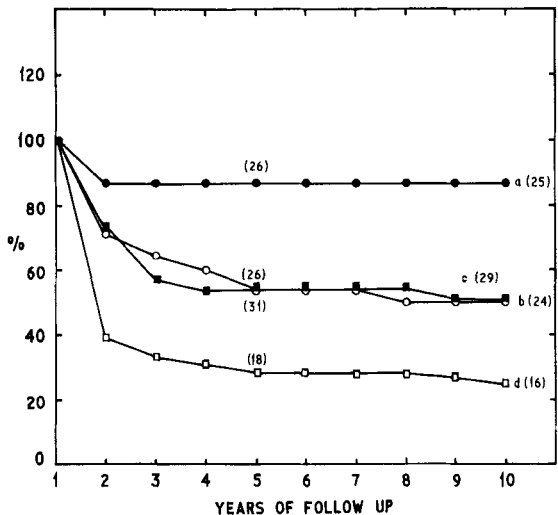


FIGURE 3 - Survival of Burkitt's lymphoma by stage. Stage AR excluded.

with SE 6.1%) than either stage B patients (50.3% with SE 6.8%) or stage C patients (50.4% with SE 6.5%) ($Z = 3.994$, $p < 0.01$). Stage D patients have a significantly poorer long-term survival (25.3% with SE 5.3%) than either stage B or C patients ($Z = 2.899$, $p < 0.01$). There is no significant difference in survival between stages B and C. The median survival of 16 Stage AR patients is 36 months (range 3-89). Seven of these (including 3 early deaths) have died while the remaining 9 (56%) are alive and disease-free.

Of the 109 patients who are alive, 69 (63%) have remained alive and disease-free for over 5 years. Ten of 53 (19%) patients who relapsed early are alive as compared to 19 of 48 (40%) of those relapsing late. There is an association between the time of relapse and survival $\chi^2 = 4.197$ ($0.02 < p < 0.05$). Patients relapsing with both CNS and systemic tumor have poorer survival (19%) than those with either CNS only (32%) or systemic tumor only (37%) (Table V). The difference, however, is not statistically significant ($\chi^2 = 1.7469$, $p > 0.05$).

Influence of treatment protocols upon remission duration and survival

Some of the treatment protocols used have an influence on the disease-free interval and survival. There is no significant difference in remission durations of 15 patients treated by single dose and 16 patients given multiple doses of cyclophosphamide after 893.5 and 658 man-months of follow-up respectively $\chi^2 = 2.8093$. The relapse-free interval for 20 patients treated with TRIKE is significantly better than that for 10 patients after multiple doses of cyclophosphamide after 902 and 186 man-months of follow-up respectively $\chi^2 = 4.401$, ($p < 0.05$). There is no significant difference in relapse-free interval between 24 patients given BCG maintenance and 18 controls $\chi^2 = 0.0449$. Similarly there is no significant difference in remission duration between 22 patients treated with 2 doses of cyclophosphamide \pm cerebrospinal irradiation (CSIR) and that for 30 patients receiving two doses of COM \pm CSIR $\chi^2 = 0.1794$.

The survival analysis (Table VI) reveals that a single dose of cyclophosphamide and 6 doses of cyclophosphamide are comparable after 1,235 and 1,204 man-months of follow-up respectively $\chi^2 = 0.0592$. Similarly, there is no significant difference between the survival of BCG-treated patients and controls after 879.5 and 711.5 man-months of follow-up respectively, $\chi^2 = 0.6927$. There is, however, a significantly better survival for patients treated with TRIKE than with six doses of cyclophosphamide after 1,212 and 266 man-months of follow-up respectively ($\chi^2 = 12.005$, $p < 0.001$). The patients treated with COM \pm CSIR also have a significantly better survival than a stage-matched group treated with two doses of cyclophosphamide \pm CSIR after 713 and 314 man-months of follow-up respectively ($\chi^2 = 9.466$ $p < 0.01$).

TABLE V
TYPE OF RELAPSE AND SURVIVAL

Clinical state ¹	CNS ² only	Systemic only	CNS + systemic	Not recorded	Total
AFD	10(32%)	16(37%)	4(19%)	0	30
Dead	18	26	17	6	67
LTFU	3	1	0	0	4
Total	31	43	21	6	101

¹ AFD, Alive and free of disease; LTFU, Lost to follow-up. - ² Central nervous system.

DISCUSSION

BL remains the commonest childhood malignancy seen in Uganda. During the last 10 years the annual admission rate was 29. The clinical presentation of the tumor remains similar to previous observations (Burkitt, 1959) with jaw tumor being commonest, abdominal involvement next in frequency and CNS disease being third commonest.

TABLE VI
TREATMENT PROTOCOLS AND SURVIVAL OF BL

Stage	Treatments	AFD ³	Dead	LTFU ⁴	Total
All	Cyclophosphamide single dose	9	6	0	15
vs	Cyclophosphamide 6 doses	9	6	1	16
III ¹ and IV ¹	Cyclophosphamide 6 doses	1	8	1	10
vs	TRIKE	14	6	0	20
All	BCG	13	10	1	24
vs	No BCG	10	6	2	18
All	Cyclophosphamide -2 doses \pm CSIR ²	4	17	1	22
vs	COM -2 doses \pm CSIR	15	13	2	30
All	COM \pm i.t. MTX	11	3	2	16
	Non-protocol patients	23	47	6	76
	Early deaths	-	33	-	33
	Total treated	109	155	16	280

¹ Old staging (Ziegler *et al.*, 1970). - ² CSIR, craniospinal irradiation; i.t., intrathecal; MTX, Methotrexate; COM, cyclophosphamide + Oncovin + Methotrexate, (Olweny *et al.*, 1976). - ³ Alive and free of disease. - ⁴ Lost to follow-up.

The complete response rate observed in this study is 81% while the partial response rate was 8%. Thus the overall response rate of 90% is in conformity with previous observations of high response rate following chemotherapy (Burkitt, 1959; Ziegler *et al.*, 1970; Olweny *et al.*, 1976). About 10% died within 1 week of starting treatment (early deaths); 90% of these were stages C and D and none was stage A. This, too, is in keeping with previous observations (Ziegler *et al.*, 1970, 1972). Thus patients with stages C or D are at risk when treatment is begun and every effort should be made to maintain adequate fluid and electrolyte balance, and peritoneal dialysis should be considered in those patients with extensive disease in the setting of azotemia and oliguria.

The main factor determining remission duration and survival is disease stage. This is not surprising as disease stage is based on a rough estimate of tumor burden. However, there is very little difference between stages B and C in terms of disease-free interval and survival. This may be because some patients with minimal abdominal disease may be understaged and regarded as stage B. Alternatively, multiple extra-abdominal tumor may well represent extensive or heavy tumor burden and should therefore be regarded as such until better discriminating factors are found. Attempts were made to find possible minor features that might better separate stages B and C, with little success. It might therefore be worthwhile combining stages B and C into one stage so that only four stages are used, namely A, B, C and AR (Table VII), stage B representing the previous stages B and C and stage C replacing stage D. It ought to be remembered, however, that the staging for some of the patients, using the Ziegler and Magrath system, was done retrospectively. It would be worthwhile testing prospectively the two "new" staging systems in order to determine which would better discriminate for remissions and survival. Of interest is the observation that the majority (70%) of stage AR patients are alive and disease-free. All these patients were in either stage C or stage D and would otherwise have done poorly had tumor reduction not been attempted. This is in conformity with the previous observation of the beneficial effect of surgical reduction of tumor bulk in the management of abdominal Burkitt's lymphoma (Magrath *et al.*, 1974).

The treatment protocols which seem to be related to long-term good results are TRIKE and COM. Multiple doses of cyclophosphamide give poor results; why this is so is not immediately clear, but this fact may be in keeping with the suggestion by Burkitt and others that host defences influence tumor regression and that intensive chemotherapy may suppress possible host immunity against the tumor (Burkitt, 1967; Davis and Burkitt, 1968). This may be true in the case of patients who receive six doses of cyclophosphamide, as four or five doses were usually given after the patient had achieved remission. It is not clear why two doses only of cyclophosphamide should give equally poor results. It might be worthwhile comparing TRIKE with COM to ascertain which of the two treatment protocols would give better results. COM, however, is a much simpler and shorter regimen to give than TRIKE.

Of the 201 patients who achieved complete response, 101 (50%) have so far relapsed. About equal numbers relapsed within 3 months and after 3 months, as observed previously by Ziegler and others (Ziegler *et al.*, 1972). The present study thus confirms earlier observations regarding the relationship between relapse pattern and survival. In addition, it reveals that survival is somewhat related to the type of relapse in that patients with either systemic or CNS relapse survive better than those who relapse with both CNS and systemic disease. In addition, relapse with CNS disease does not necessarily augur poor prognosis as about 30% of such patients achieve second long-term remissions after appropriate therapy, and some of the longest survivors had CNS disease at one time or another.

TABLE VII
PROPOSED NEW STAGING SYSTEM¹

Stage	Tumor site
A	Solitary extra-abdominal site
B	Multiple extra-abdominal sites
C	Intra-abdominal tumor with or without facial tumor
AR	Intra-abdominal tumor with sites of tumor other than facial Resected intra-abdominal tumor

¹ Modified from Ziegler and Magrath.

Twenty five percent of the patients so far treated have survived beyond 5 years. These may be regarded as "cured" although so far three patients have relapsed well after 5 years. The very late relapses underscore the need for continued surveillance even in those patients who are apparently "cured". The long-term survival of 25% is in keeping with previous observations (Clifford *et al.*, 1967; Morrow *et al.*, 1967; Ziegler *et al.*, 1979). It is, however, hoped that this will improve with time as 40 out of the 109 surviving patients have, for the most part, passed the danger zone of 28 weeks and can therefore be expected to have long-term survival.

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