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Current Treatment and Outcome for Childhood Acute Leukemia in Tanzania

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Background: In order to understand the disparity in childhood leukemia survival in low-income countries (LICs) compared to high-income countries (HICs), we evaluated the resources available at Tanzania's national pediatric oncology ward, and clinical characteristics, disease course and outcomes of children diagnosed with acute leukemia from 2008 through 2010. ***Procedures:*** A chart review and assessment of services was performed to assess childhood leukemia diagnoses, treatment, and outcomes in Tanzania at the Ocean Road Cancer Institute (ORCI) from January 1, 2008 to December 31, 2010. Results were compared to those from a 2005 evaluation that showed only one of 20 children with leukemia surviving at 1 year. ***Results:*** During the study period, 106 patients presented with leukemia, including 81 patients with acute lymphoblastic leukemia (ALL) and 25 with acute myeloid leukemia (AML). Forty-nine of 58 (84%) patients with ALL, and six of 17 (35%) with AML who received therapy and had complete data, achieved complete remission. Estimated 2-year event-free survival for all patients with ALL was 33%; for AML it was 0%. Ten patients died prior to initiation of therapy, 19 died of toxicity, and eight abandoned therapy. ***Conclusions:*** Though leukemia survival in Tanzania remains far below that in HICs, survival rates for ALL have significantly improved in recent years due to standardization of treatment regimens and better staff, though AML outcome remains dismal. Ongoing improvements in pediatric leukemia outcomes will require strategies to improve awareness and early access to treatment coupled with improvements in diagnostic capabilities, supportive care, and training. Pediatr Blood Cancer 2013;60:2047–2053.

Key words: ALL; AML; leukemia; low income country

INTRODUCTION

Over the past several decades, outcomes for childhood cancer have improved dramatically, with 5-year survival rates in the US increasing from below 30% in the early 1960s to 80% at the beginning of the 21st century [1,2]. Unfortunately, while approximately four-fifths of the 250,000 children diagnosed with cancer worldwide each year live in low-income countries (LICs) and middle-income countries (MICs), survival rates in these countries continue to average around 25% [3]. Mortality rates for acute lymphoblastic leukemia (ALL), the most common childhood cancer globally, directly correlate to country income, with long-term survivorship reaching 85% in the US but rarely above 35% in LICs [4,5]. However, because ALL may be effectively treated with fairly low-cost systemic drug treatment alone, it is a feasible target for LIC pediatric oncology programs, and an appropriate indicator of their effectiveness [6]. Acute myeloid leukemia (AML), by comparison, has a worse prognosis and requires higher intensity chemotherapy and supportive care [7–9].

In order to improve leukemia outcomes in LICs, it is necessary to assess the regional resources, as well as the disease outcomes. Tanzania is a low-income country in East Africa with a gross national income per capita of 1,328 USD and life expectancy of 58.1 years [10]. In 2004, the government of Tanzania, a country of 43 million, 44% of whom are under 15 years old, dedicated a 17 bed pediatric ward in its national oncology facility, Ocean Road Cancer Institute (ORCI), to provide free-of-charge care to all Tanzanian children with cancer. A prior assessment of ORCI's services revealed an overall 1-year survival rate for children admitted with any cancer in 2005 of only 20% [11]. At that time, only lymphoma was treated with standardized chemotherapy, and just one child of 20 diagnosed with acute leukemia in 2005 was alive at 1-year follow-up [11]. The only other report of leukemia in Tanzania was an epidemiological study of 33 children, without outcome [12]. In 2007, a trained pediatric oncologist (P.S.) arrived at ORCI and worked with the ward's medical officer to institute changes to improve outcomes, including standardized chemotherapy regimens, increased staffing, and better patient care documentation. This study aimed to assess current resources available at ORCI and to describe clinical characteristics, disease course, and outcome of children diagnosed with leukemia at ORCI from January 1, 2008 to December 31, 2010.

METHODS

Case Review

A comprehensive chart review was performed to assess childhood leukemia diagnoses, treatment, and outcomes from January 1, 2008 to December 31, 2010. Every patient admitted to ORCI's pediatric ward (1–18 years old) with a diagnosis of leukemia was included, regardless of the availability of follow-up information. The year 2008 was the first full year of standardized leukemia treatment, and the first year for which routine chart documentation existed. This review was approved by the UCSF institutional review board with permission from the Muhimbili National Hospital (MNH) and ORCI.

We recorded patient demographics, disease presentation, diagnosis, disease course, treatment, and outcome. Of 112 patients documented as confirmed leukemia cases in the ORCI admissions book in this period, 10 patient files had been lost at the time this

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review was conducted. For these files, only data routinely collected upon admission and final vital status were available. Some available files were missing sections. As a result, the number of patients with documentation of any given measure varies, so percentages given indicate the number of patients positive for a given variable, out of the number with data for that variable.

Because date of birth was rarely known with certainty, ages were based on year of birth. Height was not routinely measured, so weight-for-age measurements calculated at treatment initiation were compared to international WHO standards to estimate nutritional status. Children were considered malnourished if they fell below two standard deviations (i.e., below the 2.5 percentile) from the average weight for their age. Travel time from the patient's hometown to ORCI was calculated using the Google Maps "Directions" function.

Assessment of Services

Facilities and staff are described in Table I. The ward in which all pediatric leukemia patients were hospitalized under national coverage consisted of one ward of 17 beds and an overflow area of 10 beds. When patient census exceeded capacity, children shared beds; accompanying family members slept on the ward floors or outside. Potable water was available from a pump outside. Frequent power outages left the ward without lights and refrigerated medicines. One central pharmacy stored, but did not reconstitute

TABLE I. Facilities and Availability of Resources for ORCI Patients

Resource	Availability
Diagnostic	
X-ray	Consistently available at ORCI
CT, MRI	Consistently available at private clinic off-site
Complete blood count	Consistently available at ORCI, daily
Chemistry panel	Consistently available at ORCI, daily
Peripheral blood morphology	Consistently available at MNH, with 2–3 week delay
Bone marrow morphology	Consistently available at MNH, with 2–3 week delay
Cytogeneticsa	Not available
Immunophenotype	Not available
CSF cytology	Intermittently available at MNH, with 2–3 week delay starting end 2010
Therapeutic, supportive	
Whole blood transfusions	Intermittently available at ORCI, usually available at MNH
Platelet transfusions	Intermittently available at MNH, with delay of several hours to several days
Fresh frozen plasma	Intermittently available at MNH
Ketoconazole	Consistently available at ORCI, free of charge
Amphotericin	Consistently available at ORCI, free of charge
Trimethoprim/sulfamethoxazole	Consistently available at ORCI, free of charge
Ceftriaxone	Consistently available at ORCI, free of charge
Gentamicin	Consistently available at ORCI, free of charge
Therapeutic, cancer care	
Bone marrow transplant	Not available
Radiation therapy	Consistently available at ORCI
Dexamethasone	Consistently available at ORCI, free of charge
Vincristine	Consistently available at ORCI, free of charge
Methotrexate	Consistently available at ORCI, free of charge
6-mercaptopurine	Consistently available at ORCI, free of charge
Cyclophosphamide	Consistently available at ORCI, free of charge
Cytarabine	Consistently available at ORCI, free of charge
L-asparaginase	Usually available at ORCI, *at patient's expense*
Thioguanine	Consistently available at ORCI, free of charge
Etoposide	Consistently available at ORCI, free of charge
Prednisolone	Consistently available at ORCI, free of charge
Staffing	
Nursing:patient ratio	1:15 in day, 1:30 at night
Pediatric oncologist	One available for entire children's ward at ORCI
Pediatric residents	Two available, on rotating basis at ORCI
Social worker	One available for entire hospital at ORCI
School teacher	One available for entire children's ward at ORCI
Facilities	
Radiology	Available at ORCI
Pediatric ICU	Not available
Housing for caregivers/family	Not available

[a]Over the study periods, five histologic samples were sent to Ireland for additional cytogenetic and immunophenotypic review, to definitively diagnose ambiguous cases.

medications. Radiation therapy, radiology, and a laboratory that conducted basic blood tests and stored limited blood products were located at ORCI. Three-dimensional imaging was conducted at a private radiology clinic one mile away. No national cancer registry was in place.

The ORCI pediatric ward staff consisted of four full-time nurses per day shift and two per night shift. Throughout the study period, ORCI housed 20–64 inpatients, with daytime nurse:patient ratios of 1:5 to 1:16. Other ORCI staff included one full-time pediatric oncologist (P.S.), one full-time medical officer, and two rotating medical residents in training. No advanced training program in pediatric oncology was available and PS represented the only pediatric oncologist in Tanzania.

Diagnosis and Supportive Care

With the exception of five samples sent to Europe for cytogenetic review and/or immunophenotyping, all diagnoses at ORCI were made at MNH and based upon bone marrow or peripheral blood morphology alone. Chemistry panel, chest X-ray, abdominal ultrasound, complete blood count (CBC) with differential and platelet count, and HIV serology screen were performed on all patients. Screening of cerebrospinal fluid for evidence of central nervous system involvement was only implemented at the end of 2010 ($n = 5$), and even then was only conducted on patients with a platelet count above 25,000/μl or rarely, when platelet transfusions were available.

Patients with fever were screened for malaria and also treated with ceftriaxone and gentamicin. Ketoconazole or amphotericin B were used for clinical fungal infections. Prophylactic sulfamethoxazole/trimethoprim was given to all leukemia patients and prophylactic ketoconazole was added for AML. Patients with hemoglobin less than 7 g/dl were transfused with whole blood or packed red cells. All leukemia patients were treated with allopurinol and intravenous fluids for 24 hours prior to initiating treatment and for a full 5-day course.

Chemotherapy

All patients diagnosed with ALL were treated with the UKALL 2003 protocol [13]. Although included in this protocol, L-asparaginase was only available to patients with ability to pay. Patients were stratified into Regimen A (low-risk) or B (standard and high-risk) according to white blood count at diagnosis (<50,000 vs. >50,000/μl), age (1–10 years vs. >10 years), and bone marrow response at day 8 or 15 of chemotherapy. For females, a full course of treatment was prescribed for 112 weeks (Regimen A) or 114 weeks (Regimen B); for males, it lasted 164 (A) or 166 (B) weeks (Supplemental Table I). All patients underwent treatment induction as inpatients at ORCI; patients living in or near Dar es Salaam were discharged to receive outpatient therapy after induction, while those living farther away were discharged following consolidation.

Patients with AML were treated with daunorubicin, cytarabine, and etoposide following a chemotherapy arm of the MRC AML15 protocol [14]; or with reduction to a cytarabine/daunomycin 7 + 3 induction and cytarabine consolidation; or with oral induction with 6-thioguanine/etoposide/prednisolone followed by cytarabine consolidation, using a palliative regimen from Tata Memorial Hospital in Mumbai, India that was instituted after two consecutive toxic deaths on the more intensive regimen (Supplemental Table II and III). Hematopoietic cell transplants were not available in Tanzania during the study period.

Disease Course and Outcomes

Patient outcomes were categorized as death; abandonment (patients stopped therapy prior to completing the full treatment course against medical advice or refused initiation of treatment) [15]; on treatment (as of August 1, 2011); alive with complete remission following treatment completion; alive with progressive disease. Based on information recorded in patient charts, causes of death were classified as progressive disease; relapse; toxic (occurring during or immediately following a course of chemotherapy); unrelated; and unknown. Toxic deaths were categorized as febrile neutropenia/infection, hemorrhage, renal failure, pulmonary insufficiency, and electrolyte imbalance. Patients sent home on palliation were classified as having death from progressive disease or relapse. In situations of treatment abandonment, attempts were made to classify the reason, based on chart notes and health professional interview.

Event-free survival (EFS) from the time of diagnosis was estimated using the Kaplan-Meier method. Events were defined as abandonment of treatment; first evidence of relapsed disease (or date sent home on palliation) and death from any cause. Cox proportional hazards methods were used to assess the impact of receipt of asparaginase after controlling for known prognostic factors and potential confounders. The proportional hazards assumption was tested using time-varying covariates and was satisfied for all variables included in the model.

RESULTS

Patient Characteristics

ORCI registered 112 leukemia patients from January 1, 2008 to December 31, 2010, including 81 patients with ALL, 25 with AML, and three with chronic myeloid leukemia, one with juvenile myelomonocytic leukemia, and one with Burkitt's leukemia. Leukemia was among the top three diagnoses, constituting 12% of pediatric admissions to ORCI in this period. The single patient who presented at less than 1 year of age was excluded from further analysis, as he was not admitted but sent home on palliative care. The characteristics of the 106 included patients with ALL and AML are shown in Table II.

Prior to arrival at ORCI or MNH, 88 evaluable patients reported median symptom duration of 3 months. Most presented initially to a local hospital. At least 20 leukemia patients were treated with one or more blood transfusions and discharged, before referral to MNH or ORCI when symptoms did not resolve. Thirty-eight patients spent a median stay at MNH of 10 days (range 2–70), before referral to ORCI. Median time to initiation of therapy at ORCI was 3 days (range 1–36). Reasons for delays included delays initiating and receiving diagnostic results, and initial misdiagnosis.

Twenty-six (41%) patients with ALL and five (25%) with AML presented with a WBC greater than 50×10^3/μl. Hemoglobin levels were below 7 g/dl in 20 (31%) ALL and 11 (55%) AML patients. Serum levels of uric acid were elevated in 13 (26%) ALL and 1 (7%) AML patients with five who had uric acid levels >10 mg/dl.

Thirty patients with leukemia experienced symptoms for >3 months prior to hospitalization. Patients with ALL had median symptom duration of 2 months, usually with fever (64%) and lymphadenopathy (53%). Patients with AML had median symptom

TABLE II. Characteristics of 106 Patients Diagnosed With ALL or AML at Ocean Road Cancer Institute From January 1, 2008 to December 31, 2010

	ALL		AML	
	N=81	N evaluable	N=25	N evaluable
Year of admission				
2008	20		7	
2009	36	81	7	25
2010	25		11	
Age (years)				
Median, range	6 (1–17)	81	9 (2–18)	25
Patients >10 years	25		11	
Sex				
M:F ratio	43:38	81	13:12	25
HIV positive	1	81	0	25
Malaria	24	81	6	20
WBC ($\times 10^3/\mu l$)				
Median (range)	36.2 (1.22–603)	64	24.3 (2.9–292.5)	20
Platelets ($\times 10^3$/ml)				
Median (range)	36.1 (10.7–777)	60	34 (10.6–174)	19
Hemoglobin (g/dl)				
Median (range)	5.6 (1.1–10.8)	64	5.0 (0.4–9.7)	20
Uric acid (mg/dl)				
Median (range)	5.5 (1.0–17.0)	50	4.5 (2.3–8.9)	14
Creatinine (mg/dl)				
Median (range)	0.58 (0.24–4.68)	50	0.52 (0.38–0.84)	14
Symptom duration (months)				
Median (range)	2 (0.5–12)	64	3 (0.25–6)	20
Fever (n)	41	64	8	20
Hepatomegaly (n)	31	64	5	20
Splenomegaly (n)	28	64	5	20
Mediastinal mass (n)	8	64	3	20
Pleural effusion (n)	8	64	7	20
Lymphadenopathy (n)	34	64	6	20
Chloroma (n)	0	64	7	20
CNS involvement[a] (n)	4		0	
Wt-for-age percentile				
Median (range)	11 (0.2–92)	59	18 (0.5–99)	15
<2.5 Percentile (n)	20		3	
Distance traveled				
Median (km)	356	81	259	25
Range	(1.8–1,280)		(3.4–1,290)	
Median time (hours)	4.2		3	
Range	(0.05–16.7)		(0.15–16.75)	
Patients living within 2 hours	29		8	

[a]Five patients had CSF sampling at diagnosis, of whom one had positive cytology. Two other patients with ALL presented with cranial nerve palsy and one with seizures, attributed to CNS leukemia.

duration of 3 months, with fever as the most common symptom. In AML, pleural effusion and chloroma were each detected in seven (35%) patients. Twenty patients (25%) with ALL and three (12%) with AML had malnutrition by international weight standards upon initial admission to ORCI (Table II).

Treatment Received

Of the 81 patients with confirmed ALL, six died prior to initiation of therapy. Sixty-five received either Regimen A (n = 24) or Regimen B (n = 41) therapy (Table III). The files of the other 10 patients were lost, so detailed information about their treatment was not available; however, limited data on their diagnoses and treatment outcome was included. Among those treated, 24 received L-asparaginase of variable dosing. In total, 50/65 patients (77%) with known status achieved complete remission (Table III).

Of the 21 patients with AML for which treatment data are available, nine received MRC AML15 (seven of these had the etoposide removed and cytarabine reduced to 7 days due to fatal toxicity in the first two patients), eight received the Indian regimen included in Supplemental Table III, and four received no treatment (including one abandonment). Of treated patients, six achieved complete remission.

Outcomes

Of the 81 patients with ALL admitted to ORCI from 2008 to 2011, three patients completed a full course of planned treatment,

TABLE III. Chemotherapy Received by 81 Children With ALL at ORCI

Treatment received[a]	
Regimen A	24
Regimen B	41
None	6
Unknown	10
Received L-asparaginase	24
Duration of therapy	
Overall median, range (weeks)	43.6 (0.3–151.0)
Completed treatment or died while receiving therapy (N=59)	23.3 (0.3–121.7)
Still on therapy (N=22)	87.3 (40.1–167.6)
Achieved complete remission	50 (77%)
Regimen A	19 (79%)
Regimen B	31 (76%)

[a]Percents are the proportion of patients with known therapy or lack thereof. The six ALL patients who did not receive therapy all died of advanced disease shortly after arrival to the hospital. Ten of the total 81 ALL patients had lost files without a record of their regimen. Remission status was known for 65 ALL patients.

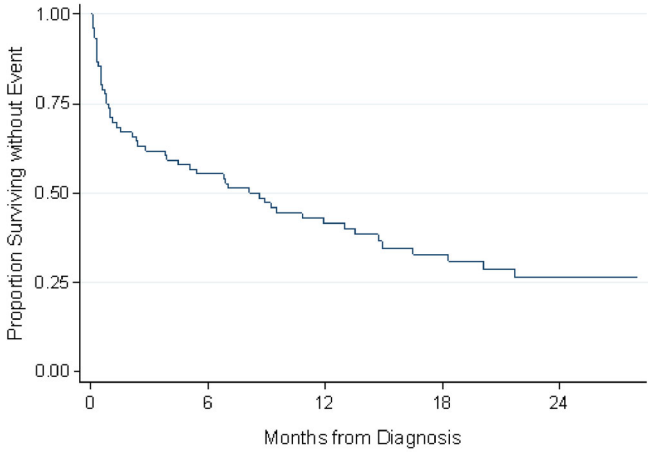

Fig. 1. Event-Free survival for all children with acute leukemia diagnosed in the ORCI from January 1, 2008 to December 31, 2010 with diagnosis and follow-up data (n = 79).

49 (60%) relapsed or died on therapy (median duration 23 weeks), seven abandoned therapy, and 22 patients were still on therapy as of August 1, 2011, with median duration of treatment of 87 weeks (range 40–168 weeks; Table III). The estimated 2-year EFS for 62 patients with ALL with paired diagnosis and follow-up date was 33% (CI 15.9–37.5). The percent of ALL deaths occurring prior to or during Induction decreased over the study period: 47% in 2008, 15% in 2009, and 23% in 2010. Disease-related deaths (due to progressive disease or relapse) accounted for 62% of ALL deaths with known cause.

Of the 24 patients who received asparaginase, 100% achieved remission compared to 66% among those who did not receive the drug ($P = 0.002$ by Fisher exact). At 24 months, 63.7% (95% CI 37.9–81.0) of patients who received asparaginase were event-free compared to 21.3% (95% CI 9.6–35.9%) of patients who did not receive asparaginase ($P = 0.004$). On multivariate analysis, receipt of L-asparaginase was associated with significantly reduced hazard for a clinical event (HR = 0.37; 95% CI [0.16–0.85]; $P = 0.02$), independent of age (<10 years vs. ≥10 years), presenting white cell count (<50 vs. ≥50 × 106/L), and year of diagnosis (2008 vs. 2009–2010).

Except for one case of abandonment, all 25 patients with AML admitted during this period died. Median duration of therapy was 3 weeks (range 0.1–35.6) and death occurred a median of 26 days following admission (range 1 day to 40 weeks). Of AML deaths with known cause, 15 included active disease as an attribution and five were due only to treatment toxicity (Table IV). Overall, 19 (26%) patients with AML died with treatment toxicity and/or infection. Febrile neutropenia with presumed or confirmed infection constituted the most common cause, accounting for 10 deaths, followed by hemorrhage (n = 5), electrolyte imbalance (n = 2), pulmonary insufficiency (n = 1) and renal failure (n = 1).

Between 2008 and 2010, 8/106 (8%) acute leukemia patients at ORCI abandoned treatment. Of the seven cases in which reasons for abandonment were known, these included seeking alternative therapy (n = 3), socioeconomic circumstances (n = 3), and one patient thought the leukemia was cured.

The 2-year estimated EFS for all patients with acute leukemia between 2008 and 2010 was 26.1% (95% CI, 15.93–37.46), with median EFS of 8.1 months (Fig. 1). For patients with ALL, the estimated 1-year EFS was 50.2% (95% CI, 37.0–62.0) and 2-year EFS was 33.3% (95% CI, 20.5–46.6), with the median EFS of 12.4 months (Fig. 2). There was a trend for improved EFS in years 2009–2011 compared to 2008–2009 ($P = 0.06$). The outcome for the children with AML was significantly lower than for ALL, with a 1-year EFS of 6.3 (95% CI, 0.4–24), 2-year EFS of 0%, and median EFS duration of 1 month (Fig. 2).

TABLE IV. Outcome of Therapy

	ALL	AML	Total
Death	49	24	73
Progressive disease	11 (22%)	10 (42%)	21 (29%)
Relapse	12 (24%)	5 (21%)	17 (23%)
Toxic	14 (29%)	5 (21%)	19 (26%)
Unknown	12 (24%)	4 (17%)	16 (22%)
Abandonment[a]	7	1	8
Currently on treatment	22	0	22
Complete remission post-treatment	3	0	3
Total	81	25	106

[a]Abandonment is defined as any patient who either stopped therapy for at least 4 weeks or refused initiation of therapy against medical advice.

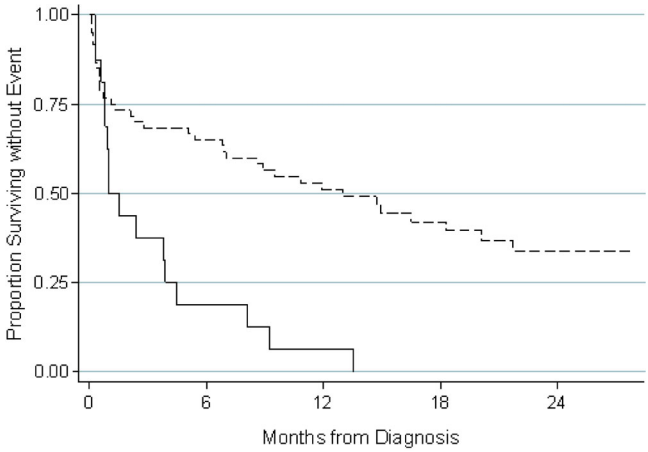

Fig. 2. Event-Free survival for children with ALL (dashed line, n = 62) and AML (solid line, n = 17) diagnosed in the ORCI from January 1, 2008 to December 31, 2010 with diagnosis and follow-up data (n = 79).

DISCUSSION

In our study, leukemia constituted 12% of all childhood cancer diagnoses. This incidence is similar to the 16% found in a recent review of nine LICs with pediatric cancer registries, and substantially lower than most HICs [5]. Tanzania lacks a national cancer registry for children, and epidemiologic studies are limited [6,12]. Though only 20% of the Tanzanian population lives in urban regions throughout the country, 35% of all ORCI patients live within the greater Dar es Salaam area alone. This suggests that patients with ALL from rural and distant areas may be underrepresented at ORCI, as has been documented in other LICs with few cancer treatment centers [6]. The relatively low rate of abandonment seen in this study of 8% compared to other LICs such as Indonesia, with 35% abandonment, may have been partly due to geographic factors, as well as the high level of motivation of the oncology team [15].

Delays in seeking and receiving definitive therapy constitute significant challenges to leukemia care in Tanzania. Health care providers' failure to recognize leukemia symptoms in both local and central hospitals such as MNH contributed to the substantial time elapsed between onset of symptoms and initiation of appropriate therapy at ORCI. Pediatricians in Tanzania have limited training in cancer care, as evidenced by the substantial number of patients who were initially misdiagnosed. Data from Nicaragua suggests that primary physician education may significantly decrease the delay in diagnosis of leukemia [16]. Distance from the ORCI and lack of finances for travel also contributed to delays.

Budget limitations precluded offering a number of diagnostic tools, drugs, and infrastructural improvements at ORCI that are routinely provided in HICs. Diagnostic procedures for bone marrow and cerebrospinal fluid at both MNH and ORCI were rudimentary, causing delays in accurate diagnosis and lack of documentation of CNS leukemia. Immunophenotyping with flow cytometry, cytogenetics, and immunohistochemistry were not available in Tanzania. Because diagnoses of leukemia were based on bone marrow or peripheral blood morphology alone, it was not possible to accurately differentiate between B and T cell progenitor ALL, nor all subtypes within AML. A number of children during this period were started on one chemotherapy regimen with a presumed diagnosis, and then switched once a revised diagnosis was reported, which likely contributed to poorer treatment outcomes.

ORCI's limited resources also made it difficult for providers to adequately manage treatment toxicity, a substantial risk when delivering chemotherapy, as evidenced by the high toxic death rate. At ORCI, the absence of microbial cultures and isolation rooms contributed to substandard infection control. Laboratory monitoring of patient electrolytes and blood counts were not readily available. Blood products were often unavailable for days, with almost no access to platelets, which may have contributed to the five deaths from hemorrhage.

While attempting to limit treatment-related deaths, ORCI also struggled to provide therapy to effectively cure without excessive toxicity. The toxic death rate was comparable to other LICs [17] but significantly higher than the 1.4% reported in a recent HIC study [18]. One-third of patients with leukemia were severely malnourished upon arrival and one-third had malaria, which may have contributed to poorer treatment outcomes [19]. The careful adjustment of therapy intensity is especially challenging in LICs such as Tanzania, which must oftentimes forego key components of HIC cancer therapy regimens to accommodate resource constraints [20]. For example, L-asparaginase—a drug known to significantly increase survival in ALL [21,22] but which costs $1,000 USD per dose—was available only to the 38% of ORCI patients whose families who could afford it. Our analysis demonstrated that ORCI patients receiving this drug had markedly improved EFS in univariate and multivariate analysis, though confounding socioeconomic factors limit interpretation of this finding. Bone marrow transplant, another important adjunctive therapy in HIC leukemia protocols, is not available in Tanzania.

Finally, poor data collection, charting and data management constituted a barrier to effective cancer care at ORCI. In this study, a substantial number of patient files were missing. Data was incomplete when patients either abandoned treatment or stopped treatment under medical advice and were subsequently lost to follow-up. Birth dates were not precisely known and nutritional status assessments were limited because only weight measurements were taken at treatment initiation[6].

Seventy-seven percent of patients with ALL who actually received treatment at ORCI achieved complete remission following induction chemotherapy. In HICs, remission rates exceed 98% [20]. Of those who did not achieve remission, the majority arrived at ORCI with very advanced disease and died prior to or shortly after initiating treatment. Tanzania's 2-year EFS for ALL was much lower than in HICs, but similar to other LIC and MIC cancer programs, especially those early in their development [6,23–25]. Survival of the patients in our study may be expected to decrease further as follow-up duration is extended. However, EFS of new patients may increase as the program becomes more established and weaknesses are identified and overcome [6]. The low survival rates despite the ability to achieve remission observed in this study may have been partly due to the inconsistent CNS diagnosis and prophylaxis, the high toxic death rate and socioeconomic barriers to early diagnosis and to follow-up care.

These ALL outcomes, though low by HIC standards, represent great progress when compared to those achieved in Tanzania just several years earlier. Only 1 of 20 children diagnosed with acute leukemia in 2005 was alive at 1-year follow-up; with the standardization of care and limited investments in staffing and

resources over the ensuing years, 2 year EFS reached 33%. Ongoing advances in diagnostic capabilities and supportive care are likely to improve ALL survival further in upcoming years. However, outcomes in LICs are unlikely to reach those of HICs in the near future due to persistent disparities in training, health care spending, and infrastructure [4]. In light of this, therapy protocols adapted to local resources may also help to limit toxic deaths while maximizing treatment efficacy [21].

In conclusion, survival rates for ALL in Tanzania in 2008–2011 are substantially improved compared to 2005. AML has proven more difficult to treat due to the lack of adequate supportive care and of transplantation. Further improvements implemented since the study period include transfer of the pediatric cancer ward from ORCI to the national children's hospital at MNH, with improved access to isolation facilities, 24-hour laboratory, and increased staffing. Other recent advances include immunophenotyping, construction of a family hostel, and a newly appointed patient liaison for patient education. Plans for a pediatric oncology training program are in place. These anticipated improvements in outcome would demonstrate that pediatric malignancies can be effectively treated in LICs.

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REFERENCES

1. Howlader N, Noone AM, Krapcho M, et al. SEER Cancer Statistics Review. National Cancer Institute Bethesda, MD, 1975–2009 http://seer.cancer.gov/csr/1975_2009_pops09/ (based on November 2011 SEER data submission).
2. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2009. CA Cancer J Clin 2009;59:225–249.
3. Kellie SJ, Howard SC. Global child health priorities: What role for paediatric oncologists? Eur J Cancer 2008;44:2388–2396.
4. Farmer P, Frenk J, Knaul FM, et al. Expansion of cancer care and control in countries of low and middle income: A call to action. Lancet 2010;376:1186–1193.
5. Howard SC, Metzger ML, Wilimas JA, et al. Childhood cancer epidemiology in low-income countries. Cancer 2008;112:461–472.
6. Howard SC, Pedrosa M, Lins M, et al. Establishment of a pediatric oncology program and outcomes of childhood acute lymphoblastic leukemia in a resource-poor area. JAMA 2004;291:2471–2475.
7. Stevens RF, Hann IM, Wheatley K, et al. Marked improvements in outcome with chemotherapy alone in paediatric acute myeloid leukemia: Results of the United Kingdom Medical Research Council's 10th AML trial. MRC Childhood Leukaemia Working Party. Br J Haematol 1998;101:130–140.
8. Creutzig U, Zimmermann M, Lehrnbecher T, et al. Less toxicity by optimizing chemotherapy, but not by addition of granulocyte colony-stimulating factor in children and adolescents with acute myeloid leukemia: Results of AML-BFM 98. J Clin Oncol 2006;24:4499–4506.
9. Ravindranath Y, Chang M, Steuber CP, et al. Pediatric Oncology Group (POG) studies of acute myeloid leukemia (AML): A review of four consecutive childhood AML trials conducted between 1981 and 2000. Leukemia 2005;19:2101–2116.
10. United Nations DoEaSA, Population Division. World populaton prospects: The 2010 revision. United Nations. http://esa.un.org/unpd/wpp/country-profiles/country-profiles_1.htm%3E. 2011.
11. Scanlan P. An assessment of paediatric oncology services at ORCI in Dar es Salaam, Tanzania. Capetown, South Africa: University of Cape Town; 2006.
12. Grimes C, Schimana W. Features of childhood leukaemia in Tanzania. Trop Doct 2007;37:117.
13. Vora A, Goulden N, Wade R, et al. Treatment reduction for children and young adults with low-risk acute lymphoblastic leukaemia defined by minimal residual disease (UKALL 2003): A randomised controlled trial. Lancet Oncol 2013;14:199–209.
14. Burnett AK, Hills RK, Milligan D, et al. Identification of patients with acute myeloblastic leukemia who benefit from the addition of gemtuzumab ozogamicin: Results of the MRC AML15 trial. J Clin Oncol 2011;29:369–377.
15. Mostert S, Sitaresmi MN, Gundy CM, et al. Influence of socioeconomic status on childhood acute lymphoblastic leukemia treatment in Indonesia. Pediatrics 2006;118:e1600–e1606.
16. De Angelis C, Pacheco C, Lucchini G, et al. The experience in nicaragua: Childhood leukemia in low income countries-the main cause of late diagnosis may be "medical delay". Int J Pediatr 2012;2012:129707.
17. Gupta S, Antillon FA, Bonilla M, et al. Treatment-related mortality in children with acute lymphoblastic leukemia in Central America. Cancer 2011;117:4788–4795.
18. Pui CH, Campana D, Pei D, et al. Treating childhood acute lymphoblastic leukemia without cranial irradiation. N Engl J Med 2009;360:2730–2741.
19. Sala A, Pencharz P, Barr RD. Children, cancer, and nutrition—A dynamic triangle in review. Cancer 2004;100:677–687.
20. Hunger SP, Sung L, Howard SC. Treatment strategies and regimens of graduated intensity for childhood acute lymphoblastic leukemia in low-income countries: A proposal. Pediatr Blood Cancer 2009;52:559–565.
21. Silverman LB, Gelber RD, Dalton VK, et al. Improved outcome for children with acute lymphoblastic leukemia: Results of Dana-Farber Consortium Protocol 91-01. Blood 2001;97:1211–1218.
22. Pession A, Valsecchi MG, Masera G, et al. Long-term results of a randomized trial on extended use of high dose L-asparaginase for standard risk childhood acute lymphoblastic leukemia. J Clin Oncol 2005;23:7161–7167.
23. Bonilla M, Moreno N, Marina N, et al. Acute lymphoblastic leukemia in a developing country: Preliminary results of a nonrandomized clinical trial in El Salvador. J Pediatr Hematol Oncol 2000;22:495–501.
24. Dakka N, Bellaoui H, Khattab M, et al. Immunologic profile and outcome of childhood acute lymphoblastic leukemia (ALL) in Morocco. J Pediatr Hematol Oncol 2007;29:574–580.
25. Metzger ML, Howard SC, Fu LC, et al. Outcome of childhood acute lymphoblastic leukaemia in resource-poor countries. Lancet 2003;362:706–708.