

First Relapse of Acute Lymphoblastic Leukemia in Children in Upper Egypt: Survival Outcome and Prognostic Factors

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Abstract

Background: Relapse is the main reason of treatment failure in childhood acute Lymphoblastic leukemia (ALL).

Aim: To study the treatment outcome of first ALL relapse in response to two different reinduction regimens and prognostic factors predicting outcome.

Methods: A retrospective study that included 82 children with ALL in the 1st relapse from two tertiary oncology centers in Upper Egypt. Patients were treated according to the St. Jude ALL-R16 protocol. Seventeen patients were treated with a standard reinduction (regimen 1) and 65 were treated with a modified reinduction regimen in which anthracycline was added and asparaginase was reduced to 9 doses (regimen 2). Response, survival and prognostic factors were analyzed.

Results: Second, complete remission (CR2) was achieved in 57% of all patients (65% with regimen 2 vs. 29% with regimen 1, $p = 0.009$). FLAG regimen resulted in achieving CR2 in all patients with reinduction failure. Treatment related mortality was more common with regimen 2 than with regimen 1 (34% vs. 12%, respectively). For all patients, the 2-year overall and event-free survival rates were 30% and 25%. In multivariate analysis, high initial total leukocytic count, isolated medullary relapse, regimen 1 and very early relapse were independently associated with worse event free survival ($p = 0.031, 0.017, 0.037$ and 0.001 ; respectively).

Conclusions: The overall outcome of treatment of first ALL relapse in children in our region is poor. New intensive chemotherapy regimens may help in improving the treatment outcome.

Keywords: Acute Lymphoblastic Leukemia, First relapse, Children, Survival, Prognostic factors, Egypt

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Introduction

During the past decades, marked treatment improvement in acute lymphoblastic leukemia (ALL) has been achieved^{1,2}. However, relapse is still the major cause for treatment failure and its outcome hasn't improved largely³⁻⁵.

Treatment of ALL relapse in countries with limited resources is further complicated because of the limited availability of salvage treatment and the lack of chance of bone marrow transplantation (BMT) or target therapy. In addition to other factors such as the high treatment-related mortality and lack of awareness⁶.

In previous salvage therapy protocols, reinduction therapy was mostly similar to the induction therapy of frontline protocols and the

policies for post-remission therapy were not uniform and the outcomes were poor^{3,7,8}. At St. Jude Children's Research Hospital (SJCRH), the use of intensified rotational combined chemotherapy in relapsing ALL protocol avoids the development of drug resistance through a rapid succession of the use of multiple agents. Moreover, fludarabine, a fluorinated purine analogue that isn't incorporated in the frontline protocols of pediatric ALL, has a great success in consolidating a second remission^{9,10}. Also, UK-ALLR3 study reported a significant benefit of mitoxantrone in progression-free and overall survival (OS) in children with relapsed ALL based on its chemosensitivity profile especially B-cell through different mechanisms¹¹. Other anthracyclines, such as daunorubicin and

doxorubicin, showed their efficacy in relapsing ALL patients in different BFM treatment protocols^{5,8}.

Previously at our institution, there was no uniform protocol for treating relapsed ALL patients. With the use of the St. Jude ALL TXIII B protocol, survival of newly diagnosed pediatric ALL improved at our institution while the relapsed patients died shortly after relapse¹². We aimed at assessing the outcome of ALL children in first relapse treated with the St. Jude ALL R16 protocol with the addition of an anthracycline during reinduction therapy. Additional aims were to confirm the established prognostic factors and to evaluate new ones in the light of this treatment strategy.

Methods

This retrospective study included 82 pediatric patients who presented at Pediatric Oncology Departments of South Egypt Cancer Institute and Sohag Cancer Center with first ALL relapse (isolated medullary relapse [IMR], isolated extramedullary relapse [IEMR], or combined) from October 2013 to May 2019. Relapse with lineage switch or subsequent relapses were excluded. In addition, patients who died within one week of admission before starting effective therapy or those who abandoned initial treatment were excluded.

Patients' records were reviewed for the diagnosis of first ALL relapse, site, and timing of relapse in addition to patients' characteristics at initial diagnosis. We classified the timing of relapse into very early if relapse occurred within 18 months of diagnosis; early if occurred ≥ 18 months of diagnosis till 6 months after finishing treatment and late if relapse occurred after 6 months from finishing¹³.

Patients were treated according to the St. Jude ALL- R16 protocol. Reinduction in 17 patients was as the original protocol (regimen 1)⁹. An anthracycline was added on days 1 and 8 of reinduction therapy in 65 patients (regimen 2) as follow: patients with very early / early relapse received mitoxantrone (12 mg/m²) or daunorubicin (25 mg/m²) and patients with late relapse received daunorubicin (25 mg/m²). Asparaginase in regimen 2 was given for 9 doses instead of 12 doses as in regimen 1. After reinduction, all patients were continued according to the original protocol, including primary consolidation (FLAG [fludarabine, cytarabine, and granulocyte colony-stimulating factor]), secondary consolidation, then 2 modules of four cycles of intensive continuation and lastly 17 months of standard continuation. Teniposide in the standard

continuation was substituted by etoposide (200 mg/m²) due to its unavailability.

Second complete remission (CR2) of bone marrow relapse was defined as $<5\%$ blasts in the recovered bone marrow in the absence of clinical signs of disease. Patients who did not achieve CR2 were considered reinduction failure and surviving patients were termed refractory¹⁴, but they continued the treatment protocol. Disease-related mortality included deaths during reinduction failure or 2nd relapse even if treatment toxicity was the direct cause. Treatment-related mortality (TRM) included deaths due to treatment toxicity and 2nd malignancy¹⁵.

Statistical analysis

Patients were followed up until August 2020. Median and range were used to describe the continuous data and number and percentage for the categorical data. Chi-square / Fisher exact test was used to compare proportions. For survival analysis, Overall survival was calculated from the date of diagnosis of first relapse to the date of death due to any cause. Event-free survival (EFS) was calculated from the date of first relapse to the date of death of any cause, reinduction failure, second relapse, or occurrence of a 2nd malignancy. Patients with reinduction failure were considered as having an event on day 0¹⁶. Kaplan-Meier method was used to estimate both OS and EFS, and comparison between groups was made using the log-rank test. Variables, that were significant in univariate analysis, were included in multivariate cox regression analysis to find the independent prognostic factors affecting EFS after relapse. P-value was always two-tailed and significant at 0.05 level. The IBM SPSS software, version 23.0. (Armonk, NY: IBM Corp.) was used for data management.

Results

Patients' characteristics

Eighty-two patients with ALL in the first relapse were eligible for this study. The median time to relapse was 27 months (range: 3-100). The initial frontline treatment included modified TXIII-B protocol¹⁷ (75 patients), BFM-90 (5 patients)¹⁸, or TXV (2 patient)¹⁹. Patients' characteristics in relation to the timing of relapse are summarized in Table 1. Sixteen (19.5%) patients relapsed late and 66 (80.5%) patients had an early relapse, 24 of them occurred very early. Older patients at diagnosis (≥ 10 years) and those with T-cell ALL relapsed very early or

Table 1: Characteristics of 82 children with acute lymphoblastic leukemia in 1st relapse

Variable	Total (n=82)	Very early relapse (n=24)	Early relapse (n=42)	Late relapse (n=16)	<i>p</i> value
Age at diagnosis (years)					
Median (range)	7 (1-16.5)	10.5 (3-16.5)	9 (1-16)	5 (1.5-9)	
< 10	51 (62.2%)	10 (41.7%)	25 (59.5%)	16 (100%)	0.001
≥ 10	31 (37.8%)	14 (58.3%)	17 (40.5%)	0	
Sex					
Male	40 (48.8%)	15 (62.5%)	19 (45.2%)	6 (37.6%)	0.242
Female	42 (51.2%)	9 (37.5%)	23 (54.8%)	10 (62.5%)	
TLC at diagnosis ($\times 10^9/L$)					
Median (range)	41.5 (1.5-542)	76 (1.9-542)	55 (1.6-198)	15.3 (1.5-99)	
<50 $\times 10^9/L$	41 (50%)	10 (41.7%)	19 (45.2%)	12 (75%)	0.065
≥ 50 $\times 10^9/L$	41 (50%)	14 (58.3%)	23 (54.8%)	4 (25%)	
CNS infiltration at diagnosis					
No	72 (87.8%)	18 (75%)	40 (95.2%)	14 (87.5%)	0.133
Yes	10 (12.2%)	6 (25%)	2 (4.8%)	2 (12.5%)	
Immunophenotyping					
B-ALL	59 (72%)	16 (66.7%)	27 (64.3%)	16 (100%)	0.02
T-ALL	23 (28%)	8 (33.3%)	15 (35.7%)	0	
Site of relapse					
Isolated medullary relapse	37 (45.1%)	20 (83.3%)	13 (31%)	4 (25%)	<0.001
Isolated extramedullary relapse	34 (41.5%)	4 (16.7%)	22 (52.4%)	8 (50%)	
Combined	11 (13.4%)	0	7 (16.7%)	4 (25%)	

CNS: Central nervous system; **TLC:** Total leucocytic count

early and none of them relapsed late. The site of relapse differed significantly as well according to the timing of relapse. Other variables had no significant association as shown in Table 1.

Response to reinduction

The treatment outcome is shown in Figure 1. Forty-seven (57.3%) patients achieved CR2, 21 (25.6%) had reinduction failure and 14 (17.1%) died during reinduction. Eight out of the 21 patients with reinduction failure had ≥25% bone marrow response. Reinduction deaths were due to infectious complications (8 patients with fulminant pneumonia, 4 with acute gastroenteritis and typhlitis, and 2 with hypoalbuminemia and sepsis).

The relationship between reinduction outcome and patients' characteristics is shown in Table 2. Reinduction outcome differed significantly according to initial total leucocytic count (TLC), immunophenotyping, site of relapse and reinduction regimen. As regards the reinduction regimen, CR2 was far more common with regimen 2 than with regimen 1 (64.6% vs. 29.4%, respectively; $p = 0.006$).

Post-reinduction therapy

Among the 7 patients who developed toxic deaths after the FLAG consolidation, 5 failed reinduction with IMR and 2 achieved CR2. The seven deaths were due to chest infection and sepsis.

During continuation treatment, 18 patients (22%) developed 2nd relapse within a median time of 11 months (range: 2- 26). There was no significant difference in the rate of 2nd relapse between regimen 1 and 2 (4/17 [23.5%] vs 14/65 [21.5%], $p = 0.184$). Second relapse was mainly CNS relapse in 12 patients. All patients who experienced a 2nd relapse died due to disease progression within 4 months. While progression occurred mainly in the bone marrow in 13 patients who survived after reinduction failure. Myelosuppression was the most frequent cause of delay of intensive continuation therapy for >4 months in 33 (54.1%) patients. Sixteen patients did not complete intensive continuation; 3 of them were referred for BMT and the others got relapse or progression. Treatment-related mortality in 8 (9.8%) patients (all of them received regimen 2) after CR2 during continuation treatment and the causes were brain abscess (1), post-infectious Guillain Barre (1), 2^{ry} AML (2), fulminant bacterial pneumonia and sepsis (1) and organ dysfunction (3).

All nonfatal complications recovered except in 2

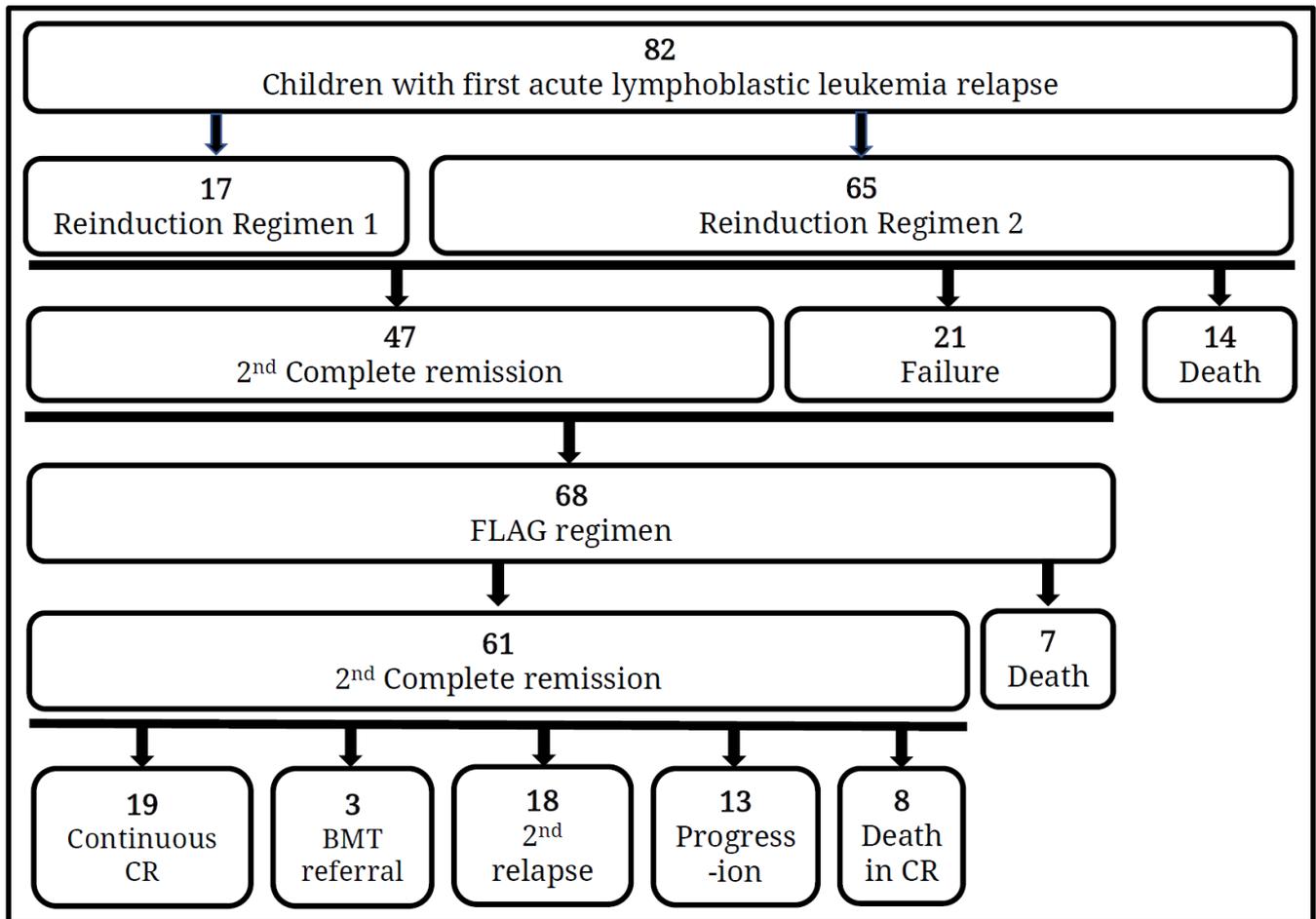


Figure 1: Flow diagram of management outcome of 82 children with first acute lymphoblastic leukemia relapse

Table 2: The relationship between reinduction outcome and variables

Variable	Reinduction outcome			p value
	2 nd complete remission (n=47)	Reinduction failure (n=21)	Reinduction death (n=14)	
Age at diagnosis (years)				
<10	28 (54.9%)	13 (25.5%)	10 (19.6%)	0.724
≥10	19 (61.3%)	8 (25.8%)	4 (12.9%)	
Initial TLC (×10⁹/L)				
<50	31 (75.6%)	6 (14.6%)	4 (9.8%)	0.004
≥50	16 (39%)	15 (36.6%)	10 (24.4%)	
Immunophenotyping				
B-ALL	34 (57.6%)	19 (32.2%)	6 (10.2%)	0.009
T-ALL	13 (56.5%)	2 (8.7%)	8 (34.8%)	
Timing of relapse				
Very early	10 (41.7%)	10 (41.7%)	4 (16.7%)	0.747
Early	25 (59.5%)	7 (16.7%)	10 (23.8%)	
Late	12 (75%)	4 (25%)	0	
Site of relapse				
Isolated medullary relapse	16 (43.2%)	17 (45.9%)	4 (10.8%)	0.003
Isolated extramedullary relapse	22 (64.7%)	4 (11.8%)	8 (23.5%)	
Combined	8 (81.8%)	0	2 (18.2%)	
Reinduction regimen				
Regimen 1	5 (29.4%)	10 (58.8%)	2 (11.8%)	0.006
Regimen 2	42 (64.6%)	11 (16.9%)	12 (18.5%)	

patients; one had subacute encephalopathy and the other had epilepsy postcranial radiotherapy. Nineteen (23.2%) patients were still living in continuous complete remission (CCR) for a median duration of 41 months (range: 21-77).

Disease-related death was more common in regimen 1 than regimen 2 (14 [82.4%] patients vs. 25 [38.5%], respectively), while treatment-related mortality was more common in regimen 2 than regimen 1 (22 [33.8%] patients vs. 2 [11.76%], respectively) ($p = 0.003$).

Survival outcome

With a median follow-up of 39 months (range: 9-141), the 2-year OS rate was 30.2% (SE: 5), and the 2-year EFS rate was 25.4% (SE: 5) (Figure 2).

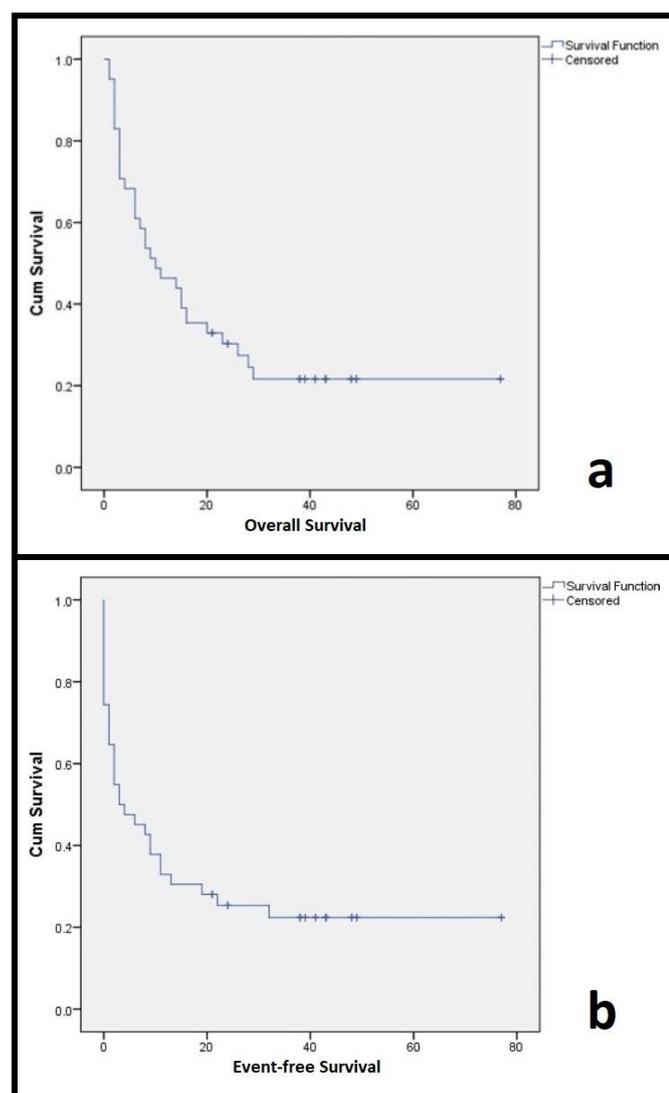


Figure 2: Kaplan- Meier curves of a) overall survival and b) event-free survival

The relationship between the studied variables and the 2-year overall and event-free survival rates is shown in Table 3.

The multivariate Cox regression analysis confirmed the unfavourable outcome of high initial TLC, reinduction regimen 1, IMR, and early / very early relapse on EFS with the highest hazard ratios were associated with IMR and very early relapse as shown in Table 4. Immunophenotyping had no impact on survival outcomes after fixing other prognostic factors (TLC, timing of relapse, site of relapse) except for that B-cell ALL had a significantly better OS than T-cell only if associated with favourable age ($p = 0.026$).

Reinduction regimen 2 improved significantly the EFS of very early relapse and early relapse patients than regimen 1 ($p = 0.011$ and 0.020). Event-free survival of late relapse did not differ significantly between regimens 1 and 2 ($p = 0.170$).

Discussion

We found that the overall outcome of children with relapsed ALL in our region is poor; however, good survival was observed in some of them. Timing of relapse was the most powerful predictor of outcome after relapse. Second CR and 2-year OS rates of patients with late relapse were 75% and 87.5%, respectively. Adding anthracyclines to the reinduction treatment had a better impact on inducing CR2 and on OS and EFS of very early / early relapse but not late relapse. These findings can help us in designing the treatment strategy after relapse in children with ALL based on the timing of relapse.

Median time until relapse of our ALL patients was 27 months (range: 3-100) with more than 80% of relapsed patients in the study were very early or early relapse. This is in agreement with others²⁰⁻²².

Late relapse in our study did not involve older age (≥ 10 years) or T-ALL, that reported by others^{4, 23-25}. It is well known that the majority of relapses occurs in the bone marrow^{4, 21, 26, 27}. While, in our study, the pattern of relapse has changed with an increase of IEMR to be near IMR (41.5% and 45.1% respectively) which was observed in an earlier study¹². This may be related to the lack of good identification and treatment of patients with CNS 2 criteria of de novo cases.

The overall 2-year OS and EFS rates (30.2% and 25.4%) in this study are much lower than those of developed countries where survival exceeds 50%^{11, 16}. While we were very similar to the 3-year OS and

Table 3: The relationship between variables and event-free and overall survival after first relapse in children with acute lymphoblastic leukemia

Variable	2-year EFS rate (SE)	<i>p</i> value	2-year OS rate (SE)	<i>p</i> value
Age at initial diagnosis (years)				
<10	30.9 (0.06)	0.340	38.8 (0.07)	0.099
≥10	16.1 (0.07)		16.1 (0.07)	
Sex				
Male	26.6 (0.07)	0.131	31.7 (0.08)	0.257
Female	23.8 (0.07)		28.6 (0.07)	
Initial TLC ($\times 10^9/L$)				
<50	41.5 (0.08)	<0.001	46.3 (0.08)	0.002
≥50	7.3 (0.05)		13 (0.06)	
Immunophenotyping				
B-ALL	27.1 (0.06)	0.969	33.9 (0.06)	0.281
T-ALL	18.3 (0.09)		18.3 (0.09)	
CNS infiltration at initial diagnosis				
No	26.1 (0.05)	0.449	31.7 (0.06)	0.772
Yes	20 (0.1)		20 (0.1)	
Timing of relapse				
Very early	0	<0.001	0	<0.001
Early	25.3 (0.07)		25.3 (0.07)	
Late	62.5 \pm 0.1		87.5 (0.08)	
Site of relapse				
Isolated medullary relapse	10.8 (0.05)	<0.001	10.8 (0.05)	<0.001
Isolated extramedullary relapse	22.1 (0.07)		34.3 (0.08)	
Combined	81.8 (0.1)		81.3 (0.1)	
Reinduction regimen				
Regimen 1	5.9 (0.06)	0.011	17.6 (0.09)	0.311
Regimen 2	30.5 (0.06)		33.6 (0.06)	

EFS: Event free survival, OS: Overall survival, SE: Standard error, TLC: Total leucocytic count, CNS: Central nervous system

Table 4: Multivariate Cox regression analysis of event free survival of 82 children with first acute lymphoblastic leukemia relapse

Variable	<i>n</i>	Hazard ratio	95% Confidence interval	<i>p</i> value
Total leucocytic count at initial diagnosis				
≥ 50	41	ref		
< 50	41	0.555	0.325 - 0.947	0.031
Reinduction regimen				
Regimen 2	65	ref		
Regimen 1	17	1.905	1.041 - 3.487	0.037
Relapse site				
Combined relapse	11	ref		
Isolated medullary relapse	37	6.479	1.401 - 29.958	0.017
Isolated extramedullary relapse	34	4.059	0.920 - 17.911	0.064
Timing of relapse				
Late	16	ref		
Very early	24	5.599	2.053 - 15.271	0.001
Early	42	2.971	1.122 - 7.866	0.028

EFS rates of 31.5% and 26.2% of relapsed ALL patients in Central America who were treated with curative intent ⁶. It should be noted that many factors exist making the comparison difficult, including many treatment protocols used for

relapsed patients with varying type and intensity of chemotherapy. Also, most of the protocols in developed countries incorporated the use of BMT and targeted therapy in addition to the availability of adequate supportive care.

Although the reported survival rates in our study are low, the 2-year OS and EFS for late relapse of 87.5% and 60% are comparable to the 3-year EFS and OS of 63.6% and 72.3% for late B-cell precursor bone marrow relapse in the AALL0433 trial of COG²⁸, 3-year progression-free survival of 60% and OS of 72% in the UK ALLR3 trial²⁹ and 64% 5-year EFS in Relapse ALL 98 Protocol Based on the Dutch COG³. While the poor 2-year survival for those with very early and early relapse in our study (0 and 25%) were comparable to EFS of other results (5% to 18%)^{7, 8, 30}.

The universal favourable outcome of late relapse irrespective of the treatment strategies, confirms that late relapse retains the chemo-sensitivity of the original clone as they arise from a common precursor¹¹.

The poor 2-year OS of IMR of our cohort (10.8%) is matched with most studies as the survival of IMR is worse than IEMR with an intermediate outcome of combined relapse^{4, 5, 16}. Combined relapse was unexpectedly associated with the most favourable survival (81.3%) that exceeded the survival of IEMR (34.3%). This may be related to the small number of patients with combined relapse and most of them showed favourable criteria (B-ALL in 8/11, favourable TLC in 9/11, no very early relapse, the least TRM) in addition to the early local control of the extramedullary sites that are hypothesized to be the origin of combined bone marrow relapse¹⁴.

While the BFM and United Kingdom ALL R3 study groups' risk stratifications are based on either the relapse B-cell or T-cell ALL^{11, 13}, the unfavourable prognosis of T-immunophenotype in patients with ALL relapse varied between studies if it is independent or differs according to time or site of relapse. The BFM group and SJCRH investigators reported that medullary T-cell ALL relapse has a much worse prognosis than B-cell ALL^{13, 22}. Rheingold *et al.* reported that the survival after relapse differed according to the site and certain time points of relapse⁴. Others demonstrated that the unfavourable outcome of T-immunophenotype is not related to the site or time of relapse^{5, 7, 26}. Oskarsson *et al.* reported its poor outcome only if associated with hyperleukocytosis at diagnosis¹⁶. Our results did not show a significant difference between B-cell and T-cell ALL either overall or by time or site of relapse. This may be due to the very small number of each group if classified by time and site.

The rate of CR2 achievement of 57.3% (41.7%, 59.5%, 75% for very early, early and late relapse

respectively) is much lower than that reported in the literature^{8, 30}. This may be due to the low CR2 among patients who received regimen 1 (29.4%) in addition to the high rate of deaths due to toxicity during reinduction.

In our study, the rate of reinduction deaths of 17.1% is much higher than the 4% in COG AALL1331 reinduction regimen using mitoxantrone^{31, 32}. Patients during reinduction should be hospitalized until count recovery with antibacterial, antifungal, and *Pneumocystis jirovecii* prophylaxis due to the high rate of infection as recommended by Hanger and Raetz's strategy³³.

The overall TRM in our study (29.3%) is much higher than that reported by others. It was 5% (4 of 76) in the 9412 protocol³⁴, 17.4% and 9.7% in the idarubicin and mitoxantrone arms of the ALL R3 protocol¹¹, 4% (5 of 124) in the AALL01P2 study protocol of COG⁸ and 15% (37 of 246) in patients treated with ALL-REZ BFM 90⁵. When compared to other low middle-income countries, 29.7% of patients suffered treatment-related toxicities, which is similar to our results⁶.

The treatment of the studied patients included the use of dexamethasone instead of prednisone which affects controlling CNS disease through penetrating the blood brain barrier and intensive use of asparaginase which also has a role in CNS control. Moreover, the treatment included the use of new chemotherapeutic agents that were not used for newly diagnosed cases to overcome the resistance and showed a marked response. Mitoxantrone was reported to have an excellent effect on the outcome of ALL relapse patients through its delayed cytotoxic effect¹¹. This can explain why all TRM during continuation was associated with regimen 2 despite the insignificant difference of reinduction deaths between the two regimens. A further study of the separate effect of mitoxantrone and daunorubicin is needed. Fludarabine, in the FLAG combination, produces a synergistic effect when combined with cytarabine and granulocyte colony-stimulating factor (G-CSF). The successful use of this regimen has been established in children for the treatment of refractory and relapsed ALL with minimal toxicity^{9, 35}. FLAG induced CR in all patients with reinduction failure in our cohort.

Conclusion

The survival of children with ALL after the first relapse at our centres has improved through the treatment with a uniform protocol but the outcome is still poorer than in developed countries. The

timing and site of relapse are strong predictors of the outcome and the addition of anthracyclines for those with early and very relapses has better control on leukemia, but the treatment-related toxicities are high. Therefore, we suggest designing a stratified treatment with the coverage of meticulous supportive care. Being a retrospective study is a limitation with the unequal representation of the two reinduction regimens studied. Conventional chemotherapeutic drugs still have a role in the treatment of ALL relapse with the incorporation of new drugs not used at initial treatment is recommended until treatment with targeted therapies becomes a reality.

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None.

Authors' contribution

Conception or design: All authors; Acquisition, analysis or interpretation of data: All authors; Drafting or revising the manuscript: All authors; Approval of the manuscript version to be published: All authors; Agreement to be accountable for all aspects of the work: All authors.

Conflict of interest

The authors declare that they have no conflict of interest to disclose.

Data availability

Deidentified individual participant data used to produce the results of this study are available from the corresponding author (AS) upon request.

Ethical considerations

This study was approved by the Institutional Review Board of South Egypt Cancer Institute, Assiut University, Assiut, Egypt (approval No.: 152).

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Study registration

None.

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