Childhood leukemia outcomes in a low-resource tertiary care setting

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Context Acute leukemia (AL) is the commonest hematological malignancy in childhood. The cause is largely multifactorial and unknown, with exogenous and endogenous factors interacting with genetic susceptibility. Its incidence is on the rise globally including developing countries like Nigeria. Although the prognosis in developed countries has improved, poor outcomes are still the norm in resource-poor areas.

Aims This review was undertaken to document the sociodemographic characteristics, management challenges, and outcomes of leukemia in an African tertiary care setting.

Settings and design The study was a retrospective review of patients managed for AL over a 30-month period.

Patients and methods This is a retrospective review of clinical case notes of children admitted with diagnosis of AL.

Results A total of 31 children had morphological diagnosis of AL; half of them had acute lymphoblastic leukemia, a third acute myeloid leukemia, and one-sixth bilineal leukemia, respectively. Most patients were from low socioeconomic status. All patients sought alternative or complimentary care, and source of health care expenditure was out of pocket. The mean duration of symptoms was 12.9±10.3, time to diagnosis in our hospital was 3.7±2.1 days, and duration of hospital stay was 36.7±43.4 days. The mean packed cell volume, white blood cell, and platelet counts were 14.2±5.3, 37.9±30.2×10^9/l, and 45.4±54.3×10^9/l, respectively. Only four patients attained remission of the 15 (48.4%) who received chemotherapy. The mortality was 11 (35.5%) cases, with eight cases being owing to hemorrhage from severe thrombocytopenia.

Conclusions The study shows delay in time from symptoms to presentation, time to diagnosis, and commencement of chemotherapy with associated poor outcomes. All patients sought alternative and/or complementary interventions before presentation.

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Introduction

Acute leukemia (AL) is the commonest hematological malignancy in childhood [1]. The cause is largely multifactorial and unknown, with exogenous and endogenous factors interacting with genetic susceptibility. Its incidence is on the rise globally, including in developing countries, presumably owing to improvement in socioeconomic status (SES) and control of communicable diseases, which hitherto had been the highest causes of morbidity and mortality [2,3]. The rising incidence of AL is also noticeable in developing countries such as Nigeria where solid tumors such as Burkitt lymphoma and retinoblastoma used to be commoner [4,5]. The risk of the disease is ~1 in 2000 for children aged 0–15 years [6]. The incidence in our setting is unknown, as most patients remain undiagnosed owing to reasons including but not limited to poor access to health facilities or inability to make a diagnosis at the facilities where they present to. Diagnostic delays abound owing to diverse reasons from patients, caregivers, and health care providers [7,8]. The diverse and nonspecific clinical features as well as similarity of features to other common childhood illnesses and infections in our environment makes early identification challenging [9,10].

Although genetic abnormalities have been associated with the development and prognosis of leukemia, certain environmental factors such as ionizing radiation, benzene chemicals, and pesticides have established roles in the risk of developing leukemia [11,12]. Parental, prenatal, and postnatal exposures to ionizing radiation, chemicals, and certain viral agents have variously been implicated as increasing the risk of developing leukemia [1,3,13,14].

With recent medical and technological advances, the prognosis for AL transformed from an incurable disease to one where 5-year event-free survival is achievable with cure rates of up to 80–95% for acute lymphoblastic leukemia (ALL) [11,14–16], and 3-year

overall survival of up to 80% for acute myeloid leukemia (AML) [17,18]. This, however, is not the situation for many resource-poor settings, where late presentations with advanced disease and diagnostic delays occur [7,8]. Moreover, management challenges arising from lack of adequate diagnostic skills and techniques, trial protocols for treatment, availability and quality of support for care, availability of genuine drugs, and financial difficulties, among others, abound [19,20].

This study was designed to retrospectively review the sociodemographic characteristics, management challenges, and outcomes of children with AL in a teaching hospital in Northwestern Nigeria.

Patients and methods

This was a hospital-based retrospective review of children aged 0–17 years admitted to a tertiary hospital in Northwestern Nigeria, with a clinical diagnosis of AL. Case notes of patients admitted over a 30-month period between January 2016 and June 2018 were manually retrieved. The search criteria were diagnoses of leukemia, lymphoma, or myeloproliferative disease. Search results were filtered according to availability of bone marrow biopsy results and a hematological diagnosis of AL.

Demographic data were collected, comprising age, sex, SES, in addition to source of health care financing, and nature of care received before presentation to tertiary care. The time elapsed from onset of symptoms to presentation to tertiary care was estimated, as well as the time from presentation to diagnosis of leukemia and from diagnosis to treatment and the total duration of hospital stay in our hospital.

Other information obtained included the morphological type of leukemia, investigations done, treatments offered to the patients, and the outcomes. For anonymity, patients' names were omitted from data entry. Data were coded and stored in a passworded file and shared only among research participants. Being a retrospective study, ethical permission to review clinical data, share the data among study participants, and publish the review was obtained from the Health Research Ethics Committee (HREC) numbered ABUTH/HREC/K25/2019, dated March 26, 2019. All procedures were carried out according to the Declaration of Helsinki guidelines, 2013. Data were entered into excel 2017 version for analysis. Data were presented in texts and tables, and averages were calculated as percentages and proportions. Student *t* test was used to determine the level of significance of the mean values at 0.5 significance level.

Results are presented in tables and figures as means, percentages, or proportions.

Results

A total of 46 children were admitted with a clinical diagnosis of AL during the 30-month period, of whom 31 had a morphological diagnosis. The remaining 15 had other diagnoses and were excluded from the analysis. Of the 31 patients, 14 were males and 17 were females, giving a male to female ratio of 0.8 : 1. The overall mean age was 6.7±3.4 years. The mean age for children with ALL was 6.2±3.3 years, whereas for AML was 7.9±3.6 years.

Three (9.6%) patients belonged to SES [21] class 3, 22 (71%) classes 4, and 5 (16.1%) class 5. None of the patients belonged to high SES class 1 or 2. All the children were referred, three (9.7%) each from private and primary health care settings, eight (25.8%) from general hospitals and the remaining 17 (54.8%) from specialist and other tertiary health care centers. All the patients had some traditional/alternative medications in form of herbal concoctions, spiritual water, and/or prayers. The source of health care expenditure was out of pocket for all the patients; five (16%) patients had additional national health insurance scheme enrollment, which took care of ~90% of noncancer treatment expenditure.

Table 1 shows the classification of the leukemia based on morphology. ALL accounted for 16 (51.6%), AML 11 (35.5%), and bilineal leukemia four (12.9%).

Table 2 shows the mean duration of symptoms before presentation to tertiary care, time from presentation to diagnosis and from diagnosis to treatment, and

Table 1 Morphological classification of acute leukemia

Morphology	*n* (%)
ALL	16 (51.6)
L1	5
L2	8
L3	3
AML	11 (35.5)
M1	2
M2	5
M4	3
M5	1
Bilinear	4 (12.9)
Total	31 (100)

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia.

Table 2 Mean duration of symptoms, time to diagnosis, time to treatment, and duration of hospital stay of patients with acute leukemia

Characteristic	Mean	Range
Duration of symptoms (weeks)	12.9±10.3	2–52
Time to diagnosis in our facility (days)	3.7±2.1	1–10
Time to treatment (days)	13.9±11	2–40
Duration of hospital stay (days)	36.7±43.4	5–196

duration of hospital stay. The median overall time lag from onset of symptoms to diagnosis was 13.4±10.5 weeks.

Table 3 shows the mean laboratory parameters. The mean packed cell volume was 14.2±5.3 l/l at presentation. The white blood cell count was 37.9 ±30.2×10^9/l at presentation with five (16.1%) patients having a count of more than 50×10^9/l. The mean platelet count was 45.4±54.3×10^9/l; four (12.9%) patients had a count above 100×10^9/l. The mean weight was 19.6 ±5.5 kg and mean height 119±18.36 cm.

Uptake of therapy and outcomes

Of the 31 patients, 23 (74.2%) accepted treatment with chemotherapy, whereas eight (25.8%) declined treatment altogether. Eventually, only 15/23 (65.3%) received chemotherapy, as 5/23 (21.7%) could not afford the treatment owing to financial constraints, whereas 3/23 (13%) died before chemotherapy was commenced. Four (17.4%) patients attained morphological remission after induction chemotherapy.

The outcomes for the 31 patients were as follows: 11 (35.5%) mortalities, four (12.9%) transferred care to other facilities, five (16.1%) discharged against medical advice, whereas 11 (35.5%) were discharged home on follow-up chemotherapy. Among the 11 discharges, nine were lost to follow-up with only two remaining on treatment.

The causes of death included bleeding in six (intracranial hemorrhage owing to severe thrombocytopenia in four, and other bleeds in two), overwhelming sepsis in three, and shock in two patients.

The adverse events encountered in the patients while on chemotherapy included pancytopenia in all the 15 cases that had chemotherapy in addition to other adverse events such as anorexia, vomiting and diarrhea, alopecia, mucositis, and hypertension. The associated comorbidities encountered were malaria in eight patients, sickle cell anemia in two, and otitis media and hepatitis C virus infection in one case each.

Table 3 Means of laboratory parameters of children with acute leukemia

Parameters	Mean value	Range
PCV (l/l)	14.2±5.3	6–22.4
WBC (×10^9/l)	37.9±30.2	2.6–137.6
Platelets (×10^9/l)	45.4±54.3	1.8–150
Reticulocyte count (%)	1.9±2.9	0.1–6.4
Creatinine (μmol/l)	90.7±42.9	47–204
Uric acid (μmol/l)	243±130.8	80–403
Calcium (mmol/l)	2.26±0.19	1.85–2.55
Phosphate (mmol/l)	1.31±0.29	0.69–1.69

PCV, packed cell volume; WBC, white blood cell.

Discussion

The sociodemographic presentations and outcomes of AL are hereby presented showing the challenges of management and associated poor outcomes. The 31 cases recorded in this review are higher than previously recorded from this center, where 53 cases of AL were documented over a period of 8 years [4]. In contrast to the review by Ahmad and colleagues and other literature globally, the incidence of ALL in this study is 51.6%, and bilineal type constituted up to 12.9% of the cases. Perhaps cytogenetic and immunohistochemical analysis would have shed more light on the genetic constitutions of these patients, thereby contributing to selection of treatment strategies and improving the outcomes. Overall, 83.9% of our cases belonged to low SES (classes 4 and 5). Although there are long-held beliefs of higher incidence of AL in children from high SES, a systematic review by Adam *et al.* [22] showed no clear evidence of SES with risk of AL. Poole *et al.* [23] posited that connections of SES to childhood leukemia are likely to vary in time and place because of different socioeconomic measures such as knowledge and occupation, and individual-level and ecological level measures represent different risk factors depending on time and place.

The source of health care financing is crucial to the success of treating cancer which needs coordinated multidisciplinary approach. All our patients were on out-of-pocket spending except a few that utilized the national health insurance scheme for ancillary investigations and treatment. However, the scheme is very limited in scope of what facilities are available to patients and certainly do not cover for most of the investigations and the chemotherapy drugs. The effect of the program on our patients was therefore quite negligible. Cancer care is resource intensive in terms of manpower, investigation facilities, hematological support such as blood and blood products, antimicrobial agents, and the like. Out-of-pocket expenditure pushes the patients into more financial

distress, inability to make objective choice, and utilization of treatment options with resultant poor outcomes.The lag time is defined as interval between first symptom and diagnosis, comprising patient delay and physician delay. In this study, the time delay to diagnosis was a mixture of patient and physician factors. All our patients were referred to our facility from other hospitals. Most had received some treatments in form of blood transfusion and antimicrobial agents. These could be the reasons for the long duration of symptoms before presentation to tertiary care. High index of suspicion is crucial to making an early diagnosis especially in our setting where anemia may be owing to other causes such as malaria, malnutrition, and sickle cell disease. Patronage of alternative/complementary medicines could have also contributed to delay in seeking care and possible toxicity. In a paper by Ezeome and Anarado [24] in Enugu, the use of complementary medicine was very common among patients with cancer. The time lag to diagnosis and treatment was also long owing to multiple factors. Most patients came in very sick with sepsis, in anemic cardiac failure, and bleeding owing to thrombocytopenia. They therefore needed immediate resuscitation which gulped down the meager finances they came in with. The poor financial resource of the patients necessitates prioritizing clinical procedures and management strategies. The lack of a multidisciplinary team and compartmentalization of the various specialties necessary to arrive at a diagnosis and manage the patient also contributed to delay in making a diagnosis and starting treatment.

All the patients presented with severe anemia requiring blood transfusion at presentation and subsequently. Likewise, the need for platelet infusion was universal as only four of the patients had platelet count more than 100 000×10^9 at presentation, but owing to nonavailability, none of our patients had platelets transfusions and two patients were transferred for this reason. It is hence not surprising that 60% of the mortalities were owing to hemorrhage. Although a few patients had high creatinine and uric acid levels, the mean values were within normal and none of the patients had acute tumor lysis syndrome before or during the induction of therapy.

Although 74.2% of the patients accepted to have chemotherapy when offered, up to a quarter of them did not get to start induction therapy largely owing to financial inability to procure the drugs. Some of the patients, however, were not stable enough to start before their demise. High cost of the chemotherapy drugs and lack of availability of some like L-asparaginase and intrathecal methotrexate were major bottlenecks encountered. Uncertainty about the genuineness and effectivity of the drugs could have contributed to the low success of remission. The high mortality recorded was not surprising owing to the challenges enumerated above among others.

Conclusion

Poor outcomes of childhood leukemia have been highlighted from delayed diagnosis, as a result of caregiver and provider-related challenges, which included financial difficulties, lack of focused multidisciplinary approach to management, and nonavailability of desired standard facilities for diagnosis, support, and treatment. Twinning programs can go a long way to support the expertise of health care providers and put in place standard of care practices.

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Conflicts of interest

There are no conflicts of interest.

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