Niger J Paediatr 2018; 45 (3):149 -152

ORIGINAL

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Treatment outcome and abandonment rates in a retrospective cohort of children with Burkitt lymphoma in Kano, Nigeria

DOI:http://dx.doi.org/10.4314/njp.v45i3.4

Accepted: 19th September 2018

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Abstract*: Background:* Burkitt lymphoma (BL) is highly chemotherapy-sensitive tumor and one of most common childhood cancers in Nigeria. Unlike in high income settings where cure rate is very high, the outcome of children with BL is still poor in low income countries like Nigeria. The main contributing factor to disparity in survival rate is treatment abandonment (TA). This study aimed to determine treatment outcomes and TA rates in a retrospective cohort of Nigerian children admitted with BL.
Methodology: We conducted retrospective charts review of all children (<13 years) with BL admitted at paediatric oncology unit of AKTH between January1st, 2014 and December 31st, 2016. Data extracted from patients' medical chart records included age, gender, duration of symptoms, clinical stage of tumor, and treatment outcome.
Results: 63 children with diagnosis of BL were admitted during the study time period, of which 56 (88.9%) medical records were retrieved and included in the final analysis. The median age was 8 years (range 3 – 18 years), with a male: female ratio of 1.6:1. Only eight patients completed therapy without relapse (14.3%). Of those who did not complete planned therapy, 7(14.6) died prior to the completion of therapy, leaving 41 (85.4%) who met criteria for TA.
Conclusion: Treatment completion and overall survival rates are poor among children with BL, due to in part high treatment abandonment rate. Leaving outside the treatment is a significant predictor of TA. Local oncology services might need to be decentralized in our environment to substantially reduced abandonment to improve overall survival.

Key words: Burkitt lymphoma, Treatment outcome, Treatment abandonment, Low income setting

Introduction

Burkitt lymphoma (BL) is an aggressive childhood B-cell tumor occurring mainly in Sub-Saharan Africa where its incidence ranges between 0.09 – 7.5 per 100,000.[1] In Nigeria, it is one of the most common cause of admissions for childhood malignancies with hospital prevalence ranging between 18.3 and 65 percent of all paediatric cancer-related admissions.[2] Previous study from AKTH reported 29.8% prevalence of BL in a retrospective cohort of children admitted with malignancy[3]. Burkitt lymphoma is potentially curable disease, with cure rate exceeding 90% in high-income settings however, in low income countries where majority of affected children live, the cure rate is less than 35%.[4,5] Treatment abandonment (TA), defined as failure to initiate chemotherapy or any interruption of treatment which lasted for a period of 4 weeks[6]is a possible explanation for this disparity and is described as a significant contributor to treatment failure and overall cancer mortality in LICs.[4,7] Reasons for cancer-related TA would differ geographically depending on local prevailing factors in these LICs. As such, knowledge of these factors could help further understanding of cancer-related TA in these countries and potentially inform policy at reducing its burden. In Nigeria, very few studies have determined the burden of TA and its associated factors.[8] This study thus investigated the treatment outcome and treatment abandonment rate in a retrospective cohort of children admitted with BL at a tertiary referral health facility in Kano, north-western Nigeria.

Methodology

Study site

We conducted retrospective charts review of children (<13 years) with BL admitted at paediatric oncology unit of AKTH between January1st, 2014 and December 31st, 2016. Aminu Kano Teaching Hospital is a fee for service tertiary referral health facility located in Kano, the second largest metropolis in Nigeria. The hospital receives patients from Kano, neighboring states and from across the border (Niger republic).

Data collection

Ethical approval for the study was obtained from the ethics committee of AKTH. Data extracted data from patients' medical record included patients' age, gender, date of admission, Address (whether resident within Kano metropolitan area or its environ or from neighboring states), time to onset of 1st symptom, number of cycles of chemotherapy completed, last visit date, , and clinical stage of tumour at presentation using modified Ziegler staging,[9] and treatment outcome (completed treatment, refused treatment/abandonment, did not return for treatment; or death during therapy from any cause). For the treatment, we adapted the practical recommendations for the management of children with endemic BL in a resource limited setting,[5]using combination of cyclophosphamide, vincristine and intra-the cal methotrexate

Statistical analysis

Basic descriptive statistics were performed on retrieved data using frequency and percentages. We used chi-square and t-tests for univariate analysis comparing between the two groups: Those who did not abandon therapy and those who abandoned therapy. Those who died from any cause during treatment were included. Statistical significance was set at 5% for this comparison.

Results

Two hundred and twenty eight (228) children with malignancies were admitted over the study period, of which 63 (27.6%) were BL. Of the 63 BL cases, clinical records were recovered for 56 (88.9%) children, and these were included in the final analysis.

Patients' Characteristics

Median age (IQR) of the study population was 8.0 years (4.0) and about two-thirds of the study population were male with M: F ratio of 1.9:1. Majority of the patients presented with jaw swellings (39.6%) and about a fourth of the cohort presented with advanced disease (Burkitt stage D). All patients were HIV sero-negative, and all had diagnoses confirmed by histo-pathology.(Table 1)

Table 1: Socio-demographic and Clinical characteristics of the study population (n=56)

Variable	Frequency (%)
Socio-demographic	
Median age in years (IQR)	8.0 (4.0)
Gender	
Male	37 (66.1)
Female	19 (33.9)
Clinical Characteristics	
Tumour site	
Jaw	21 (37.5)
Abdomen	18 (32.1)
Jaw + Abdomen	14 (25.0)
Ocular	3 (5.4)
Histologic diagnostic method	
FNAC	52 (92.9)
Tissue biopsy	4 (7.1)
*Tumour clinical staging**	
A	9 (16.1)
AR	1 (1.8)
B	6 (10.7)
C	27 (48.2)
D	13 (23.2)

* Zeigler and Magrat[9] staging

Table 2: Comparison of potential risk factors between treatment abandonment group and those who did not abandon treatment

Variable	Abandoned treatment group (%) n=41	Did not Abandon treatment group& (%) n=15	P-value	Total (%) n=56
History of use of traditional medication				
Yes	11 (26.8)	3 (20.0)	0.74[a]	14(22.9)
= No	30 (73.2)	12 (80.0)		42(77.1)
**Cancer Stage*				
Advanced	8(19.5)	5 (33.3)	0.28[b]	13(23.2)
Not Advanced	33(80.5)	10 (66.7)		43(76.8)
Place of residence				
Within Kano	13(31.7)	9 (60.0)	0.055[b]	22(39.3)
Outside Kano	28 (68.3)	6 (40.0)		34(60.7)
Median time from first onset of symptoms to presentation at treatment centre in weeks (IQR)	8(16.0)	8(12.0)	0.79[c]	8(12.0)
Median in-patient time to final diagnosis in days (IQR)	13.0 (3.0)	11.0 (3.0)	0.63[c]	13.0 (8.5)
Number of previous health encounters before presenting at treatment centre n=54[+]	2 (1)	3 (1)	0.35[c]	2 (1)

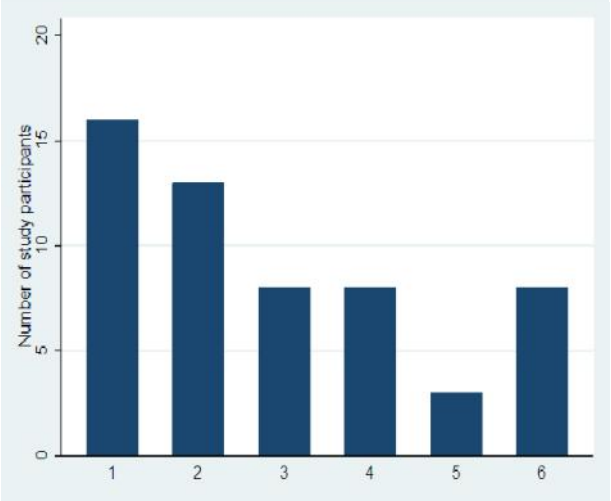
*-Advanced: stage C and D; not advanced: stage A, B, and AR, [+]-Two missing variables, IQR– interquartile range, a-Fischer's exact test b- Mann-Whitney U test c- Chi-square test. &- combines those who completed therapy and those who died from any cause during therapy

Treatment outcome

Of the 56 patients included in our analysis, only eight patients completed therapy without relapse (14.3%). Of

those who did not complete planned therapy, 7(12.5%) died prior to the completion of therapy, while 41 (73.2%) met criteria for treatment abandonment. Majority (51.8%) of patients had discontinued chemotherapy by the second cycle. (Figure 1) Median time for stopping therapy was 16.5 weeks. Lower parental income and longer distance from the treatment center were significantly associated with higher rate of treatment abandonment.

Fig 1: Bar chart showing number of chemotherapy cycles completed



Number of chemotherapy cycles

Discussion

Our study investigated treatment outcome and abandonment rates in a retrospective cohort of children who were admitted at a referral tertiary health facility in North-Western Nigeria. We found treatment abandonment (TA) was high (73.2% of our cohort) with greater than half of children discontinuing therapy by the 2nd cycle of chemotherapy. Among the risk factors for TA investigated, living outside treatment area was the only significant predictor of TA.

Similar TA rates have been previously described in other regions in Nigeria and parts of Africa. In a study by Meremikwu *etal*[10] in South-Eastern Nigeria, two-thirds of children with Burkitt lymphoma discontinued cancer treatment. In Western Kenya, Njuguna *et al*[11] reported a 54% prevalence of treatment abandonment, while Slone et al[12] and Boer et al,[13] both in Zambia reported prevalence of 45.7% and 51% respectively. Our findings however contrast those of Kulkarni and Marwaha[14] who documented a TA prevalence of 18.1% and Bonilla *et al*[6] who documented 13% in Indian and El-Salvadorian children respectively. Differences in our study populations might explain why our findings differ from these two studies. While our study was conducted in children with Burkitt lymphoma, the Indian study was conducted among those with acute leukaemia. Both cancers are known to have varying natural histories. Burkitt lymphoma is a highly chemo-sensitive cancer that gives a picture of clinical cure even after a single chemotherapy cycle and misperception that further treatment is not needed once the tumor has receded, while leukaemia on the other hand tends to be aggressive requiring frequent hospital admissions and as such, patients might be less likely to abandon treatment. The El-Salvadorian study on the other hand was conducted in a health facility that provided free cancer treatments as opposed to our study where virtually all patients paid out of pocket for their treatments. Mostert *et al*[15] have shown patients who had financial help with cancer treatment were less likely to abandon their treatment. In high-income countries, for many patients, a portion of the medical expenses is paid by their health insurance plan. For individuals without health insurance or who need financial assistance to cover care costs, resources are available, including government sponsored programs and services supported by voluntary organizations.[16] On the other hand, in low resource countries, parents of children with malignancy have to pay out-of pocket for treatment and no health insurance and resources to help families through financial difficulties and the health infrastructure are ill-equipped to provide appropriate supportive care for the affected children. In most LMICs, cancer is often detected late very late, that even the most effective treatment will not result in long-term cure, and out-of-pocket spending is often wasted because it contributes nothing to improve health. Additionally, care may be coupled with prohibitive transportation costs and investments of time that include long turn-around time to access care.[16]

Our study also documented that roughly half of patients had abandoned treatment early in chemotherapy, as it has been reported in other studies.[10,17] This finding might be explained by the highly chemo-sensitive nature of BL which could give a false impression of cure to parents.
In our study, place of residence was the most significant predictor for TA in our cohort. Patients who lived outside the state where our facility is located where more likely to abandon treatment compared to those who lived near the treatment facility. We used this categorization as a proxy to investigate the influence of distance on TA among our cohort. Such findings of distance from treatment centers affecting cancer treatment completion have been shown in other previous studies in the developing world.[12,18] Other factors such as parental inability to pay for treatment and low parental education have been demonstrated to be associated with TA in other studies.[11,13] Due to the retrospective nature of our data and missing information regarding these variables we were unable to determine what influence this might have had in our cohort.

Our study is one of few studies that investigated treatment outcome and TA rates in Nigeria. We however recognize some limitations of our study. Due to the retrospective nature of the study we could not determine the cause of death of patients with BL or investigate outcomes for those who abandoned treatment. Future studies in this region might benefit from a prospective mix method design, where phone interviews are con-

ducted with parents of children who abandoned cancer treatment.

Conclusion

Our study found high rate of treatment abandonment as the major cause of treatment failure and overall poor outcome, and distance from our treatment site seems to be an explanation for this high rates. There is a clear need for decentralization of oncology services such that they are more assessable. In the interim however, systems might need to be developed to actively monitor and trace children who have defaulted from chemotherapy.

Similarly, there is need to improve treatment outcome through advocacy and education of local health workers, through collaborations between LMIC and HIC centers, capacity building, provision of cancer centers of excellence, and standards of care. Approaches need to be innovative, yet realistic, and the LMIC team must set priorities.

Conflict of interest: None
Funding: None

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