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ABSTRACT

Background: **Effectiveness and toxicity of childhood cancer treatments have never been evaluated in Kenya since introduction of structured care in the early seventies.**
Objective: **To evaluate effectiveness and toxicity of two treatment protocols for Non-Hodgkin's lymphoma (NHL).**
Design: **Historical cohort study using medical records.**
Setting: **Kenyatta National Hospital, a tertiary care and medical teaching hospital.**
Subjects: **Children ≤ 15 years with diagnosis of non-Hodgkin's Lymphoma.**
Main outcome measures: **Primary outcomes were median survival, event free survival and toxicity.**
Results: **Out of 101 records, only 26 (25.7%) met inclusion criteria. Baseline characteristics were similar in the two treatment arms. Median survival was 0.75 months (95%CI=0.54-0.96) and 1.0 months (95% CI=0.29-1.71) for short and long arm groups. There was no difference in event free survival and haematological toxicity.**
Conclusion: **No clear difference in effectiveness and toxicity between the intensive-short and the less aggressive long course chemotherapy regimens was evident. Though lack of difference may be attributed to the small sample size, suboptimal supportive care for intensive treatment would increase risk of toxic deaths. As the short course protocol did not demonstrate obvious deterioration of median and event free survival, a strong case may be made for a randomised clinical trial within a context of improved supportive care.**

INTRODUCTION

Burkitt's lymphoma (BL) is a rapidly growing childhood tumour characterised by mature small non-cleaved B-cells and commonly presents as a jaw or abdominal swelling in tropical Africa (1, 2). In resource poor countries like Kenya, diagnosis is purely made on microscopy thus making it difficult to differentiate variants of BL and other non-Hodgkin's lymphoma accurately. About 40% of childhood cancer admissions at a national referral hospital paediatric facility are due to non- Hodgkin's lymphoma. Ninety per cent are clinically categorised as BL and a common protocol is used for treatment (3). Treatment of non-Hodgkin's lymphoma has evolved over the years from monotherapy to highly effective short intensive combination regimens. A standard structured childhood cancer treatment protocol was first introduced in Kenya in the mid seventies. It was last revised in the early eighties when the best practice world over was to treat using an acute lymphoblastic leukemia (ALL) - like regimen that stretched over a two year period. In keeping with local practice, modification of the short intensive dose LBM-89 protocol by Patte *et al* (4) was introduced in the year 2002 without assessment of its effectiveness and toxicity. There are no good quality clinical trials from developing countries to realistically inform local treatment of BL and non-Hodgkin's disease (5). A major limitation to the implementation of modern treatments in sub-Sahara Africa have been the enhancement of bone marrow toxicity and inability to provide necessary supportive care (6). This study was undertaken to review and compare effectiveness and toxicity of the short, intensive and the longer less intensive, standard ALL-like chemotherapy regimens. Study findings would assist clinicians to better understand the outcome of their care and hence inform treatment choice.

MATERIALS AND METHODS

The study was undertaken between January 2003 and June 2005 at the Kenyatta National Hospital (KNH), a national referral and medical teaching hospital in Kenya. Source of information was medical

records of in-patients. An approximately equal number of children with non-Hodgkin's lymphoma are admitted to a 30 bed children cancer ward and general paediatric, ear nose and throat and eye wards. Though cancer treatment is directed by the same team of clinicians, quality of nursing care and availability of medical supplies is better in the cancer ward. Unlike in the general paediatric wards where bed sharing is the norm, the latter does not admit beyond official capacity. Records for patients treated for non-Hodgkin's lymphoma were identified from the hospital medical records department which maintains a fairly up to date electronic data base by diagnosis using ICD 10 classification. Majority was deemed to correspond to C83 category of "diffuse non-Hodgkin's lymphoma". Coded data extraction forms were used to collect, among other, information on age, sex, nature of clinical presentation, diagnostic work up, cancer treatment, inpatient morbidity, remission status, recurrence and death. Records of all children below the age of 15 years admitted with either fine needle aspirate or histological diagnosis of BL or non-Hodgkin's lymphoma over the study period were eligible for inclusion. Those who died before completion of induction and ones on protocols other than the specified two were excluded. As routine screening for HIV was not practiced, no efforts were made to determine serological status of the patients.

Treatment toxicity was defined as (i) need for parenteral antibiotics, (ii) platelet transfusion, and (iii) packed blood cells, as surrogates for severe sepsis, severe thrombocytopenia and anaemia respectively. Requested products needed not be available or transfused for the incident to be included. As a policy, all children with two or more recordings of fever are commenced on parenteral antibiotics except for those with blood smear positive slides for malaria. Platelet transfusion is indicated for blood levels below $20x10^9$/L or overt bleeding at higher levels and packed cell transfusion for haemoglobin level below 9.5g/dl. Haemogram reports were also reviewed. Moderate to severe neutropenia was defined as neutrophil count below 750/mm^3. Frequency of toxic episodes was quantified from zero to three and above.

The two treatment protocols under examination were:

(i) *Standard protocol:* Induction - cyclophosphamide 600mg/M^2 weekly x 4 weeks, adriamycin 40mg/M^2 weekly, vincristine 1.5 mg/M^2 weekly x 4 and prednisone 40mg/M^2 daily for 4 weeks. Consolidation (2 courses 7-10 days apart) - adriamycin 50mg/M^2 in first course only, cyclophosphamide 1200mg/M^2 and cytosine arabinoside 100mg/M^2 daily x 4 days. Five doses of weekly intra-thecal methotrexate alternating with cytosine arabinoside given for central nervous system prophylaxis. Maintenance (monthly for 24 months) - oral prednisone 40mg/M^2 daily x 1 week, oral methotrexate 15 mg/M^2 weekly, monthly vincristine 1.5mg/M^2 and 75mg/M^2 oral 6-mercaptopurine daily. Intensification with addition of adriamycin and cyclophosphamide was provided thrice monthly.

(ii) *Short intensified protocol:* Induction - similar to above but adriamycin given in week 1 and 3 only. Dose of iv cyclophosphamide reduced to 500mg/M^2 weekly and IT cytosar weekly. Intensification - (i) adriamycin 50mg/M^2, iv cyclophosphamide 2gm/M^2, IT methotrexate. (ii) Adriamycin 50mg/M^2, vincristine 2mg/M^2, iv. Cytosine arabinoside 100mg/M^2 daily x 4 days and IT methotrexate. (iii) vincristine 2mg/M^2, Iv cytosine arabinoside 100mg/M^2 daily x 4 days, iv cyclophosphamide 1gm/M^2 and IT methotrexate. (iv) adriamycin 50mg/M^2, vincristine 2mg/M^2, iv cytosine arabinoside 100mg/M^2 daily x 4 days, and IT methotrexate. The four course cycle is repeated once to complete therapy.

Availability of chemotherapy was arbitrarily scored as good if 50% or more of prescribed drugs were administered.

Baseline demographic and clinical parameters were compared for the standard and short treatment course groups. Kaplan-Meier and Chi-square methods were used in analysis to determine median survival, event free survival (EFS) and rates of toxicity as the main outcomes. Institutional ethical clearance was obtained from the KNH Scientific and Ethics Committee and confidentiality of information guaranteed.

RESULTS

Out of 101 records retrieved, only 26 (25.7%) were considered suitable for further analysis. Reasons for exclusion included use of different protocol, coding error or age above 15 years. Another large. number (26.7%) died or absconded from hospital before completion of induction while 16.8% were diagnosed before the study date of January 2003. Sixteen (15.8%) records were reported as missing. Records were generally deficient in details on disease status during follow up period. Majority (77.8%) of those who died before completion of induction were in general wards. There were longer diagnostic and treatment delays in the general wards.

Table 1 shows baseline characteristics of the study cases. Follow up period ranged between one and 18 months with a median of seven months from time of diagnosis. In the short course regimen, 58.3% presented with jaw tumours compared to 35.7%

on the standard course treatment (p>0.05). Nine patients had jaw presentation (33.3%) and seven (28.6%) abdominal masses at diagnosis (p=0.22). Diagnosis was confirmed by FNA in 78% and by histology in 47.3% of the patients. There was no significant difference in baseline clinical and laboratory characteristics between the two groups. Abnormal lymphoid cells in the CSF at presentation occurred in half of the patients on both protocols but reconciliation with clinical features was not possible due to inadequacy of information. Rating of availability of drugs was considered good in 58.3% on the short course regimen and 57.1% in the standard arm (p=0.63).

Table 1
Baseline characteristics

Sex	
Male	65.4%
Female	34.6%
Follow-up	
Range	1-18 months
Median	7 months
Presentation *	
Jaw	46.2%
Abdomen	30.8%
Abnormal CSF	38.5%
FNA diagnosis	78.9%
Histology	47.3%
Radiotherapy	15%
Rx Regimen	
Short course (12)	46.2%
≥ 50% drugs	58.3%
Long course (14)	53.8%
≥ 50% drugs	57.1%
Incomplete induction	69.2%

*Site of presentation SC/LC p=0.22

Treatment toxicity profile of the two protocols is shown in Table 2. Over all, packed red blood cells transfusion was requested for 19.2%, platelet transfusion for 3.8% and intravenous antibiotic treatment for 53.8% of the patients. All those put on parenteral antibiotics had moderate to severe neutropenia. Frequency of antibiotic prescription was similar in the two treatment groups (p= 0.91). There was no statistical difference in packed cells and platelet requirements between the groups.

Table 2
Treatment toxicity

	Short course	Long course
Packed cells request	33.3%	7.1%
Platelets request	8.3%	0
Iv antibiotics use	58.3%	50%
PMN<750	50%	57.1%

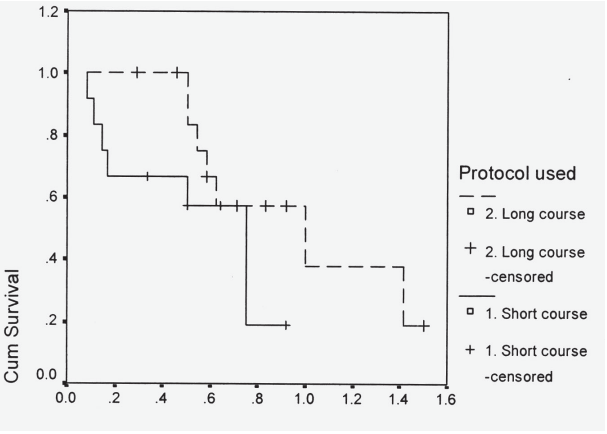
(p>0.05)

A similar proportion was alive and disease-free at the time of last hospital review in both groups; 58.3% in short treatment arm and 50% in standard arm (Table 3). Median survival was 0.75 year (95% CI=0.54-0.96) for short treatment and 1.00 year (0.29-1.71) for standard arm. There was no difference in Event Free Survival (probability of survival = 0.2) between the two groups (Figure 1).

Table 3
Main treatment outcome

	Short course		Long course		Total	
	No.	(%)	No.	(%)	No.	(%)
Alive disease free	7	58.3	7	50	14	53.8
Died or relapsed	5	41.7	7	50	12	46.2
Total	12	100	14	100	26	100

Figure 1
Survival functions



DISCUSSION

Non-Hodgkin's lymphoma is the most common childhood malignancy in Kenya, with Burkitt's lymphoma being the leading clinical sub-type.

Diagnosis is often made on basis of clinical presentation supported by either fine needle aspirate cytology or tissue microscopy. Since cyto-histochemistry, immunophenotype and cytogenetic laboratory support are not available, sub-classification is not possible. Patients are treated using one of the two protocols as determined by the primary clinician. The protocols have been in place at the Kenyatta National Hospital since 2002 when the more intensive but shorter treatment regimen, a modification of the LMB-89 protocol, was introduced (4). The older treatment protocol still in use today, with minor modifications was first introduced in the late seventies. An overlap of the two offered a unique opportunity to compare performance. Adequate amount of chemotherapy was received by 58.3% in the intensive treatment arm and 57.1% in the long treatment group. Even though many records did not indicate what the disease stage was at admission, presence of overt central nervous system disease (31.0%), abnormal cerebral spinal fluid (38.7%) and bone marrow disease (7.1%) confirmed that a large proportion presented in advanced disease. Meremikwu *et al* (7) in a review of childhood cancer hospital records in Nigeria observed that only 51.2% received what was defined as "adequate chemotherapy" while 20% received none at all. Similar to the situation in Kenya, they found availability of diagnostic services and drugs in public hospitals to be erratic and only affordable to the few with ability to buy.

In 1991, Patte *et al* (4) demonstrated that duration of treatment for B-cell lymphoma could be shortened without compromising outcome but also emphasized the need for good supportive care. Spreafico *et al* (8) later reported an 81% event free survival in children treated on a 45-day methotrexate, doxorubicin, cytosine arabinoside, cyclophosphamide and cis-platin intensified regimen. Etoposide and ifosfamide were added in treatment of those with more advanced disease. Their experience was in keeping with that of Kouroukis *et al* (9) who found haematological toxicity to be a common limitation to delivery of chemotherapy in a timely manner. Hesseling *et al* (10,11), in two separate studies, reported a modest increase in both effectiveness and toxicity from intensification of Burkitt's lymphoma treatment in Malawi, a setting with suboptimal quality of supportive care. Overall, outcomes improved despite increase in toxicity.

Preference for an older ALL-like chemotherapy protocol has continued in Kenya because of concerns that treatment intensification would result in unacceptable toxicity and mortality given gross inadequacy of supportive care in public hospitals. Local anecdotal experience of the author with a modified intensive protocol in private hospitals where supportive care is better demonstrated superior treatment outcomes. This prompted the introduction of a less aggressive treatment protocol at the KNH. Observation in this study that only 22.2% died before completion of induction treatment in the children cancer ward, which has better supportive care compared to 53.8% in the general ward, may be a reflection of importance of supportive care. The increase would not be attributable to tendency for more patients in the cancer ward to be put on the less intensive ALL-like protocol since the induction phases of the two study regimens are almost identical.

Granted that only twenty six records were suitable for evaluation, a larger sample size would be needed to determine if observed lack of statistical difference in frequency of moderate to severe neutropenia, use of parenteral antibiotics, packed red blood cells and platelet concentrates is indeed real. HIV status was not controlled for in the analysis and difference in prevalence between the groups could have affected the findings as HIV has been reported to be associated with an increase in toxicity and frequency of infections (12,13).

While an increase in toxicity would be expected with use of aggressive regimens, measures to contain toxicity should be instituted rather than discount its potential benefits. In their recent publication in a similar setting in Africa, Harif *et al* (14) observed a progressive increase in overall survival of B-cell lymphoma children on an LMB modified protocol over a three year period from 54% to 73% following improvements in supportive care. As would be expected, most early deaths in their study were therapy related. While Orem *et al* (13) only expressed the need for improvement of supportive care to help cope with more aggressive modern treatments in Africa, Meremikwu *et al* (7) went further to propose a regional initiative that would ensure chemotherapy and supportive care was available to majority of children with Burkitt's lymphoma in the African region.

CONCLUSION

Overall outcome of non-Hodgkin's lymphoma treatment at KNH remains poor and many patients die during early stages of treatment. There was no clear difference in effectiveness and toxicity between the modified short and the long course chemotherapy treatment regimens used for treatment of non-Hodgkin's lymphoma in Kenya. Rapid patient work up for early commencement of chemotherapy and improvement of supportive care may reduce mortality and loss to follow up during early treatment. A randomized controlled clinical trial is needed to determine if a short intensive regimen will provide better outcomes when supported by more efficient pre-treatment work up and improvement of supportive care.

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