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Clinical Characteristics and Prognosis of Pediatric Patients with Acute Lymphoblastic Leukemia Relapse in Saudi Pediatric Age Group – Single Center Experience

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Abstract

Context: Acute lymphoblastic leukemia (ALL) is the most common pediatric cancer worldwide, and it accounts for 30% of all cancer cases in children of Saudi Arabia. Relapsed leukemia is the fourth malignant disease in pediatrics.

Aim: This study aims to describe the clinical characteristics and outcomes of pediatric Relapsed ALL.

Settings and design: This retrospective study was conducted at a single tertiary hospital in Saudi Arabia.

Methods and data analysis: Clinical data and outcomes of all cases with relapsed acute lymphoblastic leukemia under age of 16 year diagnosed and treated from 1 January 2012 till 31 December 2020. All patients' data and information were retrieved from patients' hard and electronic medical records and collected in REDCap system. Data analysis was done by using Statistical Package for the Social Sciences (SPSS) program version.

Results: Within the first four years of the study period, 155 cases were diagnosed with acute leukemia. In this study the relapse rate for acute lymphoblastic leukemia was 13% with overall survival about 47%, and the disease progression related mortality was 54%, while the treatment related mortality was 45% with overall mortality of 52%.

Conclusion: Relapsed ALL becomes a serious problem in pediatric oncology with relatively poor outcomes. The difficulty in treating relapse disease with satisfying results compels us to enhance the therapy for the newly diagnosed patients at the front lines considering more effective and better treatment options. Promising new molecular and immunological targeted therapies and improved HSCT technologies should be rapidly integrated into trials for subsets of higher-risk patients at initial diagnosis. Further refining of the risk stratification with the increased focus on the importance of analyzing detailed cytogenetics and molecular data in the era of application of next-generation sequencing followed subsequently by tailored risk-adapted therapy is the cornerstone of modern relapse therapy. International collaboration is essential to serve as a platform for progress in the treatment of relapsed childhood ALL.

Keywords: Pediatric leukemia • Childhood leukemia • Relapsed acute lymphoblastic leukemia • Infantile leukemia

Introduction

Acute lymphoblastic leukemia (ALL) of childhood is the most common malignancy in children younger than 15 years [1], with approximately 85% of cases being B-cell precursor ALL (B-ALL). The incidence of acute pediatric ALL in Saudi Arabia was 2.35/100,000 population in 2014 [2].

Significant improvement in the overall survival rate in those children has been achieved over the past few decades, from approximately 10% in the 1960s to almost 90% today (3-4). Despite this remarkable improvement, around 2% of patients are refractory to induction chemotherapy [3-5], and up to 10–15% ALL patients still experience a relapse during or even after completion of therapy [6,7]. However, subsequent second complete remission (CR) can be achieved in most patients (7–8); approximately 55% of those patients will relapse again [8,9]. The general approach for managing those children involves using intensive chemotherapy, with or without novel agents to induce a third remission, followed by hematopoietic stem cell transplant (HSCT) if indicated [10,11]. Unfortunately, despite all these options of treatment, the overall prognosis is not significantly improved in the relapsed patients. Relapse is still a significant risk factor threatening the long-term survival of ALL pediatric patients. The age in the initial diagnosis, leukocyte count, immunophenotyping, cytogenetic, gene characteristics, minimal residual disease (MRD), and early therapeutic response are the main risks factors for assessing the relapse of ALL pediatric patients [12]. The success in treating acute ALL is achieved by applying risk-adapted therapy to individualize treatment intensity according to each patient's risk of relapse. Critical to the success of this approach has been the accurate assignment of individual patients to specific risk groups. However, some pediatric patients in the standard-risk group also suffer from relapse in the early and late-stage, indicating that the current risk stratification cannot accurately predict the prognosis. Therefore, finding new strategies to give accurate assessment for the clinical status and correlations with its outcome is needed. The current study is to study the risk factors of all the patients with relapsed ALL and their clinical outcomes.

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Methodology

Patient

Our study is a retrospective study conducted at King Fahad Specialist Hospital, Dammam. This tertiary care hospital is located in the eastern province of Saudi Arabia and provides services in the following specialties: Oncology, Neurosciences, Organ Transplant, Cardiac Services Programs, and

Genetic Sciences. Revision of the medical records for all the cases with acute lymphoblastic leukemia under the age of 16 years from the first of January 2012 to the end of December 2015 and has relapsed disease occurs before the thirty-first of December 2020. The institutional research ethics committees approved the study in our institute.

Clinical data collection

This is a retrospective single-center study that included all relapsed ALL cases diagnosed and managed within a defined study period, including B-cell ALL, T cell ALL, Infantile leukemia, mixed linage, and as well as patient with down syndrome. Both medullary and extra medullary disease recurrence were included. All the data were retrieved from patients' hard and electronic medical records and collected in the REDCap system. Data analysis was done by using Statistical Package for the Social Sciences (SPSS) program version. Risk group assignment was based on The National Cancer Institute (NCI)/Rome criteria, Remission status at the end of induction was evaluated by Minimal residual disease (MRD) testing, However, unfortunately, our laboratory cut point of positive MRD at study period was more or equal to 0.1% detectable leukemia cells, any value less than this point was considered negative. Induction failure was considered if bone marrow morphology at the end of the induction showed >25% blast (M3). Very early relapse was considered to those events occurring 36 months from remission. Medullary relapse was defined as >5% blasts in the bone marrow (BM). Isolated extramedullary relapse was defined as ≤ 5% blasts in the BM with evidence of disease in central nerve system (CNS), testicular, or other extramedullary sites. Combined relapse was defined as >5% blasts in the BM and evidence of extramedullary leukemia.

Data management and analysis

All data abstracted on the data collection form were entered into REDcap, converted to an Excel sheet, and revised for accuracy and missed information. Time of Relapsed was calculated by subtracting the date of relapse from the date of diagnosis. Descriptive statistics are presented as mean and frequencies (percentages). Kaplan-Meier survival curve analysis method was used for the comparison of 5-year OS rates in different groups.

Results

During the study period from the 1st January 2012 to the end of December 2015.160 children were diagnosed with ALL, five of them excluded because they received all or part of their first line treatment course in another institution. 21 (13.5%) patients have relapsed disease before 31 December 2020 (Figure 1). Out of 21 relapsed patients 10 (47.6%) were males and 11 (52.4%) were females (with no significant different between male and female ratio, male ratio= M/F=0.9).

Patient's characteristics

Considering our population of the relapsed disease 21 cases, we found that the overall median age at the time of diagnosis was four years, and the mean age at diagnosis is 5.6 years,15 (72%) of them are between 1 and 10 years. Regarding their initial presenting symptoms at their primary disease onset and physical examinations (Table 1), 12 (57%) presented with fever and 8 (38%) has bone pain, 14 (67%) patients have their symptoms more than one week and less than four weeks. Physical examination revealed cervical lymphadenopathy in 13 (62%) patients,11 has larger than 1cm lymph node and 12 (57%) patients has hepatosplenomegaly. 6 (29%) out of 21 patients has positive family history of malignancy. Only two patients were identified with Down syndrome, no other patients diagnosed with one of the other known cancer predisposition syndromes.

The majority of relapsed ALL cases were with B-CELL ALL, 15 cases (71%), The rest were T-CELL ALL in 3 cases (14.3%), infantile leukemia in 2 patients (9.5%) and only 1 case (4.8%) with mixed linage (B-Cell ALL and myeloid linage), approximately 43% of our relapsed patient has high WBC count >50.000 × 109/L at initial presentation. In addition, four patients had positive CNS disease, and 17 (81%) patients were negative for CNS disease. Almost two-thirds of the relapsed populations, 14/21 (67%), including the two cases of infantile leukemia, were assigned as a high-risk therapy. The rest, one-third, were assigned as standard risk group 7 cases (33%). Interestingly, around 81% of total relapsed patients showed an excellent response to induction therapy with negative MRD (defined as <0.1%) at day 29 of the first line therapy, and only 19% of them had positive MRD at day 29 of induction (Table 1).

Most of our patients (71%) had no significant chemotherapy modification or delays during their front line of therapy. However, 19% (4 cases) were found to have parts of their induction course were interrupted or delayed for more than two weeks due to documented invasive infections, and another 14% (3 cases) had significant delays in their post-induction courses. Only one patient from the high-risk group had his scheduled Pegylated asparaginase omitted from his post-induction courses due to severe allergy. Since Erwinia Asparagina was not available, the later patient had not been compensated.

Cytogenetic and molecular analysis

Routine cytogenetic studies were performed for all our 21 cases. Specific common translocations seen in childhood ALL were tested by fluorescence *in situ* hybridization (FISH). Numerical chromosomal abnormalities are detectable by karyotyping with 76% (16 cases) of the relapsed patient has diploidy number, approximately 5% (1 patient) has high hyper-diploid and other 5% has high hypodiploid. Unfortunately, the karyotyping test was not done in around 14% (3 cases) due to unavailability of the test or unsuitable sample.

Tests done at relapse setting showed that ETV6-RUNX1 abnormality was detected in 38% (8 cases) with 75% of those patients (6/8 cases) were had that abnormal clone at primary leukemia, and only 25% (2/8 cases) acquired these defects as new abnormality at relapse setting. IGH abnormalities were noticed in 24% (5 cases), with 40% of them having this defect as a new clone at relapse setting. CDKN2A abnormalities were observed in 19% (4 cases), and all of them had similar defects at their original leukemia. Similarly, Trisomy 4, 10, 17 were found in 14% (3 cases) that's again were noticed at the initial leukemia diagnosis onset. Most of our patients, 43%, had a single cytogenetic abnormality detected at relapse setting while 33% had more than one cytogenetic abnormality; in 24%, the cytogenetic abnormalities were not determined or mentioned at relapse setting, including the case of isolated testicular relapse. We found that more than half (57%) of our relapsed patients had the same cytogenetic abnormalities that were found in the initial diagnosis, while 19% acquired different cytogenetic profiles. The rest their cytogenetic profile undetermined or not done at relapsed sitting (Table 2). Molecular testing data further identified 5% (1 case) with TCR gene rearrangement and another 5% (1 case) with MLL rearrangement.

Relapse site and time

Eight patients relapsed during first-line therapy (38%), while 62% of our patients were off treatment when they relapsed. An one-third (33%) of our patients had a late relapse (more than 36 months from diagnosis), while 43% had early relapsed (18-36 months), and the rest of our patients (24%) have very early relapsed (less than 18 months from diagnosis) (Table 3). Most of our patients, 76%, were asymptomatic at relapse onset and discovered during routine clinical follow-up. Most of those patients have medullary relapsed acute lymphoblastic leukemia 76%, where approximately 20% had combined

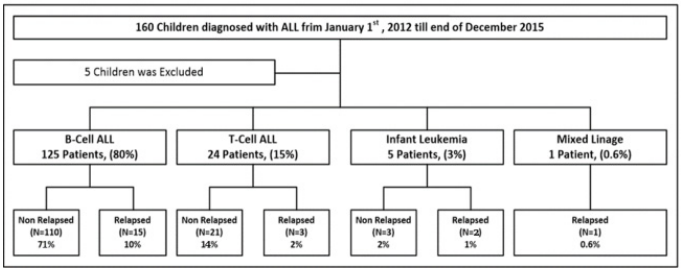

Figure 1. Consort diagram.

CNS and medullary relapsed disease. Only one case (5%) has isolated extramedullary (testicular) relapsed.

Among our relapsed population, we identified three patients with initial positive CNS 2 status at their initial leukemia onset; two out of them relapsed medullary, while the third one had isolated testicular relapsed. In addition, we have one patient with CNS 3 who initially had combined CNS and medullary relapsed disease. The very early relapse group (5 cases) were T-cell leukemia (3 patients) and mixed lineage (1 patient). Unfortunately, all the relapsed T-cell ALL did not respond to second-line therapy (0% survival rate). The early relapse group involved two cases with infant leukemia and another 7 cases with B-cell leukemia.

Multiple chemotherapy regimens (graph 1) were used to treat those patients, including AALL0433, AALL01P2, FLA protocol, clofarabine-based chemotherapy, and bone marrow transplantation. Two cases received

Table 1. Characteristics at initial diagnosis of patients with ALL (N=21).

Category	Sub-category	Frequency (f)	Percentage (%)
Age at Diagnosis	<1 Year	2	9.5
	1-9.9 Years	15	71.5
	≥ 10 Years	4	19
Presented symptoms*	Bone pain	8	38.1
	Fever	12	57.1
	Weight loss	1	4.8
	Bruises	3	14.3
	Weakness	1	4.8
	Lethargy	5	23.8
	Respiratory symptoms	0	0
	Swelling	1	4.8
	Pallor	2	9.5
Duration of symptoms	Less than 1 week	2	9.5
	More than 1 week-4 weeks	14	66.7
	More than 4 weeks	5	23.8
Gender	Male	10	47.6
	Female	11	52.4
Down syndrome	Yes	2	9.5
	No	19	90.5
Adenopathy (Site)*	Cervical	13	61.9
	Axillary	4	19.1
	Inguinal	3	14.3
	Mediastinal	0	0
	Generalized	1	4.8
	None	6	28.6
Adenopathy (Size)	<1 cm	4	19
	>1 or equal of 1 cm	11	52.4
	Negative	6	28.6
Organomegaly	Spleen	0	0
	Liver	4	19.1
	Hepatosplenomegaly	12	57.1
	Testicular	0	0
	Skin (Chloroma)	0	0
	Chloroma) 0 0.00 N	5	23.8
WBC × 109/L	<10,000	5	23.8
	10,000- 50,000	7	33.3
	>50,000	9	42.9
Initial CNS involvement	CNS 1	17	81
	CNS 2	3	14.2
	CNS 3	1	4.8
Immuno- phenotype	Infantile leukemia	2	9.5
	B-cell ALL	15	71.4
	T-cell ALL	3	14.3
	Mixed linage	1	4.8
Risk at diagnosis	SR	7	33.3
	HR	12	57.2
	Infantile leukemia	2	9.5
MRD day 29	Negative <0.1%	17	81
	Positive ≥ 0.1%	4	19
	Induction failure	0	0
Total		21	100

blinatumomab abroad after been sent at CR2 for evaluation of further therapy. Bone marrow transplantation was performed in 24% (5 cases). The primary indication for allogeneic BMT in our patients was early relapse leukemia in 3 cases. One case with infantile leukemia and one with late relapse failed to achieve CR2 after second induction chemotherapy. Unfortunately, about 40% (2/5) of the BMT cases died while they were in CR.

Among 21 relapsed 13 cases,62% had only a single relapse received two lines of therapy, while 7 (33%) cases got the second relapse 33% received three lines of therapy; only one patient (5%) received four lines of therapy (including BMT). In addition, cranial radiation is given to 2 patients as part of their treatment.

Outcome of the relapsed patient

Overall, we had 11 Out of 21 relapsed cases (52%) die within our study period; 6 out of them died with disease progression and multi-organ failure. In comparison, 5 (45%) died during remission status because of serious complications such as gut toxicities in form of typhlitis and perforated bowel (2 cases) and severe sepsis with multi-organ failure (3cases). We had 4 out of the 5 cases (80%) of the very early relapse die (including 3 cases with isolated

Table 2. Patient's characteristic at diagnosis and on relapse setting.

Patient	Immunophenotype	NCIRisk	Karyotyping	Cytogenetic	Molecular	Outcome
1	B Cell ALL	SR	46	Negative	Negative	Alive
1 R*			46	Negative	IGH rearrangement	
2	Infantile Leukemia	HR	46	TCF3/PBX1+IGH	TCF3-PBX1+ IGH rearrangement	Die
2 R*			46	TCF3/PBX1+IGH	TCF3-PBX1+ IGH rearrangement	
3	T Cell ALL	HR	46	Negative	Negative	Die
3 R*			46	Negative	Negative	
4	B Cell ALL	HR	53-56	Ttetrasomy RUNX1+ TRISOMY IGH+ trisomy 4/10/17	Negative	Alive
4 R*			52~55	Trisomy 4, 10 and 17	IGH rearrangement	
5	B Cell ALL	SR	46	Trisomy 4, 10 and 17	Negative	Die
5 R*			46	Trisomy 4, 10 and 17+ tetrasomy	IGH rearrangement	
6	T Cell ALL	HR	46	PBX1+ tetrasomy RUNX1+ trisomy IGH	TCRG rearrangement	Die
6 R*			46	Negative	TCRG rearrangement	
7	T Cell ALL	HR	46	Trisomy SIL/TAL1	TCRG and TCRB rearrangement	Die
7 R*			NA	CDKN2A homozygous deletion + trisomy 5`TCRAD	Negative	
8	B Cell ALL	SR	NA	CDKN2A homozygous deletion + trisomy 5`TCRAD	IGH rearrangement	Die
8 R*			46	Tetrasomy RUNX1+Trisomy IGH, +Trisomy 10	Negative	
9	B Cell ALL	SR	46	Tetrasomy RUNX1	Negative	Die
9 R*			47	Trisomy RUNX1	Negative	
10	B Cell ALL	HR	44	Trisomy RUNX1	IGH rearrangement	Die
10 R*			44	Pentasomy-hexasomy IGH+monosomy CDKN2A	IGH rearrangement	
11	B Cell ALL	HR	46	Deleted 5'IGH+ETV6/RUNX1+Tetrasomy-pentasomy	IGH rearrangement	Alive
11 R*			45	+monosomy CDKN2A	IGH rearrangement	
12	B Cell ALL	SR	NA	Nullisomy CDKN2A	Not done IGH, TEL/AML1-ve	Alive
12 R*			46	Nullisomy CDKN2A	IGH rearrangement+ TEL/AML1	
13	B Cell ALL	HR	46	ETV6/RUNX1 fusion genes	IGH rearrangement	Alive
13 R*			46	ETV6/RUNX1 fusion genes	Negative	
14	B Cell ALL	SR	46	Trisomy 4 and 10+ETV6/RUNX1 fusion	Negative	Die
14 R*			45	ETV6/RUNX1 fusion gene,+Partial deleted IGH	IGH rearrangement	
15	B Cell ALL	SR	NA	Trisomy IGH+ trisomy RUNX1+trisomy 4/trisomy 17	IGH rearrangement	Die
15 R*			NA	Trisomy IGH+ trisomy RUNX	Negative	
16	Mixed Linage	HR	46	Trisomy BCR+Trisomy IGH+Trisomy RUNX1+Trisomy 10	Negative	Alive
16 R*			NA	Trisomy 10	Negative	
17	B Cell ALL	HR	46	Negative	Negative	Alive
17 R*			46	Not done	IGH rearrangement	
18	B Cell ALL	HR	NA	Diminished ETV6	Not done testicular relapsed	Alive
18 R*			NA	Diminished ETV6	Negative	
19	B Cell ALL	HR	46	Trisomy RUNX1+monosomy CDKN2A	IGH rearrangement	Alive
19 R*			46	Not done (testicular relapsed)	MLL1 rearrangement	
20	Infantile Leukemia	HR	46	Homozygous del CDKN2A	MLL1 rearrangement	
20 R*			46	Homozygous del CDKN2A	Not done	Die
21	B Cell ALL	HR	46	Monoallelic loss of TCF3 gene + MLL gene rearrangement		
21 R*			46	MLL gene rearrangement +TCF3 NA	MLL1 rearrangement	Alive
			NA	Negative	Not done	
R* Relapse sitting, SR Standard Risk, HR High Risk, NA not available				Negative	IGH rearrangement	

Table 3. Relapsed site of 21 cases.

Relapse Period	Bone marrow (BM)	Testicular	Combined (CNS +BM)
Total	16 (76.2%)	1(4.8%)	4 (19.0%)
Very early relapse	4	0	1
Early relapse	7	0	2
Late relapse	5	1	1

bone marrow relapse and one case with combined BM and CNS relapse). Thus, we got five deaths out of 9 (55%) of the early relapse group (3 with isolated BM relapse and 2 with combined BM +CNS). Lastly, we had 2 out of 7 patients (28%) who belonged to the late relapse group died, and both were having isolated bone marrow relapse. In this study, the relapse rate for acute lymphoblastic leukemia was 13% (Figure 3), with overall survival for those patients about 47% (Figure 2), the disease progression related mortality was 54%, while the treatment-related mortalities were 45%, with an overall mortality of 52%.

Discussion

ALL is the most common type of acute leukemia in children, accounting for approximately 80% [13], with the commonest subtype being B-lineage expression. Our study data showed similar findings with 80% of our acute lymphoblastic leukemia are of B cell type.

In recent years, with the improvement of risk stratification, chemotherapy regimens and the approach of HSCT the cure rate of ALL pediatric patients has been up to 85% [14]. The long-term survival rate has reached approximately 90% [15]. Despite this remarkable improvement, ~2% patients are refractory to induction chemotherapy, and an additional 15-20% of ALL still experience a relapse [16], which started to be a familiar entity in pediatric oncology and currently considered as the fourth most common childhood malignancy [12], Despite emerging new second treatment lines, yet it still carries relatively poor clinical outcomes, with survival rates far inferior to what is known with the initial diagnosis. Only approximately 50% of children with the first ALL relapse survives long-term, and even worse with subsequent relapses. [17]. Our study showed a slight lower relapsed rate (13.5%), even lower than reported from a similar national study, 22%. [18].

Relapses in patients who were ten years old or older at diagnosis time have been reported as independent predictors of poor outcomes [19]. A Children's Oncology Group (COG) study further showed that those patients aged 10 to 15 years at initial diagnosis do worse than patients aged 1 to 9 years (35% *vs*. 48% 3- year post-relapse survival) [20]. Our data show poor prognosis with 75% of our patients ten years and older at diagnosis died with the five years OS approximately 25% compared to 40% death rate for those aged between 1 and ten years of age, and OS about 60%. Down syndrome patient with relapsed leukemia has a poor prognosis [21]. We have two patients, both relapsed between 18-36 months, and both died, the first one because of the disease progressions and the other one due to septicemia. Our data showed that our patients who were stratified as a standard risk at initial presentation had a better outcome with three years survival 57% in the standard-risk group and 24% in the high-risk group.

The time to relapse was 38.6 months in the standard-risk group compared to 30.9 months in the high-risk group. A similar result was reported in one study by the Children's Oncology Group clinical trials where they mentioned that the OS 50% in standard-risk *vs*. 22% in a high-risk group [19] Among all the acute lymphoblastic leukemia patients diagnosed and treated in our center within the study period, we got 125 patients with B- cell ALL who further stratified as standard risk group 62 (49.6%) patients and high-risk group 63 (50.4%) patients. interestingly, we found that the percentage relapse was nearly similar between the two groups, with 7 (47%) patients from the standard risk group and 8 (53%) patients from the high-risk group. It is worth mentioning that our data showed a higher percentage of high risk patients than another national study, 38% [18], and a higher relapsed rate in patients in the standard-risk group at diagnosis than other studies [22-23].

The onset of relapse plays an essential role in determining the prognosis.

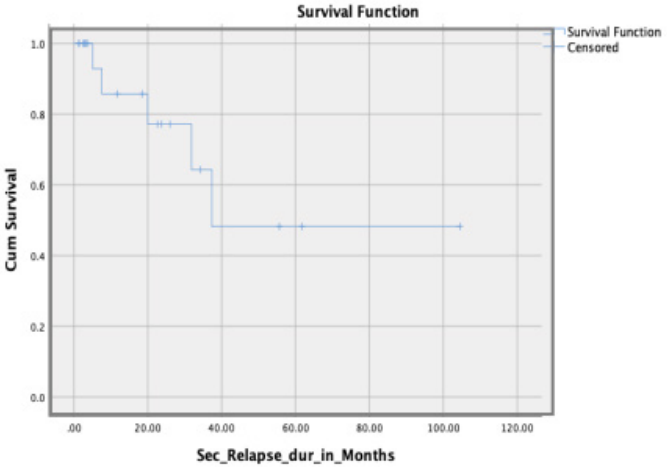

Figure 2. Kaplan-Meier survival plots showing probability of survival in relapsed leukemia (in months).

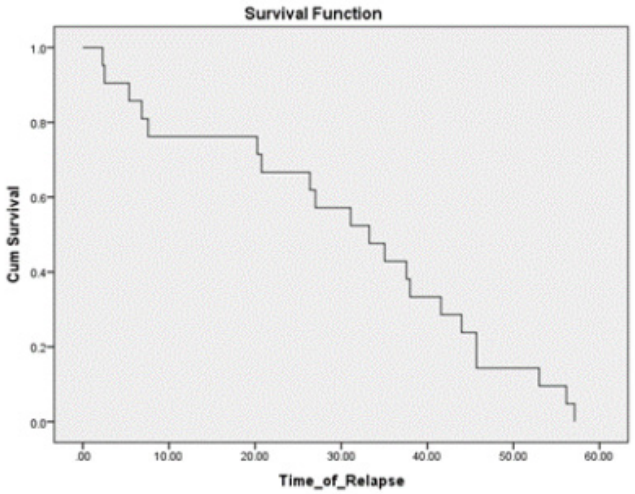

Figure 3. Kaplan-Meier survival plots showing probability of survival in relapsed leukemia (in months). Probability of relapse with time (in months).

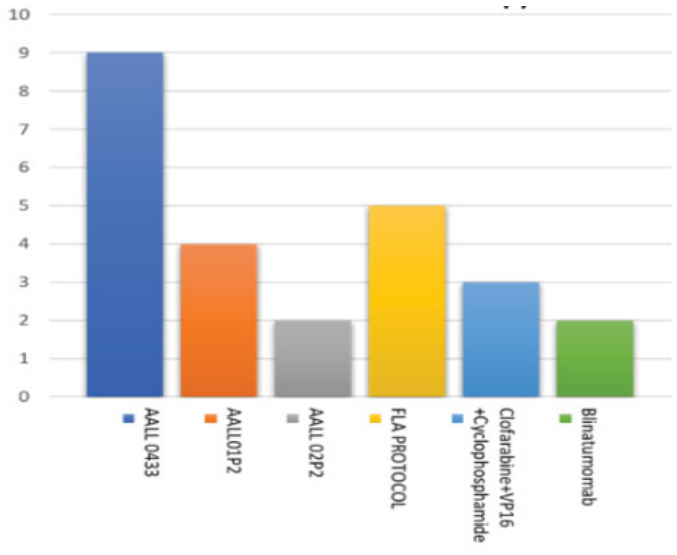

Figure 4.Chemotherapy protocols used as second and third line of therapy.

Many studies define early (very early) relapses occurring in the first 18 months from diagnosis, intermediate (early) relapses happening between 18-36 months from diagnosis, and late relapses occurring after 36 months. Survival for patients experiencing BM relapse in less than 18 months from diagnosis range from 0%-15%, while those with medullary relapses that happen between 18 to 36 months from diagnosis have survival rates from 10- 40%. For patients with late BM relapses after 36 months from diagnosis, survival rates range from 14- 50% [19]. This study demonstrates similar data, that our patients who relapsed within the first 18 months of diagnosis had worse outcome with OS only 20% compared to those with late relapse in whom the OS reached over 70%.

Another crucial prognostic feature of the relapsed acute lymphoblastic leukemia is the site of the relapse, as they found that relapses involving sites other than bone marrow tend to have a better prognosis. The survival rates of CNS relapses approach 51%, and those for isolated testicular relapses range from 53-84% [19]. Unfortunately, the medullary relapse is the most common in ALL pediatric patients, and its cure rate is poor compared to the extramedullary sites and the combined relapsed. In our study, 76% (16/21) of patients had isolated medullary relapsed, 50% (8/16) of them died during the study period. Survival rates after isolated bone marrow relapse at 0-17 months, 18-35 months, and after 36 months were 6%+/-2%, 11% +/ -2%, and 43%+/-4%, respectively [23]. However, our survival data for the isolated bone marrow relapse showed higher rates with 25% for marrow relapse below 18 months and 57% for 18-35 months, around 60% for those after 36 months.

On the other hand, we had 4 cases, about 19% with the combined central nervous system and medullary relapsed, with almost 75% mortality except for one case that belonged to the late group after 36 months. Again, this is inferior to the survival rate for this group of patients, as mentioned in one study above [19]. Our single case with isolated testicular relapse disease went in remission and remained alive by reporting this study. Another interesting observation in our research is that, as demonstrated with some other studies [24], our patients with combined CNS and medullary relapsed disease have earlier relapse onset than those with isolated medullary or testicular relapsed with a mean time to relapsed 28, 30.2, and 41.6 months respectively. Our study has four patients with CNS disease at initial presentation who had subsequent disease relapse. There was no apparent preference for any site of relapse (two had isolated CNS relapse, one with isolated testicular disease and the last one had combined CNS and medullary relapsed). MRD levels at the end of remission induction therapy measured by multiparameter flow cytometry have clinical significance in childhood ALL. High levels of MRD are strongly related to poor treatment outcomes [25]. Nevertheless, few studies on a limited number of patients studied MRD and its prognostic value during second-line chemotherapy for relapsed ALL [26]. In our study, we had four patients (19%) found to have positive MRD at the end of their initial front-line end of induction; fortunately, only one patient out of them died in our study. Unfortunately, in the earlier years of the study period, the method for the MRD measuring was not validated, and the cut-off point for the end of induction was not as less than 0.01 MRD as in current chemotherapy protocols (Figure 4).

Children with relapsed T-cell ALL present a worse prognosis than those with BCP-ALL, with a poor survival rate for T-ALL relapse, lower than 25%. The leading cause of relapse is the high rate of chemotherapy resistance initiated by novel mutations and the early infiltration observed in T-cell ALL. Further studies have shown that 80% of relapses occur within two years of diagnosis and mainly occur in the bone marrow (57.3%). [27] All our patients with relapsed T cell leukemia have very early relapsed (less than 18 months), and all of them died with a mean survival time of 1.97 months compared with those with B cell leukemia have a better mean survival time of 23 months. 5 years OS for those with B-cell ALL is 53%.

ETV6/RUNX1 significantly impacted overall survival after relapse (3-year survival= 64.7% for positive cases *vs.* 46.5% for negative patients [28]. The 5-year OS rate for ETV6-RUNX1 patients who relapsed at any site more than 36 months after diagnosis was 81%, and this group of patients specifically had favorable survival outcome compared with other late relapsing patients. On the other hand, the 3-year OS rate of ETV6-RUNX1 patients who experienced an early relapse (<36 months) was only 31% [28].

However, 38% of our total enrolled relapsed patients had ETV6-RUNX1, 55% of them experienced late relapses longer than 36 months, and 80% of them were alive till the end of our study surveillance. Compared to the rest of 44% who had early relapse between 18 to 36 months, and we found those cases had poor outcomes with only 25% five years OS. It is well known that recurrent acute lymphoblastic leukemia (ALL) is the most frequent indication for allogeneic stem cell transplantation (SCT) in children because the outcomes were shown to be dismal after treatment with chemotherapy only [27]. allogeneic hematopoietic stem-cell transplantation (HSCT) has resulted in a significant improvement of event-free survival (EFS) and overall survival (OS) in this group of patients; however, its advantage in the intermediate-risk group remained less critical considering the complications that are associated with unrelated donor (UD-SCT); future studies might help to identify the actual subgroups of the intermediate group who still could benefit from UD-SCT [28-29].

Although we had a 40% mortality rate, nearly a quarter of our patients offered allogeneic BMT during their relapse therapy had improved survival results with the mean survival period of 65 months, and those who offered BMT compared to 26.6 months for those who had not. In this study the relapse rate for acute lymphoblastic leukemia was 13% with overall survival for those patients about 47%, the disease progression related mortality was 54%, while the treatment related mortalities were 45% with overall mortality of 52%.

Considerable limitation in this study includes the small number of patients and being a single-center study. In addition, the inability to perform the MRD in earlier years of the study, lack of some cytogenetics data in some cases, and the short follow-up period from the study to the time of publication were important boundaries to this study. Hopefully, in the future, we will aim to run further joined study with another current ongoing study in our center that addresses the clinical features and outcomes for all the pediatric patients with acute lymphoblastic leukemia that could give a clearer picture about those groups of children in our institute.

Conclusion

In conclusion, relapsed ALL becomes a serious problem in pediatric oncology with relatively poor outcomes. The difficulty in treating relapse disease with satisfying results compels us to enhance the therapy for the newly diagnosed patients at the front lines considering more effective and better treatment options.

Promising new molecularly and immunologically targeted therapies and improved HSCT technologies should be rapidly integrated into trials for subsets of higher-risk patients at initial diagnosis.

Further refining of the risk stratification with the increased focus on the importance of analyzing detailed cytogenetics and molecular data in the era of application of next-generation sequencing followed subsequently by tailored risk-adapted therapy is the cornerstone of modern relapse therapy.

International collaboration is essential to serve as a platform for progress in the treatment of relapsed childhood ALL.

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