Treatment of Children with Acute Lymphoblastic Leukemia in Cambodia

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Abstract

Background. The treatment of childhood acute lymphoblastic leukemia (ALL) remains challenging in low-income countries. Here we evaluate the experience with a modified Berlin-Frankfurt-Münster (BFM) treatment protocol ALL-Moscow Berlin (MB)-91 at the Kantha Bopha hospitals, a charity-funded institution providing free pediatric care in Cambodia. Methods. This is a retrospective study including 110 unselected patients aged 9 months to 14 years diagnosed with ALL between 2015 and 2017. Patients were stratified in high- (HR) and standard-risk (SR) groups based on clinical criteria. The cumulative doses of anthracyclines were reduced to 120 mg/m2 for SR patients and consolidation was based on Capizzi methotrexate elements instead of cyclophosphamide, cytarabine and high dose methotrexate. Supportive empiric antibiotic treatment and whole blood transfusions were possible. Results. 63 patients (57 %) were HR, mostly based on high leukemia burden with hyperleukocytosis $>$ 50 G/l, massive lymph node and hepato-splenic involvement, reflecting a high disease burden. 72 patients (65.5%) reached complete remission (CR) on day 36. The estimated 3-year overall survival (OS) was 34.9 %, 50.5 % for SR and 23.4 % for HR patients. Most events were due to severe infections (40 (53.3 %)) and bleeding (15 (20 %)), mostly during induction and consolidation. Relapse was confirmed in 13 cases (11.8 %). No patients abandoned treatment. Conclusion. ALL chemotherapy is feasible in a charity-funded public institution with results comparable to other low-middle income countries, but treatment-related mortality remains limiting. This will justify investments in diagnostics to stratify more patients for reduced intensity treatment and in supportive care.

INTRODUCTION

Acute lymphoblastic leukemia (ALL) is the most common malignant disease diagnosed in children, with a prevalence of up to 26 % of all childhood malignant diseases in patients under the age of 15 [1]. While the survival rate in 1960 was only a few percent, outcome was improved successively with the development of combination chemotherapy in successive cooperative clinical trials, resulting in long term survival in over 90% of children today [2]. This progress is based on treatment optimization trials with risk-adapted treatment, on leukemia biology and response to treatment. Furthermore, supportive care was improved, in particular prevention and treatment of severe infections. Additionally, treatment was intensified such as including consolidation with stem cell transplantations (SCT)[3]. However, 70 % of children in the world live in low income countries, where the development of effective leukemia therapy remains very challenging, given the limitations in infrastructure, resources, trained personnel and thus access to care, with outcomes that are often still lower than 35% [4]. Furthermore, it is also estimated that less than 60% of children worldwide even

have access to cancer treatment [5]. There is a lot of data available about childhood ALL in Europe and in the USA, but comparable data from most Asian countries, especially from low and lower-middle income countries like Cambodia, is still scarce even though it is estimated that there are 54 000 new ALL cases per year in Asia[6]. The health care system in Cambodia has only limited resources (Yeoh et al., 2014) and gaining access to a hospital is often difficult financially and geographically. For 30 years the Kantha Bopha Foundation has provided free health care in 5 hospitals in two locations to an estimated 85 % of all Cambodian children. Based on the development of available expertise, including laboratories for infectiology and hematology with the possibility to perform whole blood transfusions and a dedicated staff, ALL therapy was introduced based on a treatment protocol with a moderate reduction of treatment intensity for all patients [7] in one central location in Phnom Penh. Here, we analyze the results of this treatment regimen over a period of three years with sufficient follow-up time as a basis for further development for pediatric oncology care.

METHODS

Patients

A total of 110 patients were included in this retrospective study. The age range was from 9 months to 14 years. All patients that were diagnosed with ALL between 2015-2017 at the Kantha Bopha II hospital in Phnom Penh were included. They had not received previous treatment, except for one patient who was transferred from Vietnam after the initial diagnosis. Parental consent was obtained in all cases before the start of treatment. Data was obtained with case report forms (CRF) by trained staff from the leukemia treatment team and provided for analysis in an anonymized format. A waiver was obtained to perform the study from the ethical committee of the Kanton of Zurich with this anonymized dataset.

Diagnosis

The diagnosis of ALL and follow-up were performed based on bone marrow morphology only and required the presence of at least 25 % lymphoblasts. Bone marrow aspiration was performed under sterile conditions on the anterior superior iliac spine. Immunophenotyping and genetic analysis were not available. Further diagnostics included complete differential blood count and chemistry, cytospins of the cerebrospinal fluid, a chest x-ray, an abdominal ultrasound, an echocardiography and CT scan of the brain. Bone marrow examinations were performed on day 0/1, day 36 and week 32.

Treatment

Patients were uniformly treated on a modified protocol based on the ALL-MB 91 protocol, as detailed in table 1. This protocol was developed by professor Günther Henze for the treatment of patients in Russia at a time when less than 10 percent of children with ALL were surviving with the aim to reduce toxicity in consolidation treatment and costs, without affecting overall survival (OS) [7]. Compared to the BFM protocol that was broadly used in Europe, the dose of anthracyclines was reduced in induction and in consolidation. In consolidation Capizzi methotrexate courses were introduced to replace the high-dose methotrexate elements of the BFM protocol. Furthermore, preventive radiation of the central nervous system (CNS) was only performed in high-risk patients. Instead, triple intrathecal chemotherapy with methotrexate, cytarabine and prednisone was administered. The main difference of the protocol used in Cambodia was the suppression of cranial radiation therapy. Also, a cumulative dose of daunorubicin of 120 mg/m^2 was given to patients with standard risk (SR, see below) which was more than the SR arm of the ALL-MB-91 protocol (45 mg/m^2, only one dose during induction), but a reduction of half of the cumulative dose compared to the standard BFM protocol [7]. Compared to current ALL protocols, this regimen did neither include cyclophosphamide nor cytarabine and used non-pegylated asparaginase to reduce costs.

Risk stratification

Patients were enrolled in the high risk (HR) group if they had an initial white blood cell (WBC) count of $>$ 50 000/ul, were aged $<$ 1 year or $>$ 10 years, had initial CNS-involvement, had a mediastinal mass on the initial chest x-ray, had more than 1000 lymphoblasts/mm^3 in the peripheral blood after the first week of monotherapy or no remission in the bone marrow after induction on day 36. All other patients were

stratified into the SR group (table 2). The main differences in the treatment between the two groups were additional applications of daunorubicin during induction and maintenance and higher doses of cytarabine in the intrathecal therapy during induction, consolidation and maintenance in the HR group.

Supportive care

Pneumocystitis jirovecii prophylaxis with sulfamethoxazole/trimethoprim was routinely administered during the whole treatment time. In case of neutropenia prophylactic fluconazole p.o. was given. In case of febrile neutropenia, standard laboratory values were assessed, blood and urine cultures were extracted and a chest x-ray examination was performed. Patients were empirically treated with ofloxacin 10 mg/kg, ceftriaxone 100 mg/kg or augmentin 80-100 mg/kg. Dependent on the antibiogram meropenem 60 mg/kg or ceftazidime 100-120 mg/kg were added. Guidelines were provided for hyperleukocytosis and acute tumor lysis syndrome. Whole blood transfusions were only given if hemoglobin was < 7 g/dl. Platelet transfusions were not available.

Statistical analysis

Complete remission (CR) was defined as less than 5% lymphoblasts in active hematopoietic marrow, absence of leukemic cells in peripheral blood, absence of leukemic cells in cerebrospinal fluid or absence of leukemic infiltrates elsewhere in the body after induction chemotherapy. Resistant disease was defined as failure to achieve CR. Relapse was defined (see protocol for more details) as recurrence of leukemic blasts at any involvement site. Treatment abandonment was defined as the treatment stop due to any reason except for death. CNS involvement was defined by the presence of leukemia cells and more than 5 nucleated cells per microliter cerebrospinal fluid (CNS 3).

Event-free survival was defined as the time from diagnosis to the date of last follow-up or first event. Events were nonresponse, relapse, or death from any cause. Failure to achieve remission due to death before complete remission or nonresponse was considered as event at time 0. Overall survival was defined as the time from diagnosis to the date of last follow-up or death. The Kaplan-Meier method was used to estimate survival rates; differences between groups were compared with the log-rank test. Standard error (SE) is provided for all estimates. Statistical analysis was done using GraphPad Prism 8 (GraphPad software) and SAS 9.4 (SAS Institute, Cary, NC).

RESULTS

Patient characteristics

Over a period of three years, we included 110 patients with ALL in the study. The patient characteristics are shown in table 3. The median age at diagnosis was 4.8 years, 23 patients (20.9 %) were older than 10 years and 2 patients (1.8 %) were infants under 1 year. The male to female ratio was 1.39, with 64 male patients (58.2 %) and 46 female patients (41.8 %). A higher male to female ratio was also reported for a large cohort in Southeast Asia [8] and by the European BFM Study group [9].

The median white blood cell (WBC) count at diagnosis was 40.65 x 10^9/l (interquartile range (IQR), 10 – 105.95 x 10^9/l). Fifty-three patients (48.2 %) initially had a WBC count of more than 50 x 10^9/l, from the latter, 29 patients (26.4 %) suffered from hyperleukocytosis with a WBC count over 100 x 10^9/l, which is more than two fold more frequent than in European patient populations [9] and in a large South Asian cohort [8]. This supports the clinical impression that patients present late at the hospital with a high disease burden. Consistently, the majority of patients, 63 (57.3 %) was stratified into the HR group, mostly based on the high leukemia burden, whereas 47 patients (42.7 %) were allocated to the SR group.

The major extramedullary disease manifestations were liver and spleen enlargement in 80.9 % of patients and nodal involvement in 57.3%. 104 patients (94.5 %) were anemic at the time of diagnosis (hemoglobin (HGB < 11 g/dl), the median HGB was 7.5 g/dl. CNS involvement was detected in 3 patients (2.7%), which is within the expected range.

Outcome

The outcome and time to death is reported in table 4. Of the 110 patients included in this analysis, 72 (65.5 %) reached complete remission (CR) by day 36, 7 (6.4 %) did not reach CR by day 36 and the remaining 31 (28.2 %) patients died before the second bone marrow examination. Because in many instances death was attributed to infection and bleeding, the documentation of the disease state with a bone marrow was not always performed. We therefore focused our analysis on the estimated 3 year OS, which for the whole patient cohort was 34.9 % (SE = 4.6), as illustrated in (Fig 1A).

As expected, the estimated 3 year OS was significantly higher for the 47 patients allocated to the SR group with 50.5% (SE = 7.4) compared to the HR group (23.4 % (SE = 5.4)) (p = 0.012). It is important to note that the majority of all patients (57. 3%) was stratified into the HR group, mostly due to their initial high WBC count or age > 10 years. Estimated 3 year OS was best (51.5% (SE = 7.1)) for patients younger than 10 years with a WBC count under 50 x 10^9/l and worst (6.3 % (SE = 6.1)) for patients 10 years or older with a WBC count of 50 x 10^9/l or more, which were significant differences (p = 0.011), as described in (Fig 1B).

Cause of Death/Toxicity

Out of the overall 75 deaths, most patients died either during induction (29 (38.7 %)) or consolidation (27 (36 %)). Thirteen patients (17.3 %) died during maintenance and 6 patients (8 %) died after the end of the treatment.

The cause of death during induction and consolidation was in all 56 patients due to treatment related toxicity, mostly due to infections and bleeding. During induction, 17 patients (15.5 %) died of infection, 11 (10 %) of bleeding and 1 (0.9 %) of a combination of the two. During consolidation, 18 patients (16.4 %) died of infection, 3 (2.7 %) of bleeding and 6 (5.5 %) died of a combination of infection and bleeding. During maintenance and after the end of treatment, a total of 5 patients (4.5 %) died of infection, 1 (0.9 %) of bleeding and 13 (11.8 %) due to relapse.

Relapse could not be treated given the limitations in this context. Treatment was stopped in 2 (1.8 %) patients after the diagnosis of a relapse while on therapy.

Information about bleeding and infection events is provided in table 5. Bleeding occurred mostly in the central nervous system (7) and the gastrointestinal tract (15). The main type of infection was mostly pneumonia (17), or unknown but was clinically evaluated as a severe systemic infection (13). In 22 out of 47 infections (46.8 %) a pathogen could be isolated. The isolated pathogens were mostly Escherichia coli (15) or Klebsiella pneumoniae (6). Two cases of a Cryptococcus neoformans infection were registered, as well as one case of Pseudomonas aeruginosa, and one of Pneumocystis jirovecii.

DISCUSSION

The introduction of effective treatment for childhood leukemia in a lower-middle income country is challenging. Reports from Southeast Asia illustrate limiting factors such as infectious and bleeding complications in a program established in neighboring Laos[10]. In Indonesia high rates of treatment refusal were documented already before and during induction chemotherapy due to socio-economical limitations [11], but also difficulty to cope with treatment toxicity and pessimism with respect to chances of cure are furthermore reported [12] . Similar observations were made in Latin America with almost 50 % of events due to abandoned of treatment or treatment related toxicity[4]. However, encouraging examples have been reported in lower-middle income countries in Central America using a BFM-adapted treatment protocol in five countries achieving an overall 3 year survival rate of 68 % and an event free survival rate of 59 % including treatment abandonment [13]. In Vietnam, 5 year relapse-free survival was 47.8 % using a French protocol (FRALLE 2000), excluding patients who had abandoned treatment. Furthermore, only children from families that could afford treatment costs could be included [5]. The approach of the Kantha Bopha Foundation was to provide free care building on trained Cambodian personnel and infrastructure. Taking the reported incidence for Europe of 46.7 cases of ALL per million children under 15 years old, and given that 31.9% of the 16.7 million Cambodian population is aged under 15 years, we estimate that we could likely reach about one sixth of the children with ALL in

the country. In this setting, a slightly modified version of the protocol ALL-MB91, combining treatment elements from the BFM and Dana-Farber consortia was used, with the intention to provide a moderately toxic regimen in a context in which the control of infections was expected to be a major limitation. Analyzing a most recent three-year period (2015-2017), we show that the estimated 3-year overall survival of 110 patients was 34.9%. These patients remained disease-free. We documented a total of 13 relapses in this cohort, but this may underestimate the number of relapses hidden in other lethal complications. In this unselected population, adherence to first line treatment was remarkable. No family abandoned treatment. The experience in Russia, where the protocol was initially established, showed that an event-free survival of 67 % could be achieved with this protocol under challenging socio-economic conditions [7]. In Cambodia, more than half of the patients presented with a large leukemia burden, which is likely explained by a very delayed access to care. Importantly, in patients with a lower leukemia burden, overall and disease-free survival was 50.5 %, implicating that education of care providers and early access to diagnostic testing is of great importance. Furthermore, malnutrition was also expected to impact treatment related morbidity as discussed in ALL studies in India [14].

The majority of events in our cohort included infections and bleeding complications. Despite a reduction of treatment intensity compared to ALL protocols in high-income countries, SR patients were still exposed to total of 8 weeks of 6 mg/m^2 dexamethasone and 8 additional 2-day pulses during maintenance, and to cumulative 120 mg/m^2 of daunorubicin. In a similar geographical region, but with a better financial background, a modified BFM-ALL treatment was developed for Malaysia and Singapore, with a risk-stratification based on molecular minimal residual disease. In this study [8], non-HR patients (85.8% of all patients) were treated without anthracyclines in induction and with cumulative 60 mg/m^2 doxorubicin in reinduction. They were exposed to a total of 6 weeks of 6 mg/m^2 dexamethasone after one week of a prednisone pre-phase and obtained up to 6 pulses with 6mg/m^2 dexamethasone for 7 days during maintenance. Treatment related complications occurred at similar rates compared to major protocols in the US and in Europe. Only 17 (3 %) non-HR patients died of a lethal infection. Six-year EFS was 80.6% on this protocol. SR patients despite significant deintensification of the chemotherapy had an EFS of 93%, which provides first strongest evidence that a massive reduction of anthracyclines is possible without compromising outcome for most of the patients. This concept is further supported by 2 studies in Brazil and Egypt, developed in cooperation with the St. Judes Children's Research Hospital, where patients with very-low-risk ALL based on their response to induction were treated with a low-intensity regimen including a maximum of 50 mg/m^2 of doxorubicin. In both studies, 5 year-overall survival was estimated over 95%[15,16].

Clearly, further reduction of both anthracyclines and glucocorticoids will have to be implemented in our treatment strategy in Cambodia.

In order to reduce treatment intensity, an affordable diagnostic set up will have to be established to reliably identify patients with favorable leukemia biology. Introduction of flow cytometry (FCM) with a robust panel to diagnose and follow ALL is warranted. FCM was shown to identify most HR patients based on response to treatment at day 15 on a BFM regimen [17]. FCM was successfully used to risk-stratify patients for low-intensity chemotherapy in the studies that we mentioned above [15,16]. This readout can be achieved at reasonable costs. Improvement of genetic- and molecular classification will hardly be affordable in the current setting. However, polymerase chain reaction (PCR) based multiplex ligation-dependent probe amplification may provide a robust way to determine gene copy number variations. With this approach, a classifier was established and validated recently across a number of different ALL study cohorts that enables to detect patients with favorable risk cytogenetics readily[18]. Thus it is feasible to improve risk stratification with the introduction of affordable technology in order to reduce treatment intensity for most patients.

To reduce treatment related mortality supportive care is also of central importance. In this cohort bacterial infections during aplasia under chemotherapy pose the predominant problem. Empirical treatment of febrile neutropenia should be revisited according to recent guidelines[19]. The option of antibiotic prophylaxis may possibly be considered during induction chemotherapy. For the reduction of bleeding complications, fractionation of platelets will have to be introduced, the key infrastructure being available on site.

In the near future, promising CD-19 and CD-22 directed immunotherapy could be explored in a first line setting where patients may clearly benefit most from reduction of treatment intensity. The chemoimmunotherapeutic inotuzumab ozogamicin shows promising results in elderly patients with ALL and the CD19-directed bispecific monoclonal antibody blinatumomab markedly improved outcome in children with relapsed ALL, with a clear reduction of treatment related toxicity in the bridge to stem cell transplantation [20]. There is a strong interest to develop clinical studies also in this region of the world with the aim to reduce toxicity of chemotherapy by replacing it at least in part by immunotherapy. The current focus in Cambodia remains to tailor an even less intensive chemotherapy backbone and to integrate the team into an international working group in the region, possibly together with experts of St. Jude VIVA forum to foster the development of pediatric oncology in Cambodia.

In conclusion, our retrospective analysis shows that the introduction of a complex chemotherapy protocol is feasible in the context of a charity-funded public institution in Cambodia but also underscores current socio-economical, geographical and institutional limitations. The outcome for patients with SR ALL is very encouraging. Our data provide the basis to justify modifications of the treatment strategy and major investments in supportive care to improve outcome for children with leukemia in Cambodia. We will aim at a further reduction of treatment intensity for non-HR patients and optimization of supportive care.

CONFLICT OF INTEREST STATEMENT

The authors declare no potential conflicts of interest.

REFERENCES

1. Howlader N, Noone AM, Krapcho M, et al. *SEER Cancer Statistics Review, 1975-2016.* ; 2019.

2. Stephen P. Hunger, M.D., and Charles G. Mullighan MD. Acute Lymphoblastic Leukemia in Children. *N Engl J Med* . 2015;373:1541-1552.

3. Kiem Hao T, Nhu Hiep P, Kim Hoa NT, Van Ha C. Causes of Death in Childhood Acute Lymphoblastic Leukemia at Hue Central Hospital for 10 Years (2008-2018). *Glob Pediatr Heal* . Published online 2020.

4. Metzger ML, Howard SC, Fu LC, et al. Outcome of childhood acute lymphoblastic leukaemia in resource-poor countries. *Lancet* . Published online 2003.

5. Hoang PTV, Ambroise J, Chi VLD, et al. Comparison of long-term outcome between white and Vietnamese children treated for acute lymphoblastic leukemia according to the FRALLE 2000 protocol. *J Pediatr Hematol Oncol* . Published online 2014.

6. Yeoh A, Tan D, Li C-K, Hori H, Tse E, Pui C-H. Oncology Summit 2013.*Lancet Oncol* . Published online 2014.

7. Karachunskiy A, Herold R, von Stackelberg A, et al. Results of the first randomized multicentre trial on childhood acute lymphoblastic leukaemia in Russia. *Leukemia* . 2008;22(6).

8. Yeoh AEJ, Ariffin H, Chai ELL, et al. Minimal residual disease-guided treatment deintensification for children with acute lymphoblastic leukemia: Results from the Malaysia-Singapore acute lymphoblastic leukemia 2003 study. *J Clin Oncol* . Published online 2012.

9. Möricke A, Reiter A, Zimmermann M, et al. Risk-adjusted therapy of acute lymphoblastic leukemia can decrease treatment burden and improve survival: Treatment results of 2169 unselected pediatric and adolescent patients enrolled in the trial ALL-BFM 95. *Blood* . Published online 2008.

10. Park KD, Hong CR, Choi JY, et al. Foundation of pediatric cancer treatment in Lao People's Democratic Republic at the Lao-Korea National Children's Hospital. *Pediatr Hematol Oncol* . Published online 2018.

11. Mostert S, Sitaresmi MN, Gundy CM, Sutaryo, Veerman AJP. Influence of socioeconomic status on childhood acute lymphoblastic leukemia treatment in Indonesia. *Pediatrics* . Published online 2006.

12. Sitaresmi MN, Mostert S, Schook RM, Sutaryo, Veerman AJP. Treatment refusal and abandonment in childhood acute lymphoblastic leukemia in Indonesia: An analysis of causes and consequences. *Psychooncology* . Published online 2010.

13. Navarrete M, Rossi E, Brivio E, et al. Treatment of childhood acute lymphoblastic leukemia in central America: A lower-middle income countries experience. *Pediatr Blood Cancer* . Published online 2014.

14. Advani S, Pai S, Venzon D, et al. Acute lymphoblastic leukemia in India: An analysis of prognostic factors using a single treatment regimen. *Ann Oncol* . Published online 1999.

15. Pedrosa F, Coustan-Smith E, Zhou Y, et al. Reduced-dose intensity therapy for pediatric lymphoblastic leukemia: Long-term results of the Recife RELLA05 pilot study. *Blood* . Published online 2020.

16. Sidhom I, Shaaban K, Youssef SH, et al. Reduced-intensity therapy for pediatric lymphoblastic leukemia: Impact of residual disease early in remission induction. *Blood* . Published online 2021.

17. Basso G, Veltroni M, Valsecchi MG, et al. Risk of relapse of childhood acute lymphoblastic leukemia is predicted by flow cytometric measurement of residual disease on day 15 bone marrow. *J Clin Oncol* . Published online 2009.

18. Hamadeh L, Enshaei A, Schwab C, et al. Validation of the United Kingdom copy-number alteration classifier in 3239 children with B-cell precursor ALL. *Blood Adv* . Published online 2019.

19. Logan C, Koura D TR. Updates in infection risk and management in acute leukemia. *Hematol Am Soc Hematol Educ Progr* . 2020;2020(1):135-139.

20. Brown PA, Ji L, Xu X, et al. A Randomized Phase 3 Trial of Blinatumomab Vs. Chemotherapy As Post-Reinduction Therapy in High and Intermediate Risk (HR/IR) First Relapse of B-Acute Lymphoblastic Leukemia (B-ALL) in Children and Adolescents/Young Adults (AYAs) Demonstrates Superior Eff. *Blood* . 2019;134(Supplement_2):LBA-1-LBA-1.

LEGENDS

FIGURE 1 Kaplan Meier estimate of overall survival of all patients (A) and estimate of overall survival for different risk groups (B)

Abbreviations: WBC, white blood cell; 50, 50 x 10^9/l; SE, standard error

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