ORIGINAL ARTICLE

Pattern of relapse in paediatric acute lymphoblastic leukaemia in a tertiary care unit

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Abstract

Objective: To determine the frequency, site and time to relapse from diagnosis, and to see the relationship of relapse with important prognostic factors.

Methods: The prospective descriptive observational study was conducted at the National Institute of Child Health, Karachi, June 2005 to May 2007, and comprised newly-diagnosed cases of acute lymphoblastic leukaemia. Bone marrow aspiration was done on reappearance of blast cells in peripheral smear and cerebrospinal fluid. Detailed report was done each time when intra-thecal chemotherapy was given or there were signs and symptoms suggestive of central nervous system relapse. SPSS 12 was used for data analysis.

Results: Of the 60 patients enrolled, 4(6.6%) expired and 1(1.7%) was lost to follow-up. Of the 55(91.6%) who comprised the study sample, 35(58%) were males and 25(42%) females. Mean age of relapse was 6.8±3.27 years. Mean time to relapse from diagnosis was 1.3±0.54 years; 12(20%) patients suffered relapse, and of them 5(14%) were boys. Central nervous system relapse in 8(67%) patients was the most common site, with 3(25%) bone-marrow relapses. Out of 12 patient with relapses, 9(75%) had white blood cell count less than 50,000/cm.

Conclusion: Relapse in acute lymphoblastic leukaemia was common, although treatment modalities are improving day by day.

Keywords: Acute lymphoblastic leukaemia, Blast cells, Bone marrow, Relapse. (JPMA 66: 961; 2016)

Introduction

Paediatric acute lymphoblastic leukaemia (ALL) is a biologically heterogeneous disease and is the most common childhood malignancy in most parts of the world. It represents approximately 30% of all malignancies in children younger than 15 years.[1-6] Moreover, it constitutes 32% of all paediatric cancers[4] and is the 5th most common paediatric malignancy, with more than 3,000 new cases in the United States annually.[5-10] The incidence of ALL is approximately 3-4/100,000 among under 15-year-olds.[3]

ALL, is a malignant disorder of blood in which lymphoblast, an early precursor of lymphoid series, replaces the normal haematopoietic cells of bone marrow (BM). This results in decreased production of normal cells leading to anaemia, thrombocytopenia and neutropenia of varying degrees.

Traditionally, its treatment is based on induction, remission, consolidation phase, followed by maintenance therapy and the prophylaxis. With the advent of modern combination chemotherapy, along with effective central nervous system (CNS) prophylaxis and risk adaptive treatment protocol, survival outcome has dramatically improved to over 80% in developed countries.[3-6] However, relapse is still observed in 15-20% of children during or even after completion of therapy. BM relapse is the major obstacle to cure in 10-15% of young patients. The most important determinant of outcome is the duration of initial remission and site of relapse.[6] ALL may also relapse in unusual extramedullary sites like bones and joints.[8]

The rate of clearing the leukemic cells from the smear after the initiation of therapy is associated with the outcome, gender (especially female), age (1-9 years), that have favourable outcome. Higher white blood cell (WBC) count at the time of diagnosis may have an increased risk of treatment failure and relapse with B-precursor ALL. Elevated WBC count is also associated with other prognostic factors such as unfavourable chromosome translocations like t (4:11) and t (9:22).

In most patients, the disease ultimately recurs. It is thought that such relapses result from a sub-clinical level of residual leukaemia known as minimal residual disease (MRD).[9] MRD-based high-risk patients have a significantly greater rate of relapse than the low-risk group. MRD detection can help in using more intensive therapy for patients who are at true risk of relapse.[10] After initial intensive chemotherapy, MRD detection is done by several methods. Literature shows that patients with MRD at the end of induction have progressed almost as poorly as those with >5% marrow blast cells i.e. treatment failure.[11] It has been identified by various studies that children with negative blood MRD by 8th day of induction had excellent prognosis while those whose BM MRD was positive by 29th day (end of induction) had high rates of relapse. Current clinical trials for children with leukaemia now incorporate MRD monitoring at the end of induction into risk stratification for additional therapy and are evaluating the sensitivity and specificity of

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MRD in predicting later relapse.[12]

The current study was planned to identify the relationship of relapse in ALL with age and gender as well as WBC count at the time of diagnosis. Besides, identification of the site of relapse was also explored and so was time to relapse after initiation of therapy.

Patients and Methods

The prospective descriptive observational study was conducted at the Oncology Unit of the National Institute of Child Health (NICH), Karachi, from June 2005 to May 2007. After ethical approval from the institutional review board, all newly-diagnosed cases of ALL on the basis of blast cells on peripheral smear or immunophenotyping, between 2-14 years of age and of either gender, were enrolled. Patients with other malignancies and those who had received initial treatment somewhere else were excluded.

Patients who fulfilled the inclusion criteria were selected for follow-up after obtaining verbal informed consent from their parents. The follow-up lasted three years, and was taken as standard for the NICH to assess the early complication or relapse. The follow-up started with the consolidation phase and continued after the completion of ALL treatment for two years. United Kingdom ALL (UKALL) protocol 2003 v 7 and Berlin-Frankfurt-Munster (BFM) protocol was used to treat the study group.[13,14] The said institution was using both protocols to treat ALL as per the clinic-pathological situation of the patients. Most of the information was taken from patients' files. During chemotherapy, BM aspiration was performed on day 1 and then on day 28. Thereafter BM aspiration was done only if complete blood count (CBC) showed reappearance of blast cells. Cerebrospinal Fluid detailed report (CSF D/R) for blast cells was performed each time when intrathecal chemotherapy was given, that is on days 1, 15 and 28 of induction phase and then in weeks 8, 9, 10, 11 and 16 during interim maintenance phase, or in the presence of signs and symptoms suggestive of CNS relapse. In the absence of any evidence, no testicular ultrasound and biopsy were performed.

SPSS 12 was used to analyse the data. Frequencies and percentages were calculated for all qualitative/categorical variables including gender, age groups, and relapse in patients. Mean and standard deviation (SD) were computed for age and time to relapse. Chi-square test of independence was used to see the association of age groups and gender with relapse (positive or negative), at 5% level of significance. A Kaplan-Meier method and log-rank test was used to see the difference in survival curves and estimation of survival over time.

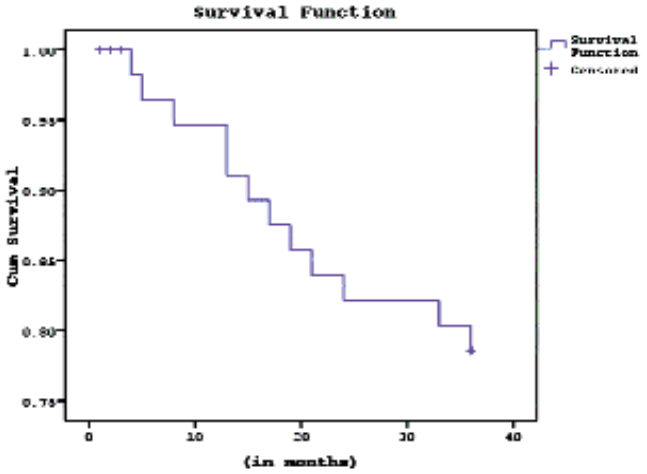
Results

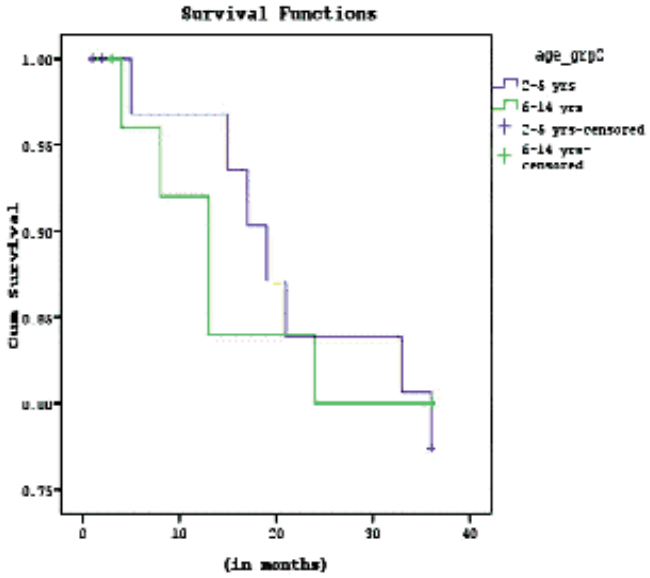
Of 60 patients enrolled, 04(6.6%) patients died and

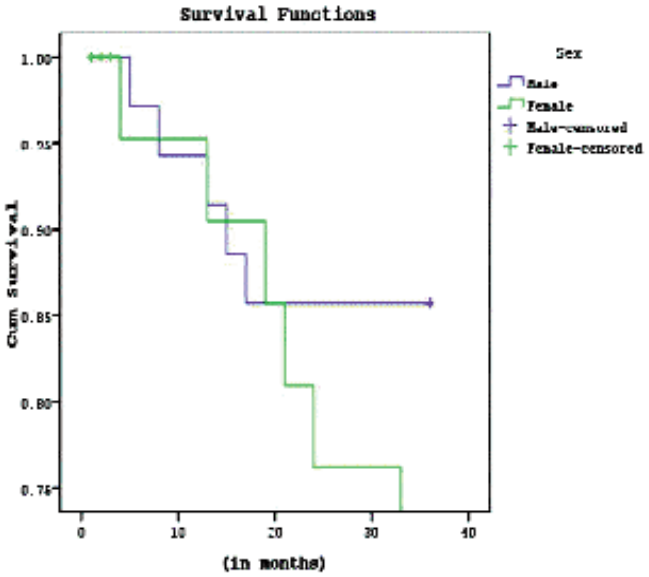
Table-1: Demography and Laboratorial data.

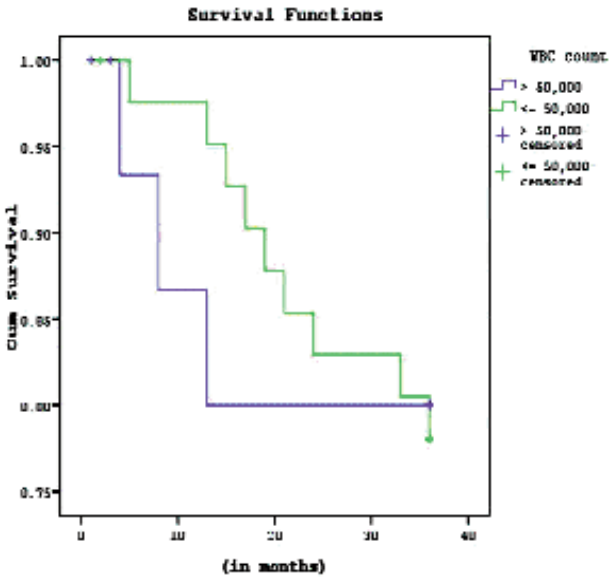
	n (%)
Gender	
Male	35 (58.3)
Female	25 (41.7)
Total	60
Age group	
2-5 years	34 (56.7)
6-9 years	13 (21.7)
10-14 years	13 (21.7)
Total	60
LFT	
Normal	56 (93.3)
De-ranged	4 (6.7)
Total	60
HBsAG	
+ve	2 (3.3)
-ve	58 (96.7)
Total	60
Coagulation screen	
Normal	57 (95)
De-ranged	3 (5)
Total	60
Hyperuricaemia	
Yes	11 (18.3)
No	49 (81.7)
Total	60
Urea and Creatinine	
Normal	58 (96.7)
De-ranged	2 (3.3)
Total	60
Tumour lysis	
Yes	1 (1.7)
No	59 (98.3)
Total	60
CSF blast	
+ve	4 (6.7)
-ve	56 (93.3)
Total	60
Treatment	
BFM	28 (46.7)
UKALL	32 (53.3)
Total	60
Relapses	
No	48 (80.0)
Yes	12 (20.0)
Total	60
Site relapse	
Bone Marrow	3 (25.0)
CNS	8 (66.7)
Combine	1 (8.3)
Total	12

LFT: Liver function test. HBsAG: Hepatitis B surface antigen.
CSF: Cerebrospinal fluid.
BFM: Berlin-Frankfurt-Munster.
UKALL: United Kingdom Acute Lymphoblastic Leukaemia.
CNS: Central nervous system.









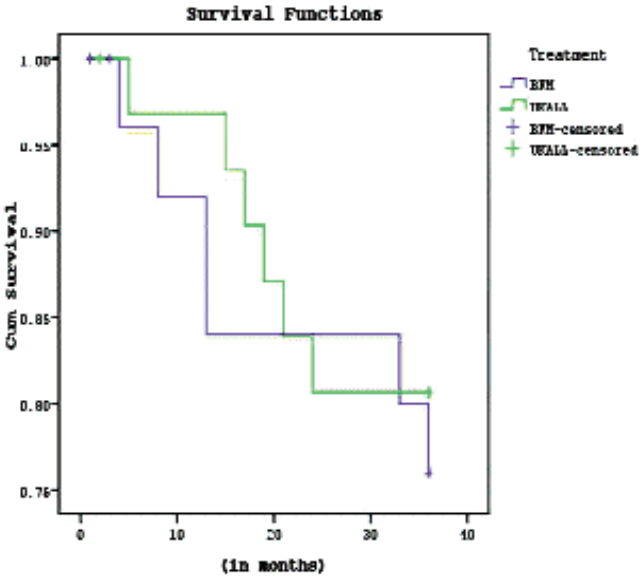


Figure: Different Kaplan-Meier survival plots showing probability of survival with time to relapse (in months).

Table-2: Percent of relapses by different associated factors.

	No-relapse N=48	Relapse N=12	Total N=60	P-value
Gender				
Male	30 (85.7)	5 (14.3)	35	0.210
Female	18 (72)	7 (28)	25	
N	48	12	60	
Treatment				
BFM	22 (78.6)	6 (21.4)	28	1.00
UKALL	26 (81.3)	6 (18.8)	32	
N	48	12	60	
Age Group				
2-5 years	27 (79.4)	7 (20.6)	34	1.00
6-14 years	21 (80.8)	5 (19.2)	26	
N	48	12	60	
WBC counts				
> 50,000	15 (83.3)	3 (16.7)	18	1.00
<= 50,000	33 (78.6)	9 (21.4)	42	
N	48	12	60	
LFT				
Normal	46 (82.1)	10 (17.9)	56	0.175
De-ranged	2 (50)	2 (50)	4	
N	48	12	60	
HBsAG				
+ve	1 (50)	1 (50)	2	0.363
-ve	47 (81)	11 (19)	58	
N	48	12	60	
Coagulation Screen				
Normal	46 (80.7)	11 (19.3)	57	0.495
De-ranged	2 (66.7)	1 (33.3)	3	
N	48	12	60	
Hyperuricemia				
Yes	7 (63.6)	4 (36.4)	11	0.206
No	41 (83.7)	8 (16.3)	49	
N	48	12	60	
Urea n Creatinine				
Normal	47 (81)	11 (19)	58	0.363
De-ranged	1 (50)	1 (50)	2	
N	48	12	60	
Tumour lysis				
Yes	0 (0)	1 (100)	1	0.200
No	48 (81.4)	11 (18.6)	59	
N	48	12	60	
CSF blast				
+ve	3 (75)	1 (25)	4	1.00
-ve	45 (80.4)	11 (19.6)	56	
N	48	12	60	

BFM: Berlin-Frankfurt-Munster
UKALL: United Kingdom Acute Lymphoblastic Leukaemia
WBC: White blood cell
HBsAG: Hepatitis B surface antigen
CSF: Cerebrospinal fluid.

01(1.7%) was lost to follow-up. Of the 55(91.6%) patients, in the study, 35(58%) were boys and 25(42%) were girls; the male-to-female ratio being 1.4:1 (Table-1). Mean age was 6.8±3.27 years, whereas mean time to relapse from diagnosis was 1.3±0.54 years. There were 12(20%) cases of relapse; 7(59%) were between 2-5 years of age, 4(33%) between 6-9 years and 1(8%) was over 10 years.

Table-3: Per cent of background characteristics by type of treatment.

	BFM N=28	UKALL N=32	Total N=60	P-value
Gender				
Male	14 (50)	21 (65.6)	35	0.221
Female	14 (50)	11 (34.4)	25	
N	28	32	60	
Age Group				
2-5 years	12 (42.9)	22 (68.8)	34	0.04
6-14 years	16 (57.1)	10 (31.3)	26	
N	28	32	60	
WBC counts				
> 50,000	18 (64.3)	0 (0)	18	<0.0001
<= 50,000	10 (35.7)	32 (100)	42	
N	28	32	60	

WBC: White blood cell.

Table-4: Kaplan Meier analysis for comparison of mean survival time between two groups.

	Mean	S.E	N	95% Confidence Interval	P-value
Treatment					
BFM	31.6	2.1	28	(27.4, 35.8)	0.658
UKALL	32.3	1.4	32	(29.5, 35.1)	
Gender					
Male	32.5	1.5	35	(29.6, 35.4)	0.122
Female	31.1	2.1	25	(27.0, 35.3)	
WBC counts					
> 50,000	30.5	2.9	18	(24.8, 36.1)	0.987
<= 50,000	32.6	1.3	42	(30.0, 35.1)	
Age Group					
2-5 years	32.6	1.5	34	(29.6, 35.6)	0.898
6-14 years	31.3	2.0	26	(27.4, 35.2)	
Over all	32.0	1.237	60	(29.6, 34.4)	

BFM: Berlin-Frankfurt-Munster.
UKALL: United Kingdom Acute Lymphoblastic Leukaemia.
WBC: White blood cell.

Among the case with relapse, 3(25%) had it within a year, while 9(75%) had relapse within two years. The mean time to relapse was 17.4±10.2 months.

The association of relapsed and non-relapsed patients with demography and laboratory factors were not statistically significant (Table-2). The treatment mode with gender and WBC count showed significant 95% confidence interval (CI) (Table-3). The mean survival time calculated was 32±1.23 months (95% CI: 29.6, 34.4) with probability of survival at 80% (Figure). Younger age group, females, and those with platelets count <50,000 had better survival outcomes (Table 4). But we did not find any significant difference between UKALL and BFM protocols (p>0.05).

Discussion

ALL is common in children aged 2-5 years. Our study demonstrated male predominance with ALL, but no significant difference could be identified among different age groups with fewer relapse rates. Both the treatment protocols had similar outcomes for cure and relapse. All patients had relapse while on different phases of chemotherapy.

ALL survival among children has improved to approximately 80%,[15] but the outcome for those who have a relapse remains poor.[16,17] This study gives us an insight into the patterns of relapse in children with ALL. Four successive Medical Research Council-ALL trials during 1985 and 2001 identified that the overall incidence of relapse has decreased to 49%,[18] though incidence and

pattern of relapses may vary according to the protocols used.

The pattern of relapse in childhood ALL has changed with respect to time and site.

Irrespective of treatment protocols, relapses in paediatric population is dependent on the duration of initial remission,[17] followed by predilection for extra-medullary relapses, especially CNS. Those who relapse within the first 18 months of diagnosis also have significantly worse outcome.

Organ of relapse is the crucial predictor for second remission, event-free survival, and overall survival after relapse.[19] The rates of isolated meningeal and testicular relapses have now been reduced to 5% and <1%, respectively. However the BM still remains the major site of relapse which is in contrast to CNS relapse observed in our study.

Rivera GP et al,[20] demonstrated a reduction of 10% relapse rate with intensive and timely first-line treatment. Similarly, an Indian study identified 29.9% relapse after complete remission of disease with BM as the most frequent site; most (73%) were receiving chemotherapy when the relapse occurred or they had it within 6 months of the therapy completion.[21] Relapse while on chemotherapy and high incidence of CNS and testicular relapse indicate the need for reappraisal of treatment protocols.[22]

ALL can relapse even after decades; two- or three-year follow-ups are too short to ascertain the types and site of relapses. However this may help to distinguish the pattern of early relapse while on chemotherapy or shortly after. We found no big difference between short- and long-term follow-ups. Huang et al. followed ALL over a period of 15 years and found 31% relapse.[23] Schmiegelow et al. found 65% BM relapse and 22% CNS relapse with 10% relapse in testes over a period of 21 years of follow-up.[24] Further, 27% of relapses were observed in the study of Children's Cancer and Leukaemia Study Group from 1981 to 1988 with BM at 70%, CNS 25% and testes 5%.[25] Isolated relapses of marrow and the CNS as documented by Kulkarni et al.[22] were different from this study. Similarly, multivariate regression analysis showed that gender and total leukocyte count (TLC) were significant predictors of relapse.

Different studies give different results, like Hiyoshi et al. identified age as important prognostic factor with disease onset; favourable between 2 and 6 years. The most significant contributions among the various individual prognostic factors were initial WBC count and the age at diagnosis.[26] However, Horibe et al. identified female gender, B-cell precursor ALL and WBC count as favourable prognostic factors for ALL in children.[27] However, univariate analysis by Donadieu et al. described male, initial WBC count of 50,000/cm^3 and age under one and more than 9 years as predictive of poor outcome.[28] But Paediatric Oncology Group Study demonstrated no difference in gender and outcome analysis.[29]

According to another study conducted at National Taiwan University Hospital for newly-diagnosed cases of childhood ALL, univariate analysis of failure-free survival showed six variables with significant detrimental effects on eventual outcome, including high TLC (greater than 50,000/cm^3).[30]

Conclusion

Relapse in ALL is common though treatment modalities are improving day by day. CNS relapse was more common, with higher rates among girls. Most patients relapsed during maintenance therapy so there is a need to introduce a more intensive maintenance therapy. To reduce the frequency of relapse, efforts should be done for early detection of high-risk patients.

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Conflict of Interest: No.

Funding Sources: No.

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