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DOI: <https://doi.org/10.1002/pbc.29184>

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ZORA URL: <https://doi.org/10.5167/uzh-213008>

Journal Article

Published Version

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Originally published at:

Küpfer, Laura; Meng, Bun; Laurent, Denis; Zimmermann, Martin; Niggli, Felix; Bourquin, Jean-Pierre; Malene, Iv (2021). Treatment of children with acute lymphoblastic leukemia in Cambodia. *Pediatric Blood Cancer*, 68(10):e29184.

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Treatment of children with acute lymphoblastic leukemia in Cambodia

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Abstract

We report a retrospective analysis of 110 unselected pediatric patients with acute lymphoblastic leukemia (ALL) treated during 2015–2017 in a charity-funded public institution in Cambodia with a reduced intensity ALL-Moscow Berlin (MB)-91 protocol. No patient abandoned treatment. Sixty-three patients (57%) were high risk (HR). Seventy-two patients (65.5%) reached complete remission (CR) on day 36. The 3-year event-free survival (EFS) and overall survival (OS) was 34.9% (50.5% for standard risk [SR]). Most deaths resulted from infections (40 [53.3%]) and bleeding (15 [20%]). With further selective reduction of treatment intensity and access to platelet infusion, leukemia therapy is justified in this setting.

KEYWORDS

ALL-MB-91, Cambodia, low-middle income country, pediatric acute lymphoblastic leukemia

1 | INTRODUCTION

Contemporary treatment of childhood acute lymphoblastic leukemia (ALL) results in long-term survival in over 90% of children today.¹ However, less than 60% of children worldwide even have access to cancer treatment,² and outcomes for ALL in low-income countries remain poor.³ More than 50,000 new ALL cases are diagnosed per year in Asia,⁴ with limited information about countries such as Cambodia, where access to care is difficult, both financially and geographically. For 30 years, the Kantha Bopha Foundation has provided free pediatric health care and introduced leukemia therapy in 2003 based on access to hematopathology (morphology), whole blood transfusions, and a well-established infectiology department. The Moscow Berlin protocol was selected, providing affordable drug combinations and a moderate reduction of treatment intensity⁵ in one central location in Phnom Penh. Here, we analyze the results of this treatment regimen

retrospectively over a recent 3-year period with sufficient follow-up time as a basis for further development of this program.

2 | RESULTS

2.1 | Patient characteristics

All 110 newly diagnosed ALL patients admitted between 2015 and 2017 at the Kantha Bopha II Hospital in Phnom Penh were included in this study. Data were obtained retrospectively with case report forms (CRF) by trained staff from the leukemia treatment team and provided in an anonymized format with waiver from the ethical committee of the Kanton of Zurich for analysis. The patient characteristics and risk group stratification criteria are shown in Tables S1 and S2. Sixty-three patients (57.3%) were high risk (HR), mostly based on the high leukemia burden (53 patients [48.2%] initially had a white blood cell [WBC] count of more than $50 \times 10^9/L$, which is more than two-fold more frequent than in other European or South Asian cohorts^{6,7}). The diagnosis was

Abbreviations: ALL, acute lymphoblastic leukemia; CR, complete remission; EFS, event-free survival; FCM, flow cytometry; HR, high risk; OS, overall survival; SE, standard error; SR, standard risk; WBC, white blood cell.

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confirmed by bone marrow morphology, performed by a trained biologist. The peripheral blood was additionally screened for lymphoblasts, central nervous system (CNS) cytopins, a chest X-ray, an abdominal ultrasound, an echocardiography, and CT (computed tomography) scan of the brain were routinely performed. Follow-up bone marrow examinations were performed on day 36 and week 32 of treatment. Flow cytometry (FCM) is not available.

2.2 | Treatment

Patients were uniformly treated as inpatients in the hospital as detailed in Table 1. This protocol was developed for the treatment of patients in Russia at a time when less than 10% of children with ALL were surviving with the aim to reduce toxicity in consolidation treatment and costs, without affecting (overall survival) OS.⁵ A cumulative dose of daunorubicin of 120 mg/m² was given to standard risk (SR) patients, which was more than the SR arm of the ALL-MB-91 protocol (45 mg/m², only one dose during induction), but a reduction of half of the cumulative dose compared to the standard Berlin–Frankfurt–Münster (BFM) protocol.⁵ To replace high-dose methotrexate, modified Capizzi methotrexate courses were introduced. Cyclophosphamide and cytarabine were omitted, nonpegylated asparaginase was used to reduce costs. In Cambodia cranial radiation therapy was not used. Supportive care included sulfamethoxazole/trimethoprim prophylaxis, prophylactic oral fluconazole, and empirical treatment with ofloxacin 10 mg/kg or ceftriaxone 100 mg/kg or co-amoxicillin 80–100 mg/kg in febrile neutropenia. Dependent on the antibiogram meropenem 60 mg/kg or ceftazidime 100–120 mg/kg were added. Allopurinol was available for tumor lysis syndrome, no cases with dialysis were reported. Whole blood transfusions were only given if hemoglobin was <7 g/dl. Platelet transfusions were not available.

2.3 | Outcome analysis

The outcome is reported in Table S3 and Figure 1. Seventy-two (65.5%) reached complete remission (CR) by day 36, seven (6.4%) did not reach CR by day 36, and the remaining 31 (28.2%) patients died before the week 32 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. Thus, event-free survival (EFS) was similar to the 3-year OS of 34.9% for the entire cohort (standard error [SE] = 4.6) (Figure 1A), 50.5% for SR patients (SE = 7.4), and 23.4% (SE = 5.4) for HR patients. Estimated 3-year OS was best (51.5% [SE = 7.1]) for patients younger than 10 years with a WBC count under 50 × 10⁹/L and worst (6.3% [SE = 6.1]) for HR patients 10 years or older with a WBC count of 50 × 10⁹/L or more, which were significant differences ($p = .011$) (Figure 1B). Median follow-up of the patients alive in CR was 3.6 years. Most of the 75 deaths occurred during induction (29 [38.7%]) or consolidation (27 [36%]) mostly due to infections and bleeding (detailed in Figure 1C, Tables S3 and S4). Six out of 13 patients died from infections or bleeding during maintenance. All deaths after end of treatment were due

FIGURE 1 Kaplan–Meier estimate of overall survival (OS) of all patients (A), estimate of OS for different risk groups (B), and cumulative incidence of relapse and toxic death (C). Abbreviations: 50, 50 × 10⁹/L; SE, standard error; WBC, white blood cell. 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. Relapse was defined (see protocol for more details) as recurrence of leukemic blasts at any involvement site. Treatment abandonment was defined as the stopping of treatment due to any reason except for death. Event-free survival was defined as the time from diagnosis to the date of last follow-up or first event. Events were nonresponse, relapse, death from any cause, or treatment abandonment. Failure to achieve remission due to death before complete remission or nonresponse was considered as event at time 0. OS was defined as the time from diagnosis to the date of last follow-up or death. Kaplan–Meier method was used to estimate survival rates; differences between groups were compared with the log-rank test. Cumulative incidence functions for competing events were constructed by the method of Kalbfleisch and Prentice and were compared with Gray's test. SE is provided for all estimates. Statistical analysis was done using GraphPad Prism 8 (GraphPad software) and SAS 9.4 (SAS Institute, Cary, NC)

TABLE 1 Treatment protocol

Drug	Standard-risk dose and route	Day(s)	High-risk dose and route	Day(s)
Prophase				
Dexamethasone p.o.	6 mg/m ²	1–7	6 mg/m ²	1–7
Induction				
Dexamethasone p.o.	6 mg/m ²	8–28	6 mg/m ²	8–28
	3 mg/m ²	29–31	3 mg/m ²	29–31
	1.5 mg/m ²	32–34	1.5 mg/m ²	32–34
	0.75 mg/m ²	35–37	0.75 mg/m ²	35–37
Vincristine i.v.	1.5 mg/m ²	8, 15, 22, 29, 36, 43	1.5 mg/m ²	8, 15, 22, 29, 36, 43
Daunorubicin i.v.	45 mg/m ²	8	45 mg/m ²	8, 22
L-asparaginase i.m.	10,000 U/m ²	36, 43	10,000 U/m ²	36, 43
Consolidation 1				
Mercaptopurine	50 mg/m ² p.o.	50–85	50 mg/m ² p.o.	50–85
Dexamethasone	6 mg/m ² p.o.	92–105	6 mg/m ² p.o.	92–105
Vincristine	1.5 mg/m ² i.v.	92, 97	1.5 mg/m ² i.v.	92, 97
Methotrexate	50 mg/m ² i.m.	50, 57, 64, 71, 78, 85	50 mg/m ² i.m.	50, 57, 64, 71, 78, 85
Asparaginase	10,000 U/m ² i.m.	51, 58, 65, 72, 79, 86	10,000 U/m ² i.m.	51, 58, 65, 72, 79, 86
Daunorubicin	30 mg/m ² i.v.	50, 71	30 mg/m ² i.v.	50, 71, 92>
Consolidation 2				
Mercaptopurine	50 mg/m ² p.o.	106–141	50 mg/m ² p.o.	106–141
Dexamethasone	6 mg/m ² p.o.	148–161	6 mg/m ² p.o.	148–161
Vincristine	1.5 mg/m ² i.v.	148, 155	1.5 mg/m ² i.v.	148, 155
Methotrexate	50 mg/m ² i.m.	106, 113, 120, 127,	50 mg/m ² i.m.	106, 113, 120, 127,
Asparaginase	10,000 U/m ² i.m.	134, 141	10,000 U/m ² i.m.	134, 141
Daunorubicin	30 mg/m ² i.v.	107, 114, 121, 128,	30 mg/m ² i.v.	107, 114, 121, 128,
		135, 142		135, 142
		106		106, 133
Consolidation 3				
Mercaptopurine	50 mg/m ² p.o.	162–197	50 mg/m ² p.o.	162–197
Dexamethasone	6 mg/m ² p.o.	204–217	6 mg/m ² p.o.	204–217
Vincristine	1.5 mg/m ² i.v.	204, 211	1.5 mg/m ² i.v.	204, 211
Methotrexate	50 mg/m ² i.m.	162, 169, 176, 183,	50 mg/m ² i.m.	162, 169, 176, 183,
Asparaginase	10,000 U/m ² i.m.	190, 197	10,000 U/m ² i.m.	190, 197
		163, 170, 177, 184,		163, 170, 177, 184,
		191, 198		191, 198
Intrathecal therapy ^a				
Methotrexate i.t.	8/10/12 mg	1, 8, 15, 22, 29, 36, 92,	6/8/10/12 mg	1, 8, 15, 22, 29, 36, 45,
Cytarabine i.t.	20/26/30 mg	148, 204	20/30/40/50 mg	59, 73, 84
Prednisone i.t.	6/8/10 mg		4/6/8/10 mg	
Drug	Standard- and high-risk dose and route	Weeks		
Mercaptopurine p.o. (once daily)	Maintenance	32–37, 40–45, 48–53, 56–61, 64–69, 72–77, 80–85, 88–93		
Methotrexate i.m. (once weekly)	50 mg/m ²	32–37, 40–45, 48–53, 56–61, 64–69, 72–77, 80–85, 88–93		
Dexamethasone p.o. (once daily for 7 days)	30 mg/m ²	38, 46, 54, 62, 70, 78, 86, 94		
Vincristine i.v. (day 1, day 8)	6 mg/m ²	38, 46, 54, 62, 70, 78, 86, 94		
	1.5 mg/m ²			
Intrathecal therapy ^b				
Methotrexate i.t. (once weekly)	8/10/12 mg	38, 46, 54, 62, 70		
Cytarabine i.t. (once weekly)	20 (30)/26 (40)/30	38, 46, 54, 62, 70		
Prednisone i.t. (once weekly)	(50) mg	38, 46, 54, 62, 70		
	6/8/10 mg			

^aDosages according to age: lowest dosage age 1–2 years, intermediate dosage age 2–3 years, highest dosage age >3 years for standard-risk patients; for high-risk patients lowest dosage age <1 year, second dosage age 1–2 years, third dosage age 2–3 years, highest dosage <4 years.

^bDosages according to age: lowest dosage age 1–2 years, intermediate dosage age 2–3 years, highest dosage age >3 years, cytarabine dosages in brackets for high-risk patients.

to relapse. No patient abandoned treatment, and no treatment was offered after relapse.

3 | DISCUSSION

The introduction of effective treatment for childhood leukemia in a lower-middle income country is challenging. Treatment-related complications such as infections and bleeding are reportedly limiting factors,⁸ together with socio-economic barriers that often lead to treatment abandonment.^{3,9,10} In the charity-funded inpatient setting of the Kantha Bopha Hospital, patients and families complied with treatment fully, providing a strong basis to develop a program in pediatric oncology. However, several constraints remain.

Almost twice as expected patients present with a large disease burden, likely related to delays in access to care. Most deaths were due to infections and bleeding, while half of the patients with a more favorable risk profile could be cured. Therefore, the focus of our attention will be on further reduction of treatment toxicity and reliable identification of patients with favorable biology for treatment stratification.

In our treatment protocol, the cumulative anthracycline dose was reduced to 120 mg/m², but induction still included daunorubicin for all patients. Reducing the cumulative dose of anthracyclines to a maximum of 50–60 mg/m² doxorubicin for non-HR patients was proven to successfully limit infectious complications without compromising EFS and OS (EFS = 93%, 5-year OS >95%) in several studies in Malaysia/Singapore, Brazil, and Egypt.^{7,11,12} Furthermore, our protocol also included 8 weeks of 6 mg/m² dexamethasone and eight additional vincristine and dexamethasone pulses during maintenance. The activity of dexamethasone is counteracted by serious toxicity,¹³ which prompted several groups to reduce exposure with weekly intervals in induction. Additionally, the value of vincristine/dexamethasone pulses is controversial and limited by serious toxicity. Indeed, six of our patients (5.5%) died from infections/bleeding during maintenance. Several study groups omit pulses, and the Children's Oncology Group recently confirmed that reduction of these pulses is beneficial for average-risk ALL patients.¹⁴ Also, we used five doses of triple intrathecal chemotherapy, which comes with additional toxicity and was not proven to be more effective than methotrexate alone.¹⁵ Leucovorin rescue should also be considered.¹⁶

In order to reduce treatment intensity, identification of favorable-risk patients by monitoring their response to treatment with affordable simple FCM will be key, and will also increase diagnostic precision.^{11,12,17} Finally, all aspects of supportive care need to be revisited.^{18,19} Collectively our analysis shows that cancer therapy can be introduced in a public charity-based institution in Cambodia and can provide the basis for joining a larger consortium and to register patients in a central database to enable prospective treatment optimization.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Küpfer L, Meng B, Laurent D, et al. Treatment of children with acute lymphoblastic leukemia in Cambodia. *Pediatr Blood Cancer*. 2021;68:e29184. <https://doi.org/10.1002/pbc.29184>