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ORIGINAL ARTICLE

Experience of Paediatric Acute Lymphoblastic Leukemia Service in A Newly Established Haemato-Oncology Center in Bangladesh: Opportunities and Challenges

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Abstract

Background: *Acute lymphoblastic leukemia (ALL) is the most common childhood malignancy and its modern management is complex. We are reporting early experience of establishing a paediatric ALL service in a multidisciplinary paediatric hospital in Bangladesh.*

Methods: *This is a retrospective review of children below 18 years of age with confirmed diagnosis of ALL from July 2020 to June 2021 in Dr. M R Khan Shishu Hospital and ICH, Dhaka, Bangladesh, who received treatment adapted from the standard arm of ICICLE (Indian Childhood Collaborative Leukemia Group) protocol. Data were collected which included demographic, clinical, laboratory features of all patients at the time of presentation and also morbidities and outcome during all phases of chemotherapy. Analysis was done using descriptive statistics.*

Results: *Of 51 patients, 16 were newly diagnosed patients, 32 received continuation care and 3 had relapsed disease. Treatment was initiated in 12 (75%) of 16 patients with newly-diagnosed ALL. Median age was three years, 50% were girls, one had T-ALL and 5 (42%) had high presentation leucocyte count (≥50,000/mm^3). Complete cytogenetic testing was available for one patient alone, no patient had Ph+ ALL. Eleven (92%) showed good prednisolone response. All nine patients who completed the induction phase achieved morphological remission, with high minimal residual disease (≥0·01%) in two (22%). At last follow-up (30-06-2021), two patients were midway through induction, two died from sepsis (one each in Induction and Consolidation, both high risk ALL) and eight (67%) are alive in remission, on treatment 2-12 months from diagnosis. Continuation care included intrathecal treatments (n=119) and vincristine-corticosteroid pulses (n=53); 94% patient remained in complete remission, while two (6%) relapsed during the course of treatment.*

Conclusion: *Risk-stratified ALL treatment is feasible in a newly established resource limited setting but limited by availability of high-quality diagnostics, specifically cytogenetics. Our study revealed that, during intensive phase approximately two-third children and during maintenance phase majority of children remained in complete remission.*

Keywords: *Acute lymphoblastic leukaemia, opportunities, challenges, Bangladesh.*

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Introduction

The number of childhood cancer is increasing day by day and 84 % of the cancer cases occur before 15 years of age in the low-income and middle-income countries (LMICs).[1] The age-adjusted incidence rate of leukemia in children and adolescents younger than 20 years is 4.7 per 100,000.[2] The reported incidence of childhood cancer in Bangladesh is 7.8 per million per year out of which leukemia is the commonest cancer (28%) and 84% of the leukemias are acute lymphoblastic leukemia (ALL).[3]

ALL is the most common childhood malignancy accounting for one-fourth of all childhood cancer and almost 72% of all cases of childhood leukemia.[4] ALL is classified as B-lymphoblastic leukemia and T-lymphoblastic leukemia. B precursor cell accounts for 80% of ALL cases, T-cell accounts for 15-20% of ALL cases and mature B cell accounts for 1 to 2% of ALL cases.[5]

Diagnostic and treatment modalities for ALL have seen tremendous advancements over the past few decades. Despite of a higher incidence and constant rise in pediatric cancers in the developed countries, their success stories are ample.[6] Remarkable progress has been achieved in childhood ALL due to adaptation of risk-stratified treatment and improved supportive care.[7,8] With survival rates in developed countries approaching 100%, there is a shift of research focus towards improvement of quality of life, reduction of morbidities and drug toxicities, targeted drug therapies and treatment of drug resistant leukemia.[9]

On the other hand, LMICs like Bangladesh still struggle for optimal results in cancer care. A large proportion of treatment options for ALL is stationed in the superspecialist centers of the country. This reduces the accessibility and feasibility of adequate treatment for leukemic children in the general pediatric hospital. Poverty and lack of parenteral education is the main cause of treatment refusal and abandonment in Bangladeshi children with ALL.[10] Poor socioeconomic conditions, gender discrimination, malnutrition, delayed diagnosis, and referral form some of the important yet modifiable factors attributed to poor outcomes in developing countries.[11] Efforts should be taken to meet the long-term challenge of providing quality care to children with ALL worldwide and improving cure rates globally. This can be passible by increasing collaborative research and international networking so that the therapeutic gains in high-income countries can be translated to patients in low-income and middle-income countries.[9]

Delivery of intensive chemotherapy for ALL requires trained manpower and infrastructure which is usually available in established pediatric haemato-oncology centers in Bangladesh. Challenges for delivering chemotherapy for newly-established pediatric haemato-oncology center are manifold. This study aimed to describe the experience of modern ALL service in a newly setup haemato-oncology unit in a multispecialty pediatric hospital in Bangladesh.

Materials and Methods

This is a retrospective review of children with ALL from July 2020 to June 2021 in Dr. M R Khan Shishu Hospital and ICH, Dhaka, Bangladesh. A total of 51 children below 18 years of age with confirmed diagnosis of ALL who received maintenance chemotherapy in collaboration with TMC (TATA Medical Center), as well as newly diagnosed patients at Dr. M R Khan Shishu Hospital were included in this study.

All patients received treatment adapted from the standard arm of ICICLE (Indian Childhood Collaborative Leukemia Group) protocol.[12] Ethical clearance was obtained from the institutional review board. Informed written consent was taken, and confidentiality of data was maintained. Standard case report forms, specifically designed for this study were used to collect data which included demographic, clinical, laboratory features of all patients at the time of presentation. A follow up case report form was filled for each patient at which recorded morbidities and outcome during induction, consolidation, interim maintenance, delayed intensification, and maintenance phases of chemotherapy.

Confirmation of diagnosis of acute lymphoblastic leukemia was done when 20% lymphoblasts or more were present in the bone marrow (BM) aspirate/ trephine biopsy. Flowcytometry was done for the immunophenotypic classification into B -cell ALL and T-cell ALL. Participants were classified into standard risk and high risk according to NCI classification using age and WBC count. Standard risk was defined as WBC count $<50 \times 10^9$/L and age one to 9.99 years, while high risk was defined as WBC count $\geq 50 \times 10^9$/L at any age or age >10 years with any WBC count at presentation. Then clinical risk factors were determined by extramedullary disease features and

genetic risk was determined by cytogenetics. Cytogenetic studies include fluorescence in situ hybridization (FISH) assays for ETV6-RUNX1; BCR-ABL1; KMT2A rearrangements; iAMP21; TCF3-HLF was done for all maintenance patient whose treatment were initiated at TMC.[13]As complete cytogenetic testing by FISH is not available in Bangladesh, we did only RT-PCR method for BCR-ABL in newly diagnosed patient at our center. Only one of newly diagnosed patient had done cytogenetic studies for other translocations including t (12;21), t (9;22), t (4;11) and t (1;19) from abroad. Diagnostic lumbar puncture was done to determine CNS involvement & patien ts were classified as CNS1,2 and 3 categories based on standard criteria. Other investigations at the time of diagnosis included liver function test (LFT), renal function test (RFT), LDH levels, chest X-ray for mediastinal mass, 2D echocardiography and serology for HIV, Hepatitis B and C virus.

Early treatment response was determined by prednisolone response (prednisolone good responder [PGR] and prednisolone poor responder [PPR] if they had <1000 blasts/μL in peripheral blood and >1000 blasts/μL in peripheral blood after 1 week of steroid prephase respectively) and minimal residual disease (MRD) estimation after 5 weeks of induction treatment. Patients were labeled to be in morphological remission if there were less than 5% blasts in the marrow with normal trilineage hematopoiesis and MRD negative if values were <0.01%. All through the patient management a collaboration was established with TMC, Kolkata in the form of knowledge sharing and monitoring of tolerance and treatment adherence. Information about all the patients were discussed weekly with the TMC team about maintenance drugs dose adjustments, management of toxicities and provision for administration of intrathecal chemotherapy locally. This included newly diagnosed patients also and was not limited to the patients receiving continuation care.

Data was analyzed using Microsoft Excel. Categorical variables were given in the form of frequency table. Analysis was done using descriptive statistics.

Results

A total of 51 patients diagnosed as ALL were included in the study. Out of them, 32 patients were diagnosed and had their intensive phase of treatment in TMC and got shared care and 19 were newly diagnosed at Dr. M R Khan Shishu Hospital. Out of the newly diagnosed children with ALL, 3 patients were diagnosed as relapsed ALL and 4 patients were referred to another center (financial constraints).

Among the 12 frontline ALL patients, 50% were male and 50% were female. A total of 92% children were <10 years of age with a median age of 3 years (IQR 2-4.5). A total of 8% children had T cell lineage and 92% patient had B cell lineage leukemia; 58% had NCI Standard-Risk and 42% had NCI High-Risk disease. The highest WBC count ≥50,000/mm^3 was observed in 42% of the cases. The cytogenetics was ETV6-RUNX1 in one patient whose cytogenetics were tested from abroad, others were BCR-ABL (RT-PCR method) negative, but others cytogenetics were not known. Only 1 patient had poor Prednisolone response (8%). At the end of induction all patients achieved complete morphological remission, but 22% patient (n=2) had MRD positive (≥0.01%) disease. One patient died during induction and one died during consolidation. Both had high risk B ALL and both died due to sepsis. At last follow-up (30-06-2021), 2 patients were midway through induction, 2 died from sepsis and 8 (67%) are alive in remission, on treatment 2-12 months from diagnosis. Maintenance cycles were started for 2 of newly diagnosed patients.

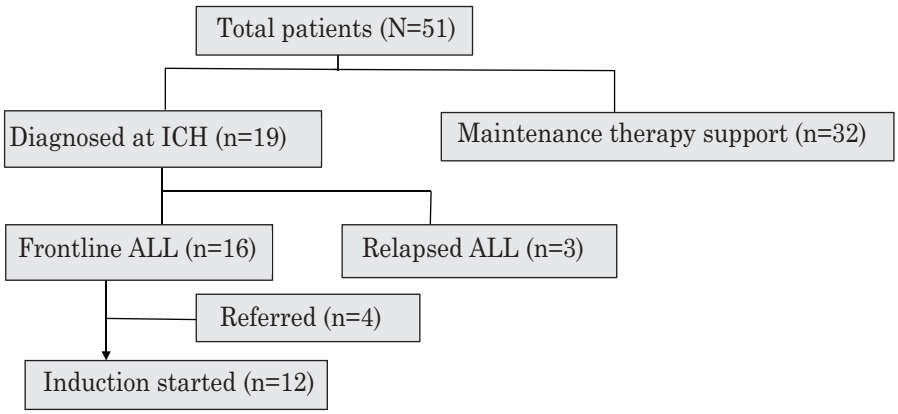

Fig.-1 *Distribution of children with ALL*

Table I
Demography of Frontline ALL patient

Parameter	Number	Percentage
Age in year (n=12)		
Less than 10	11	92
More than or equal 10	1	8
Median	3	
IQR	2-4.5	
Gender (n=12)		
Male	6	50
Female	6	50
Lineage (n=12)		
B cell	11	92
T cell	1	8
Highest White Blood cell (n=12)		
<50000/ mm^3	7	58
≥50000/ mm^3	5	42
NCI Risk (n=12)		
Standard	7	58
High	5	42
B Cell Cytogenetics (n=11)		
ETV6-RUNX1	1	9
Negative BCR-ABL	11	100
Final Risk (n=9)		
Standard	0	0
Intermediate	5	56
High	4	44

Table II
Outcome of Frontline ALL patient

Parameter	Number	Percentage
Prednisolone response (n=12)		
Good	11	92
Poor	1	8
End of induction complete morphological response (n=9)		
Yes	9	100
No	0	0
End of Induction MRD (n=9)		
More than equal 0.01%	2	22
Less than 0.01%	7	78
Event (n=12)		
Relapse	0	0
Induction death	1	8
Consolidation Death	1	8

Table III
Demography and outcome of Maintenance patient

Parameter	Number	Percentage
Diagnosis		
B Cell ALL	26	82
T Cell ALL	3	9
Relapsed ALL (B ell)	3	9
Age in year		
Less than 10	20	62
More than equal 10	12	38
Median	7.6	
IQR	6-12.8	
Sex		
Male	17	53
Female	15	47
Maintenance Type		
Standard maintenance	27	84
Vincristine dexamethasone pulse	5	16
Outcome		
Complete remission	30	94
Relapsed	2	6

Discussion

Treatment and outcome of ALL is one of the success stories in modern medicine with the overall survival reaching >90%.[14,15] However, overall survival (OS) for the St. Jude Total Therapy Study XVI (94.3%) was similar to that for the Total Therapy Study XV (93.5%).[16] But the treatment is complex and long duration and access to modern therapies is limited in developing countries like Bangladesh. In this study we wanted to show the early experiences of our newly established Hematology and Oncology unit.

Cancer treatment is more challenging for children in Bangladesh. There are multiple reasons like financial burden, absence of skilled human resources in laboratories, lack of paediatric oncologists at hospitals, and parents who can afford it, take their children to neighbouring country for diagnosis and treatment as there is a general lack of faith in local diagnostic reports.[17] Tahura S found in her study

that poverty and lack of parenteral education is the main cause of treatment refusal and abandonment in Bangladeshi children with ALL.[10] In our study treatment was not started for 4 (25%), out of 16 newly diagnosed children due to financial burden of family and were referred to Government Hospital for further management.

In our study, out of 51 patients, treatment was initiated in 12 (75%) of 16 patients with newly-diagnosed ALL. We found the median age of child with newly diagnosed ALL was 3 years and a total of 92% children was <10 years of age and 50% were girls. Diba F et al found in her study that most of the patients were 1 to 9 years of age (87.4%), which is almost similar to our study.[18] Sampagar A et al reported that male to female ratio of newly diagnosed ALL was 1.15:1.[19] In our study male to female ratio of newly diagnosed ALL was 1:1.

In our study, 1 child (8%) had T cell lineage and 92% patient was B cell lineage which is comparable to another Bangladeshi study where among 87 analyzed patients, 93.1% were B-cell ALL and 6.9% were T-cell ALL.[18]

In our study the highest WBC count ≥50,000/ mm^3 was 42%. These counts were higher when compared to studies in the west but in concordance with studies from other Low-and Middle-income countries (LMIC), where baseline white blood cell (WBC) count of >50,000/mm^3 was seen in 23-37%.[20,21] The probable reason for this could be delayed presentation.

Complete cytogenetic testing was available for 1 patient alone in frontline ALL children, no patient had Ph+ ALL in our study. Incidence of Philadelphia chromosome was much lesser than its known incidence in childhood ALL (12%) probably due to small sample size.[20,22]

In this study, eleven (92%) children showed good prednisolone response and 8% patient had poor prednisolone response, which is comparable to another Indian study, where the day 8 prednisolone response was poor in 9.72%. [19]

Our Induction outcome based on morphological and MRD assessment showed promising results. All 9 patients (100%) who completed the induction phase achieved complete morphological remission, which is higher than another Bangladeshi study where 87% went into complete remission.[23] Morphological remission is similar to an Indian study done by Sampagar et al[19] Minimal residual disease is currently the most powerful prognostic indicator in ALL. and it was positive in 22% of the patients which is higher than the established centers.[19] There is no study from Bangladesh commenting on the MRD post induction earlier than our study.

Our induction mortality rate of 8% is higher than that seen in HIC.[24] Review of Indian data in ALL by RS Arora et al covering 3761 children reported a death rate of 2-13% during induction.[19] In this study, all deaths were due to bacterial infection and its complications which is corresponding to another Bangladesh study.[23] Bacterial sepsis is indeed the leading cause of mortality during induction.[25]

In this study, 32 children received maintenance chemotherapy, whose treatment was initiated in TMC, India and received their intensive phase of treatment there, but they got the maintenance chemotherapy support to our newly established center in Bangladesh. We successfully continued maintenance phase of treatment including administration of IV vincristine and intrathecal methotrexate without any notable adverse effects. Tuong et al[26] showed, there was 16.7% relapse of the 156 newly diagnosed ALL in between 2012 to 2018, out of them 53.8% cases were relapsed during the maintenance phase. In our study among the maintenance patient 94% remained in complete remission, but 6% (n=2) had relapsed during the course of treatment.

Any inference on the outcome is limited by the very small sample size with short follow up. It is painful to note here that we could not test the cytogenetics for all patients, because the FISH probe testing for cytogenetics is still unavailable in Bangladesh. We could do this test only for one patient by sending the sample to India which was expensive and not bearable for other patients. The best we could do is to test for BCR-ABL by RT-PCR method for other patients.

Conclusion

This study revealed during intensive phase of treatment, approximately two-third children and during maintenance phase majority of children remained in complete remission in ALL. So, Risk-stratified ALL treatment is feasible in a newly established resource limited setting, but there is limitation of availability of high-quality diagnostics, specifically cytogenetics.

Recommendation

Partnership with a specialist cancer center in treatment of the same group of patients allows sharing of expertise and experience. The collaboration could alleviate the anxiety of distant care and be helpful in building confidence of patient to get treatment in their own country with long term reduction in patient exodus.

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References

1. Magrath I, Steliarova-Foucher E, Epelman S, Ribeiro RC, Harif M, Li CK, et al. Paediatric cancer in low-income and middle-income countries. *The lancet oncology* 2013;**14**:104-16.
2. Facts 2020-2021. American Cancer Society's *Cancer Facts & Figures 2021*.Estimated numbers of new blood cancer cases and estimated numbers of deaths due to blood cancers. National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) Program, *Cancer Statistics Review (CSR*). Available from: https://www.cancer.org/research/cancer-facts-statistics. html.
3. Hossain MS, Begum M, Mian MM, Ferdous S, Kabir S, Sarker HK, et al. Epidemiology of childhood and adolescent cancer in Bangladesh, 2001-2014. *BMC Cancer* 2016;**16**. DOI 10.1186/s12885-016-2161-0.
4. Pizzo PA, Poplack DG. Principles and practice of pediatric oncology. Lippincott Williams & Wilkins; 2015 Jun 24.
5. Viana MB,Maurer HS, Ferenc C. Subclassification of acute lymphoblastic leukaemia in children: analysis of the reproducibility of morphological criteria and prognostic implications. *British journal of haematology* 1980;**44**:383-88.
6. Hubbard AK, Spector LG, Fortuna G, Marcotte EL, Poynter JN. Trends in international incidence of pediatric cancers in children under 5 years of age: 1988-2012. *JNCI Cancer Spectrum* 2019;**3**:pkz007.
7. Pui CH, Yang JJ, Hunger SP, Pieters R, Schrappe M, Biondi A, et al. Childhood acute lymphoblastic leukemia: progress through collaboration. *Journal of Clinical Oncology* 2015;**33**:2938.
8. Pui CH, Mullighan CG, Evans WE, Relling MV. Pediatric acute lymphoblastic leukemia: where are we going and how do we get there? *Blood* 2012;**120**:1165-74.
9. Pui CH, Yang JJ, Bhakta N, Rodriguez-Galindo C. Global efforts toward the cure of childhood acute lymphoblastic leukaemia. *The Lancet Child & Adolescent Health* 2018;**2**:440-54.
10. Tahura S, Hussain M. Treatment refusal and abandonment in pediatric patients with acute lymphoblastic leukemia in Bangladesh. *Int J Sci Res* 2017;**6**:643-45
11. Lee JW, Cho B. Prognostic factors and treatment of pediatric acute lymphoblastic leukemia. *Korean Journal of Pediatrics* 2017;**60**:129-37.
12. Das N, Banavali S, Bakhshi S, Trehan A, Radhakrishnan V,Seth R, et al. Protocol for ICiCLe-ALL-14(InPOG-ALL-15-01):a prospective, risk stratified, randomised, multicentre, open label, controlled therapeutic trial for newly diagnosed childhood acute lymphoblastic leukaemia in India. *Trials* 2022;**23**:1-20.
13. Parihar M, Singh MK, Islam R, Saha D, Mishra DK, Saha V, et al. A triple-probe FISH screening strategy for risk-stratified therapy of acute lymphoblastic leukaemia in low-resource settings. *Pediatr Blood Cancer* 2018;**65**:e27366.
14. Möricke A, Zimmermann M, Valsecchi MG, Stanulla M, Biondi A, Mann G, et al. Dexamethasone vs prednisone in induction treatment of pediatric ALL: results of the randomized trial AIEOP-BFM ALL 2000. *Blood* 2016;**127**:2101-12.
15. Larsen EC, Devidas M, Chen S, Salzer WL, Raetz EA, Loh ML, et al. Dexamethasone and high-dose methotrexate improve outcome for children and young adults with high-risk B-acute lymphoblastic leukemia: a report from Children's Oncology Group Study AALL0232. *Journal of Clinical Oncology* 2016;**34**:2380-88.
16. Jeha S, Pei D, Choi J, Cheng C, Sandlund JT, Coustan-Smith E, et al. Improved CNS control of childhood acute lymphoblastic leukemia without cranial irradiation: St Jude Total Therapy Study 16. *Journal of Clinical Oncology* 2019;**37**:3377-91.
17. Antara NF. Cancer treatment inadequate for children in Bangladesh. Dhaka Tribune; February 14th,2020.
18. Diba F, Karim MA, Soma SA, Chowdhury I, Mamun S, Mondal MN. Immunophenotypic Pattern and

Treatment Outcome after Completion of Induction Remission in Children with Acute Lymphoblastic Leukemia. *Journal of Current and Advance Medical Research* 2021;**8**:59-64.

19. Sampagar A, Patil N, Dias M, Kothiwale V, Reddy NA, Hundekar R et al. A Study of Demography and Induction Outcome of Pediatric Acute Lymphoblastic Leukemia in A Newly-Established, Resource-Limited Setting In India. *Authorea* 2020. DOI: 10.22541/au.160225943.38483501/v1.
20. Arora RS, Arora B. Acute leukemia in children: A review of the current Indian data. *South Asian Journal of Cancer* 2016;**5**:155-60.
21. Jaime-Perez JC, Garcia-Arellano G, Herrera-Garza JL, Marfil-Rivera LJ, Gomez-Almaguer D. Revisiting the complete blood count and clinical findings at diagnosis of childhood acute lymphoblastic leukemia:10-year experience at a single center. *Hematology, Transfusion and Cell Therapy* 2019;**41**:57-61.
22. Pui CH, Roberts KG, Yang JJ, Mullighan CG. Philadelphia chromosome-like acute lymphoblastic leukemia. *Clinical Lymphoma Myeloma and Leukemia* 2017;**17**:464-70.
23. Hossain MB, Selimuzzaman M, Choudhury NA, Wahab A. Outcome of childhood Acute Lymphoblastic Leukaemia after induction therapy: Three-year experience in a tertiary care hospital in Bangladesh. *Journal of Enam Medical College* 2017;**7**:25-28.
24. Seif AE, Fisher BT, Li Y, Torp K, Rheam DP, Huang YS et al. Patient and hospital factors associated with induction mortality in acute lymphoblastic leukemia. *Pediatric Blood & Cancer* 2014;**61**:846-52.
25. Kiem Hao T,NhuHiep P,Kim Hoa NT, Van Ha C. Causes of death in childhood acute lymphoblastic leukemia at Hue Central Hospital for 10 years (2008-2018). *Global Pediatric Health* 2020;**7**:2333794 X20901930.
26. Tuong PM, Hao TK, Hoa Nguyen TK Relapsed Childhood Acute Lymphoblastic Leukemia A Single-Institution Experience. *Cureus* 2020;**12**:e9238.