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OUTCOME OF CHILDHOOD ACUTE LYMPHOBLASTIC LEUKAEMIA IN A PAEDIATRIC ONCOLOGY UNIT IN GHANA

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Abstract

Background

Despite high cure rates for childhood acute lymphoblastic leukaemia (ALL) in developed countries, this success is not mirrored in resource-poor countries where most children with cancers live. The study objective was to determine the clinical presentation and treatment outcomes of ALL in children admitted to the paediatric oncology unit of Korle Bu Teaching Hospital, Accra, Ghana.

Methods

Hospital records of all children aged <13 years, diagnosed with ALL between January 2006 and December 2010 were retrospectively reviewed. The date of last follow-up was December 31, 2010. Patients with Burkitt's leukaemia were excluded. Day 29 bone marrow determined morphologic remission following induction phase of therapy.

Results

Thirty four patients were included for analysis. Median age was 5.9 years (range: 1.4 - 12.1 years) and 18 (53%) were males. The commonest presenting symptom was fever (79%). Mean initial WBC was 95,000/mm^3 (range: 1800 – 704 000/mm^3). Induction-related mortality rate was 17.6% and overall mortality rate in the study population was 23.5%. Morphologic remission rate on day 29 was 44%. The commonest post-induction event was abandonment of therapy. From the initial study population, only 10/34

patients (29%), were known to be alive and in continuing remission at last follow-up. These ten patients had a median follow-up of 23 months (range: 4 - 49 months).

Conclusion

In KBTH, high rates of abandonment and treatment-related mortality contribute to poor outcomes in childhood ALL. Identification of factors contributing to abandonment and improved supportive care would help reduce treatment failure.

Key words

Acute lymphoblastic leukemia, children, treatment, Ghana

Background

Worldwide, acute leukaemias account for about a third of all childhood cancers and ALL represents about 80% of all acute leukaemias in children below the age of 15 years [1]. Survival rates for childhood ALL have improved significantly in developed countries over the past fifty years and are currently at about 90% [2]. Improved laboratory diagnostic capabilities with more precise risk-directed treatment regimens, availability of adequate supportive care and biologically targeted therapies have contributed to these improved outcomes [3]. In comparison, outcomes of children with ALL in resource-poor nations remain sub-optimal [4]. The reasons for these poor outcomes are multi-factorial and

include lack of recognition of childhood cancers as a health priority, poor health infrastructure with few specialized paediatric oncology units and trained personnel, limited laboratory facilities, missed diagnoses, poverty (rendering chemotherapy and other related healthcare costs unaffordable), delayed presentation to hospital and abandonment of therapy [4]. Inadequate supportive care for patients undergoing chemotherapy also results in high mortality rates due to organ failure, infections and other complications of bone marrow suppression [5].

In Ghana, like other developing African countries, scarce resources for healthcare are often directed towards the control of infectious diseases like malaria, diarrhoeal diseases, pneumonia and HIV/AIDS [6]. Although leukaemias are amongst the commonest childhood malignancies seen in Ghana [7], there is a paucity of recent data on treatment outcomes of ALL in Ghanaian children. Such information would help identify factors that would help improve survival as well as stimulate further research.

Methods

Setting

Ghana is situated on the west coast of Africa and has about 25 million inhabitants, of which 37% are below age 15 years. Almost a third of the population lives below the international poverty line (US$1.25/day). Korle Bu Teaching Hospital (KBTH), Accra, is the largest teaching hospital in Ghana and one of only two tertiary centers in the country with a paediatric oncology unit. On average, the oncology unit admits about 8 new cases/month, all aged <13 years and referred from all over the country. Patient care is

provided by 4-5 junior doctors (residents and interns), who are in turn supervised by any one of two full time paediatric oncologists, the second having joined staff in September 2010. There are no trained paediatric oncology nurses. A government-funded National Health Insurance Scheme (NHIS) was established in 2003, providing limited coverage for costs of hospital admission and basic laboratory tests for those registered on the scheme. However, chemotherapy costs are out-of-pocket expenses for all patients. Blood bank services are available on site and provide red cell and platelet transfusions on request, although the latter is often not readily available. Central lines are not used routinely and there is no paediatric intensive care unit.

Patients

The records of patients diagnosed with ALL in the paediatric oncology unit of KBTH between 1 January 2006 and 30 November 2010 were retrospectively reviewed. The date of last follow up was December 31, 2010. Demographic data, details of presenting clinical signs and symptoms at diagnosis of ALL, as well as initial laboratory findings were evaluated. Treatment duration and outcome, in addition to follow-up laboratory results, were also recorded.

Diagnosis

Diagnosis of ALL was made by morphologic examination of bone marrow (BM) aspirate specimens (at least 25% lymphoblasts present). Patients with L3 morphology (Burkitt's leukaemia) were excluded from the study as they were treated with a different protocol. Cerebrospinal fluid (CSF) samples were sent for cytology at the time of the first intrathecal treatment. Patients were considered to be CNS positive at diagnosis if

lymphoblasts were present in the CSF or clinical signs of CNS leukemia, such as cranial nerve palsies, were seen.

Risk-stratification of patients with ALL

Risk stratification for patients was based on the NCI/Rome criteria. Patients aged between 1 & 9.99 years at the time of diagnosis and an initial white blood cell (WBC) count of < 50,000/µL were classified as standard risk (SR) ALL. Those aged ≥ 10 years or any patients with an initial WBC of ≥ 50,000/µL were classified as high risk (HR) ALL. Immunophenotyping, molecular and cytogenetic analyses were not done as these studies were unavailable in the country.

Treatment

Prior to beginning chemotherapy, all patients received allopurinol and fluid hydration. All SR-ALL patients were treated based on Regimen A of the United Kingdom Children's Cancer Study Group (UKCCSG) '99 protocol while HR-ALL patients were treated as per Regimen B of the same protocol [8]. Any patients who were not in morphologic remission on day 29 of induction therapy were given one or two further weeks of therapy (extended induction) and then escalated to Regimen C if a subsequent BM still did not show morphologic remission (i.e. <5% lymphoblasts). Girls who completed therapy were treated for a total of 2 years while boys were treated for 3 years. Prophylaxis against pneumocystis jiroveci pneumonia (oral co-trimoxazole administered twice weekly) was prescribed routinely for the duration of chemotherapy. All patients with febrile neutropenia were admitted and treated with broad-spectrum intravenous antibiotics, as per local guidelines. Patients with prolonged fever (>5-7 days) were prescribed oral antifungals, parenteral antifungal agents being unavailable.

Definitions

Event-free survival (EFS) was defined as the time from diagnosis to the date of last follow up or to the first event. Events were induction failure (>25% lymphoblasts on day 29 OR ≥5% lymphoblasts, following extended induction), relapse (BM, CNS or testicular), abandonment of therapy (missing four or more consecutive weeks of treatment) or death. Induction-related mortality was any death occurring on or before the last day of induction therapy. Remission was defined as <5% blasts on BM smear and absence of blasts in the CSF. In boys, absence of testicular swelling was also required.

Data analysis

Descriptive statistics were used to summarize patient demographics, clinical and laboratory characteristics and treatment outcomes.

Results

Demographics

During the study period, 474 new cases of cancer in children aged <13 years were diagnosed. Of these, 109 (23%) were leukaemias, forming the second commonest cancers after lymphomas. ALL comprised 78/109 (72%) of the leukaemia cases. Twelve patients had Burkitt's leukaemia by morphology and were excluded while 32 patients were excluded due to missing or incomplete hospital records. The clinical and laboratory features at diagnosis for the 34 patients who were included in the study are shown in Table I. Twenty (59%) were classified as HR ALL and 24 (71%) had blasts present on peripheral blood smear.

Remission-Induction

Nine patients did not complete induction therapy due to abandonment of therapy (3 patients) and death (6 patients). Induction-related mortality rate was 17.6%; 4 of the 6 patients (66.7%) who died had presumed or confirmed infections. Of the remaining patients, only 11/25 (44%) were in morphologic remission on day 29 of induction.

Post-induction events

20/25 patients (80%) had a post-induction event. The commonest post-induction event was abandonment of therapy (Table II). Most patients who abandoned therapy did so within the first year of diagnosis. Six patients relapsed (4, isolated BM and 2, isolated CNS) at a median time of 6 months from diagnosis (range: 2.5 - 44 months). Three out of the six patients (50%) who relapsed were successfully re-induced and were alive and on continuing therapy at last follow-up. The remaining three patients subsequently abandoned therapy. Three patients failed induction therapy: 2 subsequently abandoned therapy and the third patient was alive and in remission, thirty three months from diagnosis. Two deaths occurred as first post-induction events – one patient presented with seizures two weeks after completing induction therapy and died the following day. CNS relapse was not confirmed. The second patient died post-operatively four months after diagnosis of ALL, following surgery for intussusception.

Overall, 17 out of the 34 patients in the study population (50%) abandoned therapy, either as an initial event or subsequent to relapse/resistant disease.

Survival data

Overall, the median EFS was 2 months (range: 0.3 – 44 months). From the initial study population, only 10/34 patients (29%) were known to be alive and in continuing

remission at last follow up. These 10 patients had a median follow up of 23 months (range: 4-49 months).

Discussion

Our data showed less than 30% known overall survival for children at KBTH diagnosed with ALL, one of the most easily treatable childhood cancers [9]. The study was limited by its retrospective nature and the large percentage of missing patient records, as only 51.5% of eligible cases seen during the study period were analyzed. However, all active patients being followed by the oncology unit as at December 2010 were accounted for in the study population of 34 patients.

Using age ≥ 10 years and leukocyte count ≥ 50,000/μL, more than half of our patients were classified as having high risk ALL. Although these are widely accepted prognostic features, it has been suggested that use of these risk factors alone might result in undertreatment or overtreatment of a significant number of patients [4]. Immunophenotype, leukemia cell cytogenetics and minimal residual disease are incorporated into risk-stratification in contemporary ALL protocols [10,11]. However, the reality in many resource-poor countries is that patient age and leukocyte count are often the only readily available and inexpensive means of risk-stratifying ALL patients, with

inability to differentiate T-lineage from B-lineage disease or perform any specialized laboratory testing.

Our induction-related mortality rate of 17.6% was unacceptably high and most deaths occurred from infections. A recent meta-analysis of randomized paediatric ALL studies by Blanco et al [12], reported an induction death rate of only 1.38%. However, similar to our study, deaths comprised a significant proportion of first events during induction. In Central America, Gupta et al [13] found that 59% of treatment-related mortality occurred within 42 days of beginning induction therapy; more than half of the induction deaths were caused by infections, with bleeding being the second commonest cause. In the same study, independent predictors of induction deaths were high risk status, lower initial platelet counts and longer travel time to clinic. Studies from India, Turkey and the Nordic countries have also shown that majority of deaths in induction are from infections [5,14-16]. Improved supportive care with establishment of a paediatric intensive care unit, availability of trained paediatric oncology nurses, education of healthcare staff and enforcement of infection control measures such as rigorous handwashing may help reduce the high rate of induction deaths in our patients.

The goal of initial ALL therapy is to induce remission and eradicate the leukaemic cell burden, while restoring normal haematopoiesis [17]. The backbone of induction therapy is similar across protocols, usually including a corticosteroid, vincristine, asparaginase, +/- an anthracycline [3]. With modern ALL protocols, 97-99% remission-induction rates are reported in children [10]. Even in low and middle income countries, over 90%

complete remission rates after induction have been reported [16,18]. Surprisingly, only 44% of patients who completed induction in our study were in morphologic remission on day 29. This poor initial response to therapy might reflect genetics of the leukaemia cells and host pharmacodynamics and pharmacogenetics [3]. Further studies are required in our patient population to help identify optimal treatment strategies to improve remission-induction outcomes. Slow early response to treatment is associated with a poorer prognosis and can easily be assessed using Day 14 BM morphology [18]. Day 14 BM aspirates are not routinely done in KBTH but perhaps should subsequently be incorporated into the treatment regimens to help improve patient risk-stratification.

The commonest post-induction (and overall) event in the study was abandonment of therapy, most cases occurring within the first year of diagnosis of ALL. An earlier study in KBTH also showed a 60% patient default rate after a mean follow up period of six months [19]. Abandonment has been identified as a significant cause of treatment failure in low and middle income countries [20-23]. In Turkey, however, overall rate of treatment abandonment was comparatively low at 3.5% [16]. In Ghana, chemotherapy is not covered under the NHIS and many patients are unable to afford the high cost of treatment. With ALL therapy being prolonged over many months, we speculate that this may have been a major factor causing abandonment in our patient population. Other predictors of abandonment reported in the literature include low monthly household income, increased number of household members, longer travel time to hospital and lack of social support services [6,21]. Parental illiteracy, cultural and religious beliefs and fear of disease incurability and side effects of chemotherapy have also been shown

to be contributory [24]. A study done in Indonesia by Mostert et al [25] showed that after introduction of an educational program for parents of children with cancer, treatment refusal and abandonment decreased from 14% to 2% and EFS increased from 13% to 29% among poor patients. Although the causes of abandonment in our study were not determined, general interventions to reduce abandonment include providing support for out-of-pocket expenses related to therapy, appropriate communication with families, early contacting of families who miss appointments, development and implementation of educational programs and twinning partnerships between pediatric cancer units in developed and developing countries [21]. In Recife, Brazil, treatment of childhood ALL in a dedicated paediatric oncology unit using a comprehensive multidisciplinary team approach, protocol-based therapy, and a locally funded family support system resulted in a reduction in abandonment from 16% to 0.5% and a dramatic increase in 5-year-EFS, from 32% to 63% [9].

Conclusion

In conclusion, high rates of abandonment and induction-related mortality contributed to poor outcomes in childhood ALL at KBTH. Prospective studies to determine the specific factors that contribute to abandonment of ALL therapy in Ghana would be useful. Improved supportive care to reduce deaths from infection during the induction phase of therapy and availability of chemotherapy drugs on the NHIS would also help improve outcomes. Local data collection and record keeping practices also need to be improved. Of note, since January 2011, the KBTH paediatric oncology unit has used the online, paediatric oncology networked database (POND), to store patient data and allow

uniform and consistent data collection [6]. It is hoped that this will greatly facilitate future research work and ultimately improve patient care and survival.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

NB reviewed medical records, collected data and wrote the manuscript; CS conceived the study, reviewed and analyzed the data and wrote the manuscript; LR reviewed the data and critically reviewed the manuscript; YDA analyzed data and critically reviewed the manuscript; IE critically reviewed the manuscript.

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Tables

Table I. Patient demographics, clinical and laboratory features at diagnosis of ALL	
Demographics	**Number of patients (% of total; N=34)**
Age (y)	
1 – 9.99	28 (82%)
≥ 10	6 (18%)
Sex	
Male	18 (53%)
Female	16 (47%)
Clinical/Laboratory features at diagnosis	
Fever	27 (79%)
Bleeding	7 (21%)
Bone pain	5 (15%)
Lymphadenopathy	27 (79%)
Hepatosplenomegaly	23 (68%)
Blasts on peripheral film	24 (71%)
CNS positive (CSF blasts and/or clinical CNS disease)	3 (9%)
Full blood count at diagnosis	**Mean (range) N=34**
Hemoglobin (g/dl)	4.9 (1.6 – 8.7)
WBC (/µL)	95,300 (1,800 – 704,600)
Platelet count (/µL)	49,000 (7,000 – 186,000)

Table II. First events occurring in 20 children following four weeks of remission-induction therapy

Sex	Age (years)	Event	EFS (months)
M	2.5	Failed extended induction – 8% blasts on day 43; (abandoned therapy 4 months later)	1.5
F	7	Abandonment of therapy	6
M	8.4	Abandonment of therapy*	1
F	3.3	CNS relapse (abandoned therapy 3 months later)	3
M	6.75	Abandonment of therapy	2.5
F	7.25	CNS relapse	2.5
M	1.4	Failed induction - 65% blasts on day 29 (abandoned therapy 10 months later)	1
F	3	Bone marrow relapse (abandoned therapy 5 months later)	8
M	11	Died post-operatively, following surgery for intussuception	4.5
M	1.8	Died following multiple afebrile seizures	1.5
M	1.5	Abandonment of therapy	1.1
F	7	Abandonment of therapy	7.5
M	8	Failed induction – 35% blasts on day 29	1
F	9.5	Bone marrow relapse	10
F	4.9	Abandonment of therapy	1.4
M	2	Bone marrow relapse (abandoned therapy subsequently)	4.75
F	4	Abandonment of therapy	1
M	11.5	Abandonment of therapy	5.5
F	10.8	Abandonment of therapy	20
F	6	Bone marrow relapse	44

M, male; F, female; EFS, event-free survival; CNS, central nervous system

*Patient returned to the hospital two months later and restarted induction; currently on therapy

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