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Naureen Mushtaq Aga Khan University

Zehra Fadoo Aga Khan University, zehra.fadoo@aku.edu

Ahmed Naqvi Aga Khan University

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Childhood acute lymphoblastic leukaemia: experience from a single tertiary care facility of Pakistan

Naureen Mushtaq, Zehra Fadoo, Ahmed Naqvi

Abstract

Objective: To evaluate the demographic features, outcome and prognostic factors seen in children with acute lymphoplastic leukaemia at a tertiary care hospital.

Methods: The retrospective descriptive study was conducted at Aga Khan University Hospital, Karachi, comprising data related to children below 15 years of age and treated between January 1997 and December 2006. Kaplan Meir survival curves were used to describe overall and event-free survival rates. Cox Proportional Hazards model was used to describe factors associated with death and relapse. SPSS 16 was the main statistical tool.

Results: Of the total 121 children diagnosed with the condition, 79 (65.3%) were males; 86 (71.1%) patients were between 1-9 years of age; Immunophenotyping was done in 99 (81.81%) patients: 86 (87%) cases had precursor B and 13 (13.13%) had precursor T. Of the total, 106(87.6%) patients opted for treatment, while 15 (11.6%) were lost to follow-up. Besides, 26(21.7%) patients had at least one relapse; the most common site being bone marrow in 13 (50%) followed by central nervous system in 9 (36.6%). There were 20(16.5%) deaths in the sample. Infection was the most frequent cause of death. The event-free survival and overall survival was 63% (n=76) and 65%(n=79) respectively.

Conclusion: Through the clinical characteristics of children with acute lymphoblastic leukamia were similar to those reported in literature, the outcomes were inferior. The high rate of infections and relapse warrant better supportive care and risk-based approach.

Keywords: Acute lymphoblastic leukaemia, Survival, Developing country, Prognostic factors. (JPMA 63: 1399; 2013)

Introduction

There is no population based tumour registry in most of the developing countries and Pakistan is no exception to it. The annual incidence of cancer, therefore, remains unknown. The reported annual incidence of Acute Lymphoblastic Leukaemia (ALL) from other countries is almost 30-40 per million children below the age of 18 years.1 This is the most common malignancy of childhood¹⁻³ representing almost a quarter of all cancers diagnosed in this age group. The peak incidence is in children aged between 2 and 5 years. In the US, each year 2000-2500 new cases of childhood ALL are diagnosed. Internationally and in Pakistan as well, the incidence is thought to be similar. Children treated on current chemotherapy protocols have an event-free survival (EFS) that exceeds 85%. This success is mainly due to treatment stratification according to the risk of relapse and provision of better supportive care.4

The incidence of ALL is higher among boys than in girls;⁵ the difference being the greatest among pubertal children. In earlier studies, male gender was a distinctly

Department of Paediatrics and Child Health, Aga Khan University Hospital, Karachi, Pakistan.

Correspondence: Zehra Fadoo. Email: zehra.fadoo@aku.edu

poor prognostic factor.⁶ Some of the inferior outcome in boys were related to the higher percentage of poor prognostic features.⁶ These children generally present with signs of bone marrow failure, including anaemia, thrombocytopenia and neutropenia with clinical manifestations of fatigue, pallour, bleeding and fever.⁶

A proportion of these patients maintain sustained remission which allowe investigators to define sub-group with a higher or lower risk for relapse. The National Cancer Institute NCI criteria divide patients into standard and high-risk categories. Children between 1 and 9 years of age with a white blood cell (WBC) count at presentation of $<50 \times 10^9/L$ fall into the standard risk category. Children older than 10 years or of any age with an initial WBC count of $\geq 50 \times 10^9/L$ are categorised as high-risk. Other factors that have an influence on the outcome of treatment include certain cytogenetic or molecular changes in leukaemia cells. The presence of central nervous system (CNS) or testicular disease at presentation also puts a child at a higher risk of relapse.

The understanding of the biological features of childhood leukaemia has increased over the past decade.¹²⁻¹⁴ The ability to discern genetic differences among morphologically and immunologically similar populations of leukaemic cells has helped to establish the basis for a

revised classification of leukaemia. This advance, in turn, has pointed the way towards new approaches to clinical management.

Very little is known about the demographics and outcome of children with ALL in Pakistan. The study was aimed at identifying the clinical features, laboratory markers and the outcome of children diagnosed and treated with ALL. This would help clarify if these variables were different from those reported elsewhere and would determine some of the prognostic factors. Though a single-centre study, this will serve as a platform for future studies and facilitate in improving the treatment outcomes.

Patients and Method

The retrospective descriptive study was conducted at the Aga Khan University Hospital, Karachi. Data of all children <15 years of age who were newly diagnosed to have ALL between January 1997 and December 2006 was eligible. Children who presented with relapse or who were diagnosed elsewhere were not included. The data, including age, gender, clinical features at presentation (pallor, fever, bruises, weight-loss, nausea, vomiting, testicular swelling, headache, hepatomegaly, bone pains) and laboratory data, including initial WBC count, bone marrow and immunophenotyping results, cerebrospinal fluid (CSF) analysis, number and type of relapses, were retrieved by retrospective chart analysis from the Medical Record Department, which uses International Classification of Disease version 9 databases (ICD 9.0). A proforma was structured for the purpose.

The treatment protocol was based on the BFM (Berlin-Frankfurt-Munich) backbone. Induction phase over 4 weeks included 4 drugs namely vincristine 1.5gm/m² weekly, oral prednisolone 60mg/m² daily, L-asparaginase 2500 IU/m² (9 doses) and daunomycin 25mg/m² weekly with intrathecal methotrexate on day 1, 15 and 28. This was followed by consolidation over 4 weeks with cyclophosphamide 1000mg/m² day 1 and 14, cytosine arabinoside 75mg/m² for 4 days every week and oral 6MP daily with weekly intrathecal methotrexate. Interim maintenance of 2 months consisted of methotrexate 75mg/m² every two weeks and oral 6MP daily. Delayed intensification over 2 months consisted of vincristine 1.5 mg/m² weekly for 4 weeks, adriamycin 25mg/m² weekly for 4 weeks, dexamethasone 10mg/m² daily for 4 weeks, cyclophosphamide 1000mg/m² on day 35, cytosine arabinoside 75mg/m² 4 times per week for 2 weeks starting day 36 and intrathecal methotrexate day 39 and 46. The maintenance therapy included daily oral 6mercaptopurine, weekly doses of oral methotrexate and 4 weekly pulses of vincristine with prednisolone with intrathecal methotrexate every 3 months. Prophylactic CNS radiation was given only to children with T-ALL (1200 Gy), whereas all patients (both B- and T-cell) with overt CNS disease received radiation therapy in a dose of 1800 Gy. The total duration of therapy was 30 months for girls and 36 months for boys.

The data was analysed using SPSS version 16.0. For categorical data frequencies along with percentages were calculated. For continuous variables with a skewed distribution, median with Inter Quartile Range (IQR) were described. To account for censoring and lost to follow-up, Kaplan Meir survival curves were used to describe overall and event-free survival rates. A univariate Cox proportional hazards regression model was employed for deaths and relapses as the event and time to death and relapse as the time variable. Cases with missing values were dropped from further analysis. Hazard Ratios (HR) along with 95% confidence (CI) were calculated to identify variables associated with an increased risk of death or relapse. 15

Results

Patient characteristics were identified at the time of diagnosis (Table-1). A total of 121 ALL patients were

Table-1: Patient Characteristics.

Variables	n	Percentage
Overall	121	
Gender		
Male	79	65.3
Female	42	34.7
Age		
<1 year	8	6.6
1.0 – 9.9 years	86	71.1
≥10 years	27	22.3
Fever	98	81%
Pallor	100	82.6
Bruises	56	46.3
Weight-loss	52	43
Nausea/Vomiting	20	16.5
Hepatomegaly	78	64.5
Testicular swelling	2	1.7
Bone pains	26	21.5
Precursor B — cell Immunophenotype	86*	87
T-cell immunophenotype	13*	13
Risk category^		
High Risk	46	38
Standard Risk	75	54.5
WBC		
<50X10 ⁹ /L	106	87.5
>50X10 ⁹ /L	15	12.5

*Out 99. ^Risk category - High risk defined as WBC >50,000 and/or age >9.99yrs at diagnosis. Standard risk defined as WBC<50,000 and/or age <9.99yrs at diagnosis. WBC: White blood cells.

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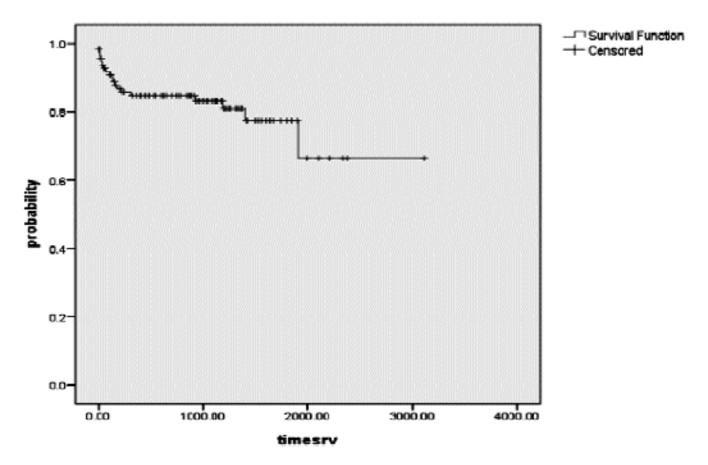


Figure-1: Overall survival.

diagnosed during the study period. Of them, 15(11.6%) patients were lost to follow-up.

The majority of patients (n=86; 71%) were between 1.0 = 9.9 years of age, followed by 27 (22%) who were \geq 10 years old and only 8(6%) were below one year of age. There were 79 (65.3%) males and 42 (34.7%) females. Fever (n=98; 81%) and pallor (n=100; 82.6%) were the most common presentation' followed by weight-loss in 52 (43%) patients. Two (1.7%) patients presented with testicular swelling. Besides, 106 (87.5%) children had a WBC count of $<50\times10^9/L$, while 15(12.5%) had $\geq50\times10^9/L$. Overt CNS symptoms were documented in 11 (9.1%) cases. All these patients complained of headache at presentation, while two (1.7%) had seizures and one (0.8%) presented with paraplegia. Eight (72.72%) patients in this sub-group were male. The cerebrospinal fluid contained >5 blasts/cmm in all the 11 patients.

Immunophenotyping results at diagnosis were available for 99 (81.81%) patients. Of them, 86 (87%) cases were classified as having Precursor-B ALL and 13 (13%) as T-ALL. Day 28 bone marrow results were available for 96(79.33%)

patients; out of whom remission (M1 marrow status) was attained in 93 (97%).

Twenty-six (21.5%) patients had a relapse. Median time to relapse was 14.6 months from diagnosis. Out of these 26 patients, immunophenotyping results from initial diagnosis were available in 21 (80.76%) patients; 15 (71%) had Precursor- B ALL, while 6 (28.5%) had T- ALL. All of the 6 patients with T-ALL relapsed as CNS disease. Site of relapse was bone marrow in 13 (50%), CNS in 9 (30%), testes in 3 (11%) and combined in 1 (4%) of the patients. All of them were treated as per BFM relapse ALL protocol. Three (14.3%) children died during treatment because of progressive disease.

There were 21 (17%) deaths; 9 (45%) during the induction phase (induction death rate of 8.5%), 3 (15%) during the consolidation phase, and 8 (40%) during the maintenance phase of chemotherapy. The most common cause of death was infection in 15 (71.4%), progressive disease in 3 (14.3%) and haemorrhage in 3 (14.3%) patients.

Given a median follow-up of 28 months (IQR 8-43), the

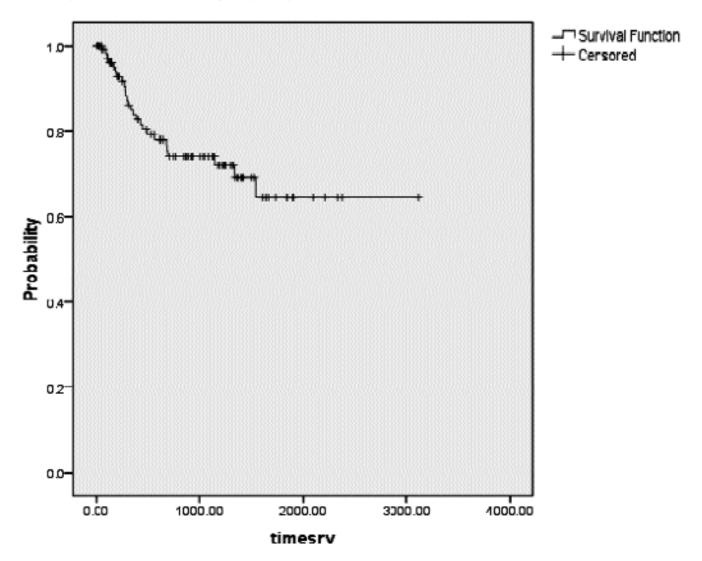


Figure-2: Event-free survival.

Table-2: Cox proportional hazard model presentation.

Variables	Hazard Ratio (HR) with 95% Cl ¹⁵	
Age		
<1 year		
1.0- 9.9 years	0.42(0.12-1.4)	
≥10 years	0.75(0.21-2.7)	
Gender		
Male		
Female	1.2(0.64-2.31)	
WBC Count		
<50x10 ⁹ /L		
>50x10 ⁹ /L	2.71(1.28-5.71)	
Final Diagnosis		
Pre B ALL		
T cell ALL	1.36(0.57-3.23)	

ALL: Acute Lymphoplastic Leukaemia. WBC: White blood cells. CI: confidence interval.

overall survival(OS) and event-free survival (EFS) were 65%(n=76) and 63%(n=79) respectively, (Figures-1 and 2). Cox proportional hazard model (Table-2) showed that only WBC count had a statistically significant association with relapse or death. The rate of death or relapse in those patients who had a WBC count \geq 50 x 109 /L was 2.7 times the rate of relapse or death in patients with WBC count <50 x 109/L throughout the study period. Hazard ratios as low as 1.28 and as high as 5.71 were observed at 95% level of confidence.

Discussion

The exact incidence of childhood cancer in Pakistan is not known because of the non-existence of a populationbased tumour registry. There has been an attempt to develop a tumour registry for one district of Karachi. According to this registry, the incidence of childhood N. Mushtaq, Z. Fadoo, A. Nagvi

cancer is 9/100,000.16 Extrapolating the registry for the whole country, approximately 8000-9000 new cases of cancer, and 3000 new cases of leukaemia occur in children each year.16 Of this, only half reach a facility where treatment is available. Even there, the survival is not more than 50%, making the OS not more than 25-30%.1 Reason for this is inaccessibility to tertiary care centres with paediatric cancer units, poverty, lack of knowledge and awareness among our general practitioners, and illiteracy. In our study, 15 patients were lost to follow-up. Higher rates of abandonment have been reported from China and neighbouring countries.17,18

Studies from Asia have reported that over half of the cases could be categorised as high-risk, based on age, WBC counts on presentation, presence of CNS disease at diagnosis and male gender.¹⁷ In contrast high-risk disease is encountered in only 10% of the cases in developed nations.¹⁹⁻²¹ In our cohort of patients, almost 40% were in the high-risk group based on age, initial WBC count, CNS/testicular disease and T-ALL phenotype. This is consistent with the data from other resource-poor countries.²³⁻²⁵ This difference may be because of late referrals but inherently different biology of leukaemia cells needs to be investigated. In contrast to the reported equal incidence of disease in males and females from the developed nations,^{26,27} we observed a definite bias towards the male gender. This probably reflects the neglect of the female child in our society. High WBC count at presentation was documented in 15 (12.5%) of our patients. Investigators from Europe and USA have also observed hyperleucocytosis in 10-15% of the patients.²⁶ These patients are at higher risk for developing tumour lysis syndrome and other complications needing aggressive supportive management.

Relapse was documented in 26 (21.5%) cases, which is higher in comparison to figures from the developed countries.²⁸ Relapse of disease while on chemotherapy and high incidence of CNS relapse indicates the need to re-evaluate our treatment protocols especially for T-ALL. The high incidence of CNS relapse re-emphasises the need for the use of intravenous high-dose methotrexate, especially in high-risk patients, including T-ALL.

The age and the WBC count on presentation have been shown to have significant impact on the outcome of childhood ALL. The NCI devised criteria of putting children to the standard risk group where the age is between 1 and 10 years and the WBC count less than 50 x 10^9 /L, whereas children of age 10 years or above with any WBC count or of any age with WBC count of $\geq 50 \times 10^9$ /L to the high risk group. We also found WBC count $\geq 50 \times 10^9$ /L

at any age, associated with a less favourable outcome in univariate analysis. Most of the Asian and USA-based studies have also shown the same results. ¹⁰ Investigators in Chile, South Africa and USA have also identified age as an important prognostic factor. ^{22,23} Although the data is retrospective and from a single institute, but the estimated OS and EFS in our study is inferior compared to the more developed countries, but it still fares better than some of the other South East Asian countries, ²⁵ and the only other study so far published from Pakistan.

The contributing factors for low EFS and OS have previously been reported to be associated with the higher numbers of toxic deaths, increased relapse rate, poor nutritional status, poor socioeconomic conditions, delay in diagnosis and lack of approach to a tertiary care unit.²⁸ High rates of toxic deaths related to infections during induction as well as maintenance warrants better supportive care, more aggressive approach to manage febrile neutropenia and risk adapted less intense (three drugs) induction therapy for standard risk patients. Though recently there has been limited availability of facilities to conduct cytogenetic and molecular studies for better risk assessment for appropriate therapy, these needs to be more generally available. There should be more multi-centre studies to identify other risk factors behind poor outcomes.

Conclusion

There is a strong need to educate the paediatricians and family physicians to be able to suspect childhood leukaemia and early referral to appropriate centres. There is a need to increase the awareness of general public regarding childhood malignancies. The general belief of cancer being incurable should be addressed and information about excellent outcome in majority of the children diagnosed with leukaemia be propagated at a large scale.

References

- Pui CH, Evans WE. Acute lymphoblastic leukemia. N Eng J Med 1998; 339: 605-15.
- Zahid M, Khalid A, Ahmed ZD, Aziz Z. Acute leukemia of childhood: a retrospective analysis of 62 patients. J Pak Med Assoc 1996; 46: 147-9.
- Chessells JM. Recent advances in the management of acute leukemia. Arch Dis Child 2000; 82: 438-42.
- Pui CH, Sandlund JT, Pei D. Results of therapy for acute lymphoblastic leukemia in black and white children. JAMA 2003; 2901: 2001-7.
- Pui CH, Evans WE. Treatment of acute lymphoblastic leukemia. N Eng JMed 2006; 354: 166-78.
- Shanta V, Maitreyan V, Sagar TG, Gajalakshmi CK, Rajalekshmy KR. Prognostic variables and survival in pediatric acute lymphoblastic leukemia: cancer institute experience. Pediatr Hematol Oncol 1996; 13: 205-16.

- Vaidya SJ, Advani SH, Pai SK, Nair CN, Kurkure PA, Saikia TK, et al. Survival of childhood acute lymphoblastic leukemia: results of therapy at Tata Memorial Hospital, Bombay, India. Leuk Lymphoma 1996; 20: 311-5.
- Advani SH, Iyer RS, Pai SK, Gopal R, Saikia TK, Nair CN, et al. Fouragent induction/consolidation therapy for childhood acute lymphoblastic leukemia: an Indian experience. Am J Hematol 1992; 39: 242-8.
- Hussein H, Sidhom I, Naga SA, Amin M, Ebied E, Khairy A, et al. Outcome and prognostic factors of acute lymphoblastic leukemia in children at National Cancer Institute, Egypt. J Pediatr Hematol Oncol 2004; 26: 507-14.
- Hiyoshi Y, Fujimoto T, Kuriya N, Otani Y, Mibu K, Yanai M, et al. Prognostic factors in children with acute lymphoblastic leukemia. Part II: Multivariate analysis. Children's Cancer and Leukemia Study Group. Jpn J Clin Oncol 1985; 15: 13-23.
- Shing MM, Li CK, Chik KW, Lam TK, Lai HD, Ng MH, et al. Outcome and prognostic factors of Chinese children with acute lymphoblastic leukemia in Hong Kong: preliminary results. Med Pediatr Oncol 1999; 32: 117-23.
- 12. Shrappe M. Prognostic factors in childhood acute lymphoblastic leukemia. Indian J Pediatr 2003; 70: 817-24.
- Pui CH, Relling MV, Downing JR. Acute lymphoblastic leukemia. N Engl J Med 2004; 350: 1535-48.
- Moricke A, Reiter A, Zimmermann M, Gadner H, Stanulla M, Dordelmann 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 2008; 111: 4477-89.
- Lee ET, Wang JW. Statistical Methods for Survival Data Analysis.
 3rd ed. John Wiley & Sons, Inc: New York; 2003.
- Bhurgri Y, Bhurgri A, Hassan SH, Zaidi SH, Rahim A, Sankaranarayanan R, et al. Cancer incidence in Karachi, Pakistan: first results from Karachi Cancer Registry. Int J Cancer 2000; 85: 325-9.
- Luo XQ, Ke ZY, Huang LB, Guan XQ, Zhang YC, Zhang XL. High-risk childhood acute lymphoblastic leukemia in China: factors

- influencing the treatment and outcome. Pediatr Blood Cancer 2009; 52: 191-5.
- Brown S, Belgaumi A, Ajarim D, Kofide A, Al-Saad R, Sabbah R, et al. Loss to follow-up of patients with malignant lymphoma. Eur J Cancer Care (Engl) 2004; 13: 180-4.
- Campana D, Behm FG. Immunophenotyping of leukemia. J Immunol Methods 2000: 243: 59-75.
- Rivera GK, Raimondi SC, Hancock ML, Behm FG, Pui CH, Abromowitch M, et al. Improved outcome in childhood acute lymphoblastic leukemia with reinforced early treatment and rotational combination chemotherapy. Lancet 1991; 337: 61-6.
- Evans WE, Relling MV, Rodman JH, Crom WR, Boyett JM, Pui CH. Conventional compared with individualized chemotherapy for childhood acute lymphoblastic leukemia. N Engl Med 1998; 338: 499-505
- Vora A, Frost L, Goodeve A, Wilson G, Ireland RM, Lilleyman J, et al. Late relapsing childhood lymphoblastic leukemia. Blood 1998; 92: 2334-7.
- Campbell M, Salgado C, Quintana J, Becker A, Vargas L, Cabrera ME, 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 1999; 33: 88-94.
- Howard SC, Pedrosa M, Lins M, Pedrosa A, Pui CH, Ribeiro RC, et al. Establishment of a pediatric oncology program and outcomes of childhood acute lymphoblastic leukemia in a resource-poor area. JAMA 2004; 291: 2471-5.
- Kulkarni KP, Marwaha RK, Trehan A, Bansal D. Survival outcome in childhood ALL: experience from a tertiary care centre in North India. Pediatr Blood Cancer 2009; 53: 168-73.
- Pui CH, Ribeiro RC. International collaboration on childhood leukemia. Int J Hematol 2003: 78: 383-9.
- 27. Metzger ML, Howard SC, Fu LC, Peña A, Stefan R, Hancock ML, et al. Outcome of childhood acute lymphoblastic leukemia in resource-poor countries. Lancet 2003; 362: 706-8.
- Bonilla M, Moreno N, Marina N, deReyes G, Shurtleff SA, Downing JR, et al. Acute lymphoblastic leukemia in a developing country: preliminary results of a nonrandomized clinical trial in El Salvador. J Pedatr Hematol Oncol 2000; 22: 495-501.