UCSF
UC San Francisco Previously Published Works

Title
Outcomes of Low-Intensity Treatment of Acute Lymphoblastic Leukemia at Butaro Cancer Center of Excellence in Rwanda

Permalink
https://escholarship.org/uc/item/5q37r5f3

Journal
Journal of Global Oncology, 4(4)

ISSN
2378-9506

Authors
Rubagumya, Fidel
Xu, Mary Jue
May, Leana
et al.

Publication Date
2018-12-01

DOI
10.1200/jgo.2017.009290

Peer reviewed

Outcomes of Low-Intensity Treatment of Acute Lymphoblastic Leukemia at Butaro Cancer Center of Excellence in Rwanda

original report

Fidel Rubagumya

Mary Jue Xu

Leana May

Caitlin Driscoll

Frank Regis Uwizeye

Cyprien Shyirambere

Katherine Larrabee

Alexandra E. Fehr

Umuhizi Denis Gilbert

Clemence Muhayimana

Vedaste Hategekimana

Shekinah Elmore

Tharcisse Mpunga

Molly Moore

Lawrence N. Shulman

Leslie Lehmann

abstract

Purpose Children with acute lymphoblastic leukemia (ALL) in low-income countries have disproportionately lower cure rates than those in high-income countries. At Butaro Cancer Center of Excellence (BCCOE), physicians treated patients with ALL with the first arm of the Hunger Protocol, a graduated-intensity method tailored for resource-limited settings. This article provides the first published outcomes, to our knowledge, of patients with ALL treated with this protocol.

Methods This is a retrospective descriptive study of patients with ALL enrolled at BCCOE from July 1, 2012 to June 30, 2014; data were collected through December 31, 2015. Descriptive statistics were used to calculate patient demographics, disease characteristics, and outcomes; event-free survival was assessed at 2 years using the Kaplan-Meier method.

Results Forty-two consecutive patients with ALL were included. At the end of the study period, 19% (eight) were alive without evidence of relapse: three completed treatment and five were continuing treatment. Among the remaining patients, 71% (30) had died and 10% (four) were lost to follow-up. A total of 83% (25) of the deaths were disease related, 3% (one) treatment-related, and 13% (four) unclear. Event-free survival was 22% (95% CI, 11% to 36%), considering lost to follow-up as an event, and 26% (95% CI, 13% to 41%) if lost to follow-up is censored.

Conclusion As expected, relapse was the major cause of failure with this low-intensity regimen. However, toxicity was acceptably low, and BCCOE has decided to advance to intensity level 2. These results reflect the necessity of a data-driven approach and a continual improvement process to care for complex patients in resource-constrained settings.

J Glob Oncol 00. © 2017 by American Society of Clinical Oncology Licensed under the Creative Commons Attribution 4.0 License

BACKGROUND

Acute lymphoblastic leukemia (ALL) is the most common pediatric cancer worldwide.[1] In high-income countries, survival rates have drastically improved from < 30% to 90% in the past 50 years.[2-5] However, therapy remains challenging: most children require 2 to 3 years of ongoing therapy, and intensive supportive care is often needed during the early phases. In low- and middle-income countries (LMICs), conversely, survival rates remain poor—often < 35%.[6-10] This reflects many challenges, including gaps in implementation of care, delayed or incorrect diagnosis, comorbid conditions, lack of needed treatment components, increased relapse rates, abandonment of therapy, death from toxicity, and suboptimal supportive care.[1,8,11,12]

Monitoring ALL outcomes can provide a useful metric of a program's capacity to address delivery of complex longitudinal oncology care. Successful models for treating ALL in resource-limited settings have been reported in South America. For example, 5-year event-free survival (EFS) rates in a Brazilian hospital increased from 32% to 63% from 1980 to 2002 because of improvements in clinician training, patient social support, supportive care, and treatment availability and standardization.[13] Data on similar models in sub-Saharan Africa are limited, but a Tanzanian cohort of 81 patients following the United Kingdom Acute Lymphoblastic Leukaemia 2003 (UKALL2003) protocol had a 2-year EFS rate of 26%.[14] Obstacles included availability and affordability of chemotherapy and supply of blood products.

Located in northern rural Rwanda, Butaro Cancer Center of Excellence (BCCOE) is housed in the Ministry of Health's Butaro District Hospital and provides free cancer care in partnership with Partners In Health/Inshuti mu Buzima and the

Table 1. Disease Work-Up

Assessment	No.	%
No. of patients	42	
Pathology		
Bone marrow biopsy or aspirate	41	97.62
Biopsy, lymph node	3	7.14
Other biopsy	4	9.52
Imaging		
Chest x-ray	31	73.81
Abdominal ultrasound	12	28.57
CT chest	3	7.14
CT abdomen	2	4.76
Other		
CNS assessment (LP, CT brain, other)	1	2.38
Testicular examination		
Number of males	23	
Examinations documented	1	

Abbreviations: CT, computed tomography; LP, lumbar puncture.

Dana-Farber/Brigham and Women's Cancer Center. BCCOE has been described in greater detail elsewhere.[15,16] After a national consensus meeting in March 2012, BCCOE began treating patients with ALL in accordance with the graduated intensity regimen proposed by Hunger et al,[17] an approach developed specifically for low-resource settings. Treatment facilities begin with regimen 1, a low-intensity medication regimen, and advance to an increased medication regimen only after demonstrating that treatment-related toxicity is acceptably low (less than one death for every 25 patients). To our knowledge, no prior studies have reported on this regimen in a low-resource setting. Therefore, the objective of this study is to report the outcomes of using regimen 1 of the Hunger protocol on pediatric patients at BCCOE, as well as the quantitative measures of resource demands and delays in care.

METHODS

Setting and Treatment

During the study period, BCCOE treated 169 pediatric oncology patients, in whom ALL was the

Table 2. Duration Between Pathology Specimen and Report

Institution	No.	Median Days (IQR)
Overall, average per patient*	22	16 (8-26)
Brigham and Women's Hospital	18	21 (15-27)
Other pathology institutions	6	3.5 (3-5)

NOTE. As documented on pathology report.
*Some patients had reports from different institutions.

second most common diagnosis (after nephroblastoma). At the time of this study, BCCOE offered patients with ALL basic imaging (x-ray and ultrasound), laboratory tests, bone marrow biopsy, and pathology processing. In addition, social services covered costs for transportation and nutritional support. Pathologists at Brigham and Women's Hospital (Boston, MA) or Rwandan referral hospitals or visiting pathologists at BCCOE interpreted tissue specimens.

BCCOE used regimen 1 of the Hunger protocol, composed of vincristine, prednisone, cyclophosphamide, intrathecal methotrexate, 6-mercaptopurine, dexamethasone and L-asparaginase (Appendix Table A1). There is no anthracycline administered in level 1 of this protocol. Given health system limitations, patients were not uniformly evaluated for CNS involvement, bone marrow response to therapy, or prednisone response, factors often required for clinical risk stratification, but in regimen 1 all patients receive identical therapy. Most patients remained continuously hospitalized during induction and consolidation, given the frequent chemotherapy doses and associated adverse effects. On-site visiting Dana-Farber/Brigham and Women's Cancer Center nurses trained Rwandan nurses in chemotherapy preparation and management of patients with cancer. Radiotherapy was not included in the protocol, and currently there is no radiotherapy care available in Rwanda.

Data Management and Analysis

Data were collected for consecutive patients with ALL presenting at BCCOE from July 1, 2012 to December 31, 2015. Patients were identified and data were collected using the electronic medical records system OpenMRS; additional data were collected from patient charts using a structured chart abstraction form. Analysis was performed using STATA v12 (StataCorp, College Station, TX). This study was approved by the Rwanda National Ethics Committee, the Inshuti Mu Buzima Research Committee, and the Institutional Review Board at Partners Healthcare, Boston, Massachusetts.

Patients were considered to start a phase of treatment once the first chemotherapy agent was administered. A phase of treatment was considered complete if documented in the medical record. Documented treatment delays were those that postponed chemotherapy administration for any duration. Disease-related deaths were defined as occurring either before treatment began or after relapsed or refractory disease. Relapse was confirmed by clinical symptoms, derangement of CBC,

Table 3. Patient Demographics and Disease Characteristics

Demographic or Characteristic	No.	%
No. of patients	42	
Male	23	54.76
Age, years, median (range)		10.04 (0.38-0.35)
Country		
Rwanda	36	85.71
Burundi	6	14.29
Prior health facility		
Referral hospital	31	73.81
District hospital	5	11.90
Outside Rwanda	6	14.29
Prior chemotherapy		
Allopurinol and steroids	12	28.57
Steroids	7	16.67
Allopurinol	3	7.14
None	20	47.62
Duration of symptoms, weeks, median (IQR)	36	10.5 (4-20)
Presenting symptoms		
Lymphadenopathy	32	76.19
Fever	32	76.19
Malaise/fatigue	24	57.14
Bleeding	15	35.71
Infection	15	35.71
Weight loss	15	35.71
Arthralgia	10	23.81
Extramedullary involvement		
Lymphadenopathy	33	78.57
Splenomegaly	28	66.67
Hepatomegaly	23	54.76
Mediastinal mass	9	21.43
Immunophenotype		
B-cell	9	21.43
T-cell	8	19.05
Unknown	25	59.52
Reason leukemia type unknown		
Total	25	
Report unavailable	18	72.00
Subtype not reported	4	16.00
Technical issues	2	8.00
Sample of poor quality	1	4.00

Abbreviation: IQR, interquartile range.

and presence of blasts in the peripheral blood film after a period of remission. Refractory disease was defined as failure to achieve remission after completion of either induction or consolidation. The remaining deaths were deemed either treatment related (those after initiation of chemotherapy) or unclear (treatment failure clinically suspected but not confirmed before death). Loss to follow-up (LTFU) was strictly defined as missing the most recent appointment.

EFS from intake for all patients diagnosed with pathology was assessed at 2 years using the Kaplan-Meier method. This was calculated twice. First, events were death from any cause, relapsed disease, and LTFU. Second, events were death from any cause and relapsed disease; LTFU was right-censored.

RESULTS

Patient Demographics and Disease Characteristics

Fifty-four patients were evaluated or treated for ALL from July 1, 2012 to June 30, 2014. Diagnoses of eight patients were not pathologically confirmed before exiting the program, three patients had prior treatment presenting with relapsed or residual disease, and one patient was treated with an alternative protocol because of stroke. The remaining 42 patients had newly diagnosed, pathologically confirmed disease and were started on level 1 of the Hunger protocol at BCCOE.[17] Forty-two patients were evaluated with a new pathologically confirmed diagnosis of ALL (Tables 1 and 2). Median age was 10 years (range, 0.38 to 40.35 years), and 55% (23) of patients were male. Eighty-six percent (36) of patients lived in Rwanda, and 14% (six) lived in Burundi (Table 3). Seventy-nine percent were HIV negative, 5% were positive, and 17% had unknown HIV status. Seventy-four percent (31) were transferred to Butaro from national referral facilities. Before arriving at BCCOE, 29% (12) of patients received allopurinol and steroids (17% [seven] steroids, 7% [three] allopurinol), and 48% (20) of patients received no prior cancer-directed treatment.

Patients presented to BCCOE a median of 10.5 weeks (interquartile range [IQR], 4-20 weeks) after onset of symptoms, the most common of which were lymphadenopathy 76% (32), fever 76% (32), and malaise 57% (24). The most common extramedullary sites of involvement were lymph nodes 80% (33), spleen 67% (28), and liver 55% (23).

Disease immunophenotype was unknown for 60% (25) of patients, 21% (nine) had B-cell, and 19% (eight) had T-cell. In addition to subtype, other information, such as CNS involvement, was often unavailable (Tables 1 and 2). Using the limited information available for stratification, > 75% of

Fig 1. Treatment and patient events. (*) Started phase of induction, consolidation, and maintenance defined as having received chemotherapy. LTFU, lost to follow-up.
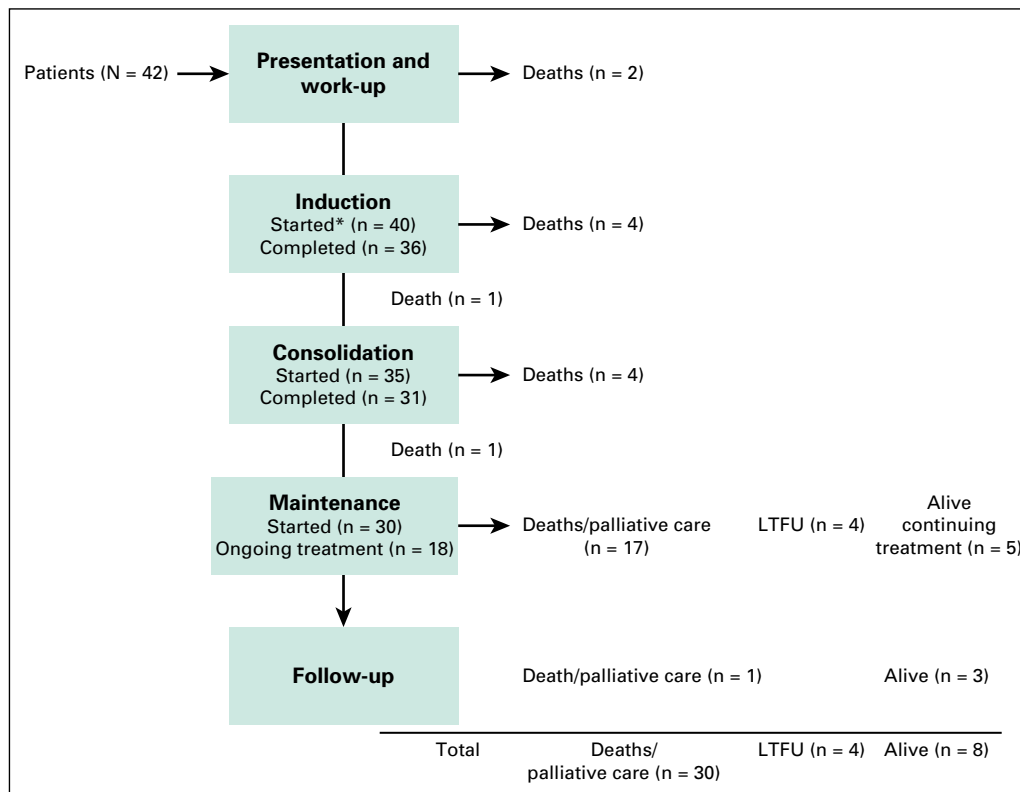
patients in the study would have been classified as high or very high risk (Appendix Table A5).

Treatment and Outcomes

Of the 42 patients who began therapy for ALL, 95% (40) initiated induction, 83% (35) consolidation, and 71% (30) maintenance (Fig 1). At the end of the analysis period, 19% (eight) of patients were alive without evidence of relapse: three completed treatment and were in follow-up and five were still receiving treatment. Seventy-one percent (30) had died, and 10% (four) were LTFU (Table 4). When LTFU was considered an event, estimated 2-year EFS was 22% (95% CI, 11% to 36%); when LTFU was right-censored, estimated 2-year EFS was 26% (95% CI, 13% to 41%). Overall, the median time from enrollment at BCCOE to time of event was 9 months (IQR, 2-19 months).

For patients alive at time of analysis, treatment duration was a median of 699.5 days (IQR, 577-1,168.5 days). Of the 30 deaths, 83% (25) were disease related (16 relapsed, seven were refractory, and two died before treatment initiation), 3% (one) were treatment-related, and 13% (four) were unknown. Deaths occurred throughout all phases of treatment, although concentrated in two periods: within the first 2 months after

presentation, and 6 to 8 months after initiation of therapy, most frequently during the first cycles of maintenance (Fig 2).

Resource Demands of Treatment

Even with this low-intensity approach, many resources were required to support these patients with ALL (Appendix Table A2). For the 42 patients evaluated before initiating therapy, 52% (22) required packed red blood cells and 43% (18) required platelets. Throughout, the median hemoglobin was 8.3 g/dL (IQR, 7.7-9.8 g/dL; n = 31) and the median platelet level was 25.5 × 10³/μL (IQR, 12-51 μL; n = 30). For the 40 patients who started induction therapy, 63% (25) required packed red blood cells and 50% (20) required platelets (Fig 3).

The most common cause of treatment delay was thrombocytopenia, present in 55% (23) of patients (Fig 3), and delayed platelet availability as products were transported from blood banks at offsite locations. Fluctuations in supply of two chemotherapy drugs, L-asparaginase and methotrexate, led to rescheduling of treatment cycles affecting care in 38% (16) of patients (Appendix Table A3). Medical-related delays included infections, neutropenia, elevated liver transaminases, neutropenic fever, and bleeding. Of note, delays resulting from

Table 4. Outcomes

Outcome	No.	%	Median Days (IQR)
No. of patients	42		
Status			
Alive	8	19.1	
Deceased*	30	71.4	
LTFU†	4	9.5	
Alive			
Total	8		
Continuing treatment	5		
Completed treatment	3		
Treatment duration‡			699.5 (577.0-1,168.5)
Causes of death			
Total	30		
Disease related	25		
Relapsed	16		
Refractory	7		
Before treatment	2		
Treatment related	1		
Unclear§	4		

Abbreviations: IQR, interquartile range; LTFU, lost to follow-up.

*Relapsed patients categorized under deceased.

†LTFU defined as missed most recent appointment; LTFU occurred for both patients during maintenance.

‡Treatment duration calculated from intake until December 31, 2014 (end of analysis period).

§Unclear deaths often occurred once patient started treatment but not due to relapse or refractory disease.

Fig 2. Censored event-free survival (EFS; N = 42). (A) Estimated 2-year EFS lost to follow-up (LTFU) as event: 22% (95% CI, 11% to 36%). (B) Estimated 2-year EFS LTFU censored: 26% (95% CI, 13% to 41%).

socioeconomic barriers to care were few (one from lack of money for transport and one from illness of the patient or family member). Socioeconomic-related delays, however, were likely not fully captured in this retrospective review.

DISCUSSION

ALL is the most common hematologic malignancy in children,[1] and the ability to provide care for patients with ALL is an essential component of oncology programs serving LMICs. However, given the duration of therapy, the recurrent periods of neutropenia, and the supportive care requirements, including transfusions and antibiotics, delivery of care requires a robust medical infrastructure. To our knowledge, our results represent the first published outcomes from a rural cancer center in a low-income country using the strategy proposed by the Hunger group[17] that restructures treatment into stratified levels of therapeutic intensities. This model recommends an initial, low-intensity regimen and data capture to assess the incidence of treatment-related deaths. Once care can be demonstrated to be safely provided, intensity of care can be increased.

We piloted this approach at BCCOE, a rural-based cancer center where care is provided by pediatricians, internists and general practitioners follow strict treatment protocols, and there is support from visiting on-site oncologists and regular remote support from affiliated oncologists. As expected, given the initial low-intensity and anthracycline-free regimen, relapse was the major cause of treatment failure and led to survival rates similar to the 26% estimated 2-year EFS and 8.1 month median survival of a Tanzanian cohort.[14] In North American cohorts, an estimated 5% to 25% of patients with ALL receive cranial radiation for treatment and prophylaxis of CNS lymphoma.[18] In our patient cohort, 53% of patients experienced relapse. Given this high relapse rate in patients receiving low-intensity treatment, it is likely the low-intensity treatment was insufficient for long-term survival. For some critically ill patients, the precise cause of mortality was difficult to determine when signs of infection coincided with treatment initiation. Nevertheless, definitive treatment-related toxicity was sufficiently low to advance to the next level of therapy per Hunger guidelines.[17]
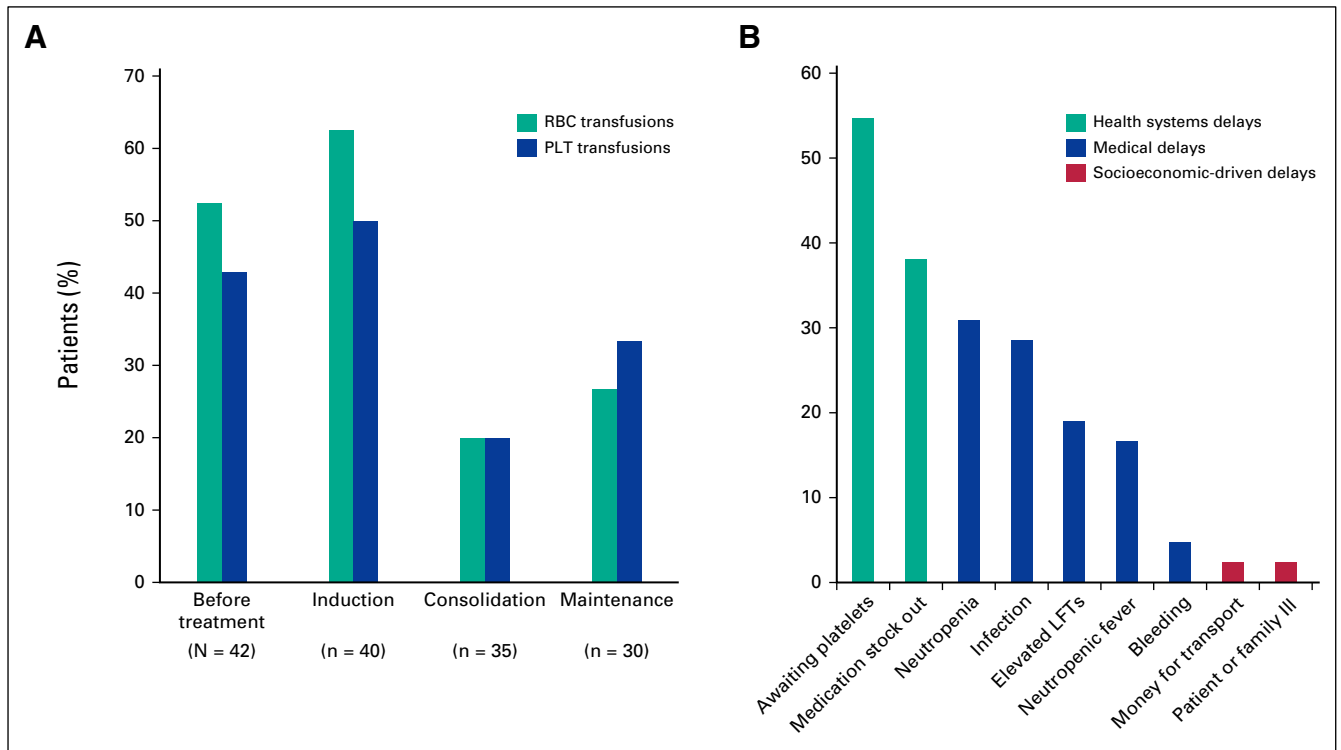
A

B
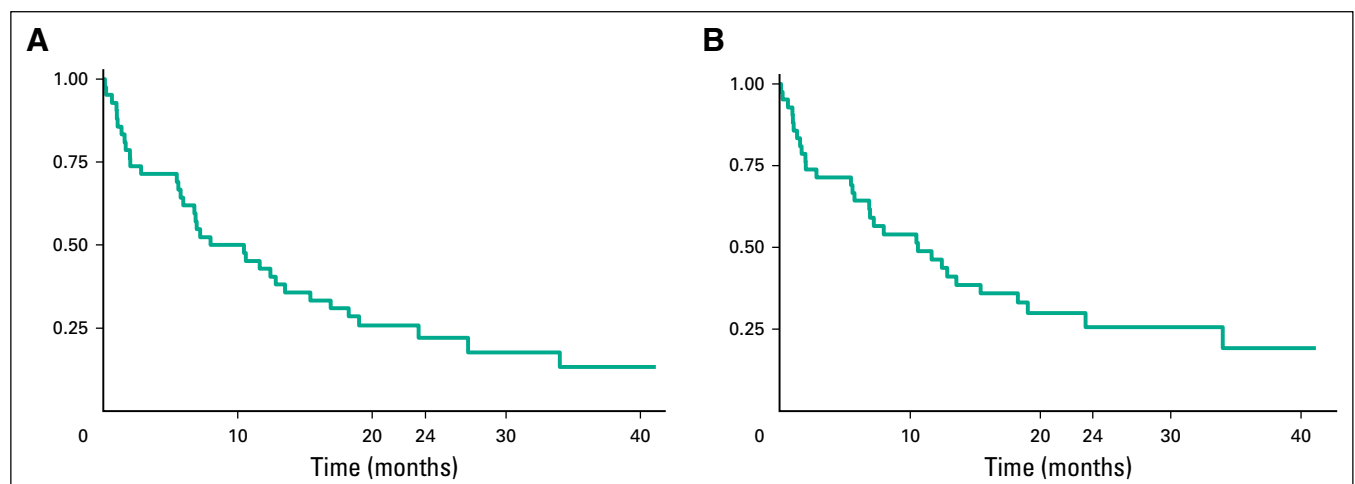
Fig 3. Treatment-related resource demands. (A) Patients requiring blood products. (B) Causes of chemotherapy delay (N = 42). LFTs, liver function tests; PLT, platelet.

Intensification of treatment, however, requires disease stratification, a challenge given the limited number of physicians, inconsistent access to CSF diagnostics, difficulties in reliably obtaining immunophenotyping, and delays in pathology reports (Tables 1 and 2).[8,14] In addition, the lack of in-country radiation therapy poses financial and operational challenges. When disease stratification can be achieved along with simultaneous training of hospital personnel, strengthening of supportive care, and standardizing of treatment regimens, outcomes can markedly improve, as was seen with the 63% 5-year EFS in Brazil.[13] This data-driven approach to improving care can only be achieved in the context of collecting and analyzing high-quality patient data, a challenge in all health care settings and particularly in a resource-constrained environment.

Treatment abandonment, often cited as a cause of treatment failure for patients with ALL, was uncommon at BCCOE. Although additional follow-up will be needed, the 10% lost to follow-up rate was modest compared with 35% in Indonesia[19] and 22% in El Salvador.[8] Patient social support, such as coverage of transportation and chemotherapy costs as provided at BCCOE, have helped in similar settings and have led to lower abandonment rates of 9% in Tanzania[14] and 0.5% in Brazil.[13] Given its mission to provide care to all patients, both social and clinical, BCCOE has also noted low levels of abandonment and delays in treating other cancers, such as nephroblastoma.[20]

In the presented approach to classifying delays, health system delays, such as waiting for blood products and availability of chemotherapy agents, were the most common in our patient population. Inconsistent sources for both blood products and some chemotherapy (Appendix Table A3) were major challenges. An estimated 8 million units of blood are needed in sub-Saharan African countries annually, and only 3 million units are collected.[21] At BCCOE, > 40% of patients who started treatment required transfusions; this drastically underscores the importance of a reliable system to provide supportive clinical care.[13,14,22] Quantitatively documenting this need could serve as a tool to predicting and planning for future transfusion needs in similar settings. Some minor lapses in availability of chemotherapeutics led to additional delays. Alterations in chemotherapy regimens because of lack of drug availability have led to poorer survival in both resource-rich and resource-constrained settings,[14,23] and, therefore, more accurate predictions and a reliable supply chain for ALL medications and transfusions has become a crucial goal at BCCOE.

In the context of Rwanda's dedication to providing cancer care, the Rwandan Ministry of Health has hosted regular national consensus meetings for cancer protocol development. The BCCOE clinical team presented these data at the pediatric protocol meeting in the spring of 2015. After reviewing the results, the committee supported intensifying

the national ALL treatment protocol, given the high relapse rate and acceptable treatment-related death rate. This data-driven approach that focuses particularly on resource demands of care is critical to patient outcomes in this and other resource-constrained settings.

In conclusion, this study details our experience treating patients with ALL in a rural Rwandan cancer center and to our knowledge reports the first published outcomes using the lowest intensity level of the Hunger ALL protocol. As expected with a low-intensity regimen, a high rate of disease-related mortality occurred, interestingly clustering in two time periods. However, treatment-related toxicity was below the threshold suggested for increasing treatment intensification. In addition to supplementing the limited literature on ALL care in sub-Saharan Africa, the quantification of transfusion needs and classification of treatment delays can be used to predict challenges to care in similar settings.

Overall, we have demonstrated that an iterative model of cancer care, delivered by nononcologists with remote oncological support, where implementation is followed by analysis of outcomes and subsequent evidence-based changes for improvement of care, allows for accountable delivery of ALL treatment in LMICs using the Hunger approach. We are now risk-stratifying patients and advancing to regimen 2 for high-risk patients after an intensive educational program for providers. These results point to the necessity of a data-driven approach to optimize care for complex patients in resource-constrained settings.

AUTHOR CONTRIBUTIONS

Conception and design: Fidel Rubagumya, Mary Jue Xu, Leana May, Caitlin Driscoll, Cyprien Shyirambere, Shekinah Elmore, Lawrence N. Shulman, Leslie Lehmann

Collection and assembly of data: Fidel Rubagumya, Mary Jue Xu, Caitlin Driscoll, Frank Regis Uwizeye, Katherine Larrabee, Umuhizi Denis Gilbert, Clemence Muhayimana, Vedaste Hategekimana, Molly Moore

Data analysis and interpretation: Fidel Rubagumya, Mary Jue Xu, Alexandra E. Fehr, Tharcisse Mpunga, Lawrence N. Shulman, Leslie Lehmann

Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

Affiliations

Fidel Rubagumya, Muhimbili University of Health and Allied Sciences, Dar es Salaam, Tanzania; **Mary Jue Xu**, University of California, San Francisco, San Francisco, CA; **Leana May**, Children's Hospital Colorado, Aurora, CO; **Caitlin Driscoll**, Mount Sinai Medical School, New York, NY; **Frank Regis Uwizeye**, **Cyprien Shyirambere**, and **Alexandra E. Fehr**, Inshuti Mu Buzima/Partners In Health; **Umuhizi Denis Gilbert**, **Clemence Muhayimana**, **Vedaste Hategekimana**, and **Tharcisse Mpunga**, Ministry of Health, Kigali, Rwanda; **Katherine Larrabee**, Geisinger Commonwealth School of Medicine, Scranton; **Lawrence N. Shulman**, University of Pennsylvania, Philadelphia, PA; **Shekinah Elmore**, Harvard Radiation Oncology Program; **Leslie Lehmann**, Dana Farber Cancer Institute; Boston Children's Hospital, Boston, MA; and **Molly Moore**, University of Vermont, Burlington, VT.

REFERENCES

1. Kellie SJ, Howard SC: Global child health priorities: What role for paediatric oncologists? Eur J Cancer 44:2388-2396, 2008

2. Howlader N, Noone AM, Krapcho M, et al (eds): SEER Cancer Statistics Review, 1975-2009 (Vintage 2009 Populations), National Cancer Institute. http://seer.cancer.gov/csr/1975_2009_pops09/

3. Hunger SP, Lu X, Devidas M, et al: Improved survival for children and adolescents with acute lymphoblastic leukemia between 1990 and 2005: A report from the children's oncology group. J Clin Oncol 30:1663-1669, 2012

4. Conter V, Bartram CR, Valsecchi MG, et al: Molecular response to treatment redefines all prognostic factors in children and adolescents with B-cell precursor acute lymphoblastic leukemia: Results in 3184 patients of the AIEOP-BFM ALL 2000 study. Blood 115:3206-3214, 2010

5. Tsuchida M, Ohara A, Manabe A, et al: Long-term results of Tokyo Children's Cancer Study Group trials for childhood acute lymphoblastic leukemia, 1984-1999. Leukemia 24:383-396, 2010

6. Wagner HP, Antic V: The problem of pediatric malignancies in the developing world. Ann N Y Acad Sci 824:193-204, 1997

7. Metzger ML, Howard SC, Fu LC, et al: Outcome of childhood acute lymphoblastic leukaemia in resource-poor countries. Lancet 362:706-708, 2003

8. 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 22:495-501, 2000

9. Pedrosa F, Bonilla M, Liu A, et al: Effect of malnutrition at the time of diagnosis on the survival of children treated for cancer in El Salvador and Northern Brazil. J Pediatr Hematol Oncol 22:502-505, 2000

10. Ribeiro RC, Bonilla M: A leukaemia treatment programme in El Salvador. Lancet 356:s7, 2000 (suppl)

11. Campbell M, Salgado C, Quintana J, et al: Improved outcome for acute lymphoblastic leukemia in children of a developing country: Results of the Chilean National Trial PINDA 87. Med Pediatr Oncol 33:88-94, 1999

12. Magrath I, Shanta V, Advani S, et al: Treatment of acute lymphoblastic leukaemia in countries with limited resources; lessons from use of a single protocol in India over a twenty year period [corrected]. Eur J Cancer 41:1570-1583, 2005

13. Howard SC, Marinoni M, Castillo L, et al: Improving outcomes for children with cancer in low-income countries in Latin America: A report on the recent meetings of the Monza International School of Pediatric Hematology/Oncology (MISPHO)-Part I. Pediatr Blood Cancer 48:364-369, 2007

14. Kersten E, Scanlan P, Dubois SG, et al: Current treatment and outcome for childhood acute leukemia in Tanzania. Pediatr Blood Cancer 60:2047-2053, 2013

15. Shulman LN, Mpunga T, Tapela N, et al: Bringing cancer care to the poor: Experiences from Rwanda. Nature Reviews Cancer (London) 14:815-821, 2014

16. Tapela NM, Mpunga T, Hedt-Gauthier B, et al: Pursuing equity in cancer care: Implementation, challenges and preliminary findings of a public cancer referral center in rural Rwanda. BMC Cancer 16:237, 2016

17. 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 52:559-565, 2009

18. Pui CH: Central nervous system disease in acute lymphoblastic leukemia: Prophylaxis and treatment. Hematology (Am Soc Hematol Educ Program) 2006:142-146, 2006

19. Mostert S, Sitaresmi MN, Gundy CM, et al: Influence of socioeconomic status on childhood acute lymphoblastic leukemia treatment in Indonesia. Pediatrics 118:e1600-e1606, 2006

20. Shyirambere C, Xu MJ, Elmore SN, et al: Treating nephroblastoma in Rwanda: Using International Society of Pediatric Oncology guidelines in a novel oncologic care model. J Glob Oncol 2:105-113, 2016

21. Bloch EM, Vermeulen M, Murphy E: Blood transfusion safety in Africa: A literature review of infectious disease and organizational challenges. Transfus Med Rev 26:164-180, 2012

22. Gupta S, Antillon FA, Bonilla M, et al: Treatment-related mortality in children with acute lymphoblastic leukemia in Central America. Cancer 117:4788-4795, 2011

23. Metzger ML, Billett A, Link MP: The impact of drug shortages on children with cancer—The example of mechlorethamine. N Engl J Med 367:2461-2463, 2012

Table A1. Regimen 1

Drugs	Dose	Duration
Induction (4 weeks)		
Prednisone prophase	60 mg/m^2/d	Days 1-7
Prednisone	40 mg/m^2/d	Days 8-29
Vincristine	1.5 mg/m^2	Days 8, 15, 22, 29
L-asparaginase	6,000 IU/m^2 × 3 weeks starting at day 8	
Extra IT MTX on days 15, 22 if CNS3		
Consolidation (4 weeks)		
Vincristine	1.5 mg/m^2	Day 1
6-mercaptopurine	75 mg/m^2	Day 1-28
IT MTX days 1, 8, 15		
Maintenance (84-day cycles until 30 months from start of therapy)		
Dexamethasone	6 mg/m^2/d	Days 1-5, 29-33, 57-61
Vincristine	1.5 mg/m^2	Days 1, 29, 57
6-mercaptopurine	75 mg/m^2	Days 1-84
MTX	20 mg/m^2	Starting day 1

IT MTX Days 1, 29 for first four cycles then day 1 only (omit oral MTX when IT MTX given)

Abbreviations: IT, intrathecal; MTX, methotrexate.

Table A2. Resource Availability, 2012 to 2014

Resource	Availability
Diagnostics	
X-ray	Consistently available at BCCOE
CT	Usually available at CHUK and KFH
MRI	Not requested but available at KFH
CBC	Consistently available at BCCOE, daily
Chemistry panel	Consistently available at BCCOE, daily
Peripheral blood morphology	Could be done but no hematologist to read
Bone marrow morphology	Consistently available at BWH, BCCOE, CHUK with average delay of 4-6 weeks
Immunophenotype	Intermittently reported by BWH
CSF cytology	Not available
Supportive care	
Whole blood transfusions,	Intermittently available at Transfusion Center, with delays of days
Platelet transfusions	Intermittently available at Transfusion Center, with delays of days
Fresh frozen plasma	Intermittently available at Transfusion Center
Ketoconazole, amphotericin,	Consistently available at BCCOE, at patient expenses
Trimethoprim/sulfamethoxazole, ceftriaxone, gentamicin	Consistently available at BCCOE, at patient expenses
Cancer therapeutics	
Bone marrow transplant	Not available
Radiation therapy	Not Available
Dexamethasone	Consistently available at BCCOE, free of charge
Vincristine	Consistently available at BCCOE, free of charge
Methotrexate	Consistently available at BCCOE, free of charge
6-mercaptopurine	Consistently available at BCCOE, free of charge
Cyclophosphamide	Consistently available at BCCOE, free of charge
Cytarabine	Not available
L-asparaginase	Usually available at BCCOE, free of charge
Etoposide	Consistently available at BCCOE, free of charge
Prednisolone	Consistently available at BCCOE, free of charge
Staffing	
Nursing:patient ratio	1:15 in day, 1:30 at night
Pediatrician	Consistently available at BCCOE, mentored remotely by DFCI pediatric oncologist
Social worker	One available for all cancer wards and outpatients at BCCOE
Facilities	
Radiology	Available at BCCOE
Pediatric ICU	Not available
Housing for caregivers/family	Not available
Food packages	Available at BCCOE: given by PIH
Transport	Available at BCCOE: given by PIH

Abbreviations: BCCOE, Butaro Cancer Center of Excellence; CHUK, University Central Hospital of Kigali (a public teaching hospital in the capital city); CT, computed tomography; DFCI, Dana-Farber Cancer Institute; ICU, intensive care unit; KFH, King Faisal Hospital (a private hospital in the capital city); MRI, magnetic resonance imaging; PIH Partners In Health.

Table A3. Medication Stock Out

Medication	No. of Patients Whose Chemotherapy Was Delayed by Medication Unavailability
Stock out	16 (38.1%)
IT MTX	10
PO MTX	3
L-asparaginase	4
VCR	1

Abbreviations: IT, intrathecal; MTX, methotrexate; PO, orally; VCR, vincristine.

Table A4. Limited Stratification

Lower Risk	Higher Risk	Very High Risk
B-precursor ALL and age 1.00-9.99 years and initial WBC count < 50,000/μL and prednisone good response and CNS 1 or CNS 2 and day 15 M1/M2 marrow and day 29 M1 marrow	CNS 1 or CNS 2 **and T-cell ALL and WBC count < 100,000/μl OR** CNS 1 or CNS 2 **and B-precursor ALL with age < 1 or > 9.99 years or WBC count > 50,000/μL** and prednisone good response and day 15 M1/M2 marrow and day 29 M1 marrow	Prednisone poor response or CNS3 **or T-cell ALL and WBC count > 100,000/μL or** day 15 M3 marrow or day 29 M2/M3 marrow

NOTE. Bold factors were included in stratification; regular factors were not included because of unavailable/ limited information.
Abbreviation: ALL, acute lympholastic leukemia.

Table A5. Butaro ALL Patients (N = 42)

Risk	N	%
Standard	6	14.29
High	9	21.43
Very high	2	4.76
Unclassified	25	59.52
Could be standard, pending ALL type	5	11.90

NOTE. 75% to 85% of patients would be high or very high risk per Hunger protocol.
Abbreviation: ALL, acute lympholastic leukemia.