Adverse Events during Treatment of Pediatric Acute Lymphoblastic Leukemia South Egypt Cancer Institute, Retrospective study

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Abstract

Background: Acute lymphoblastic leukemia (ALL) is the most common malignancy in children. The breakthrough in ALL treatment granted long event free survival reaching 90 % of the patients. Even though the patients still show many adverse events during their treatment journey. These events were assignable to the disease or the side effects of the chemotherapeutic agents. Here, we sighted these adverse events in pediatric patients with ALL at South Egypt Cancer Institute, Assiut University, Egypt.

Method: we performed a retrospective descriptive cohort study on 309 pediatric ALL patients with ages >1 to < 18 years old at Pediatric Oncology Department, South Egypt Cancer Institute (SECI), Assiut University during the period from January, 2002 to December, 2017 and their follow up data were collected until December, 2019 . All adverse events that occurred during management of those patients and their outcome were analysed according to the clinical and laboratory characteristics of the patients.

Results: During study, 309 patients were eligible. Continuous complete remission was achieved in 159 (51.4%) of these patients. The adverse events emerged were evident in 66 (21.3%), 59 (19%) leukemic relapses, and 106 (34.3%) deaths. Adverse events due to chemotherapy were bone marrow suppression (grade II and III) in 45.3% and 25% respectively. Chest infection in 20% from which75% bacterial and 25% fungal. Sepsis was diagnosed in 6.5% and gastrointestinal toxicity in 20%.

Conclusion: The incidence of the adverse events during treatment was high in our institute.

Keywords: Acute lymphoblastic leukemia, adverse events, induction failure, Relapse, Mortality rate.

Introduction:

Acute lymphoblastic leukemia is the most common cancer among children and the most frequent cause of death before 20 years of age, with incidence 80% of pediatric leukemia (1). Most of ALL pediatric patients are seen in young childhood with peak incidence from (3-5) years old and the severity of the disease increase below the age of 1 year old and above 18 years (2). The main modalities of ALL treatment are chemotherapy, radiotherapy, targeted therapy and stem cell transplantation, with all the advances in these modalities we are still facing a lot of obstacles and drawbacks leading to many adverse events like treatment failure and relapse (3).

Induction failure (IF) is rare, occurring in only 2 to 3% of all patients, but it constitutes one of the most unfavorable outcomes in pediatric ALL (4). Patients who were refractory to initial induction therapy and didn't achieve complete remission (CR) were at very high risk of early relapse. Even intensive chemotherapy regimens appeared to be unsuccessful at maintaining remissions in this subset of patients (5).

Relapse is the main reason for adverse events during treatment of childhood ALL. Despite improvements in the up-front therapy, survival after relapse is still relatively poor, especially for high-risk patients (6). The adverse immunophenotyping (IPT), unfavorable cytogenetic and response to induction treatment are all an essential risk factors for relapse as well as prognostic factors (7). Treatment of relapsed ALL is typically more intensive than for newly diagnosed ALL. With all current protocols, the long-term overall survival rates ranging from 15 to 50% and cure rates after relapse of 30% to 40% are reported (8).

About 1 to 2% of ALL patients die from toxic effects during remission. Relapse deaths, considered the most common by more than 63% of the patients in some studies (9). The causes of deaths are divided into disease related mortality from the disease itself and treatment related mortality from the complication of treatment, these causes included infections, hemorrhage,

delay in diagnosis, chemo-drugs shortages, abandonment of therapy, chemotherapy-induced toxicity, and relapse (10).

Early toxic events are those toxicities occurring early during treatment and are classified according to severity into 4 grades; Grade 1 which is asymptomatic or mild symptoms, Grade 2 is Moderate, Grade 3 is Severe or medically significant that requires hospitalization and Grade 4 is Life threatening consequences that indicates urgent management and hospitalization (11).

In our study, we assessed the adverse events during treatment of pediatric ALL patients and correlated those events with different available prognostic factors to find and improve any drawbacks in our medical plans.

Patients and Methods:

The study was carried on pediatric patients with ALL at Pediatric Oncology Department, South Egypt Cancer Institute (SECI), Assiut University during the period from January, 2002 to December, 2017 and their follow up data were collected until December, 2019 to study the adverse events and their outcome during treatment. Patients were not enrolled in the study if they were < 1 year or >18 years old, diagnosed with mature B cell ALL (L3), patients died early at presentation or early induction (not completing 2 weeks), patients with unavailable medical records or complete data .

The data were collected from the patients' records**.** Detailed clinical history and examination were reported. Routine Laboratory investigations including complete blood count (CBC), liver and kidney function tests, bone marrow aspirate (BMA), cerebrospinal fluid (CSF) cytological examination, cytogenetic studies (Philadelphia chromosome done in 82 patients only) and risk stratification. Treatment protocols used were modified BFM 90 in 119 patients from January 2002 to December 2008 (12) and modified Total Therapy XIIIB at St Jude Children's Research Hospital(TXIIIB of SJCRH) in 190 patients from January 2009 till the end of the study (13) . Response assessment as early or late response by CBC on day 8, BMA at day 15 during induction therapy and BMA post induction and accordingly patients were classified into; M1: blast cell count in BMA <5% ,M2: blast cell count in BMA 5-24% and M3: blast cell count in BMA > 25 . (14)

The data of all adverse events were analysed according to number of patients (%), age, sex, clinical and laboratory data, IPT, risk stratification at diagnosis, management and outcome.

Definitions of collected adverse events: The definition of induction failure was the persistence of leukemic blasts in the bone marrow (M2 or M3) after induction phase of therapy. The definition of refractory disease was patients with induction failure who failed to attain complete remission after consolidation and reinforcement phase of therapy .The definition of relapse, which occurred after the first complete remission was > 5% blasts in the bone marrow, or leukemic infiltration elsewhere. Treatment-related deaths were defined as deaths due to chemotherapy complications or allogeneic stem cell transplantation (SCT). (15)

Ethical consideration:

The research proposal was approved from ethical committee of South Egypt Cancer Institute, Assiut University. All the data was collected from patient's records after written consent. All other rules advised by the ethical committee were applied.

Statistical analysis:

Statistical analysis was carried out using SPSS statistical software version 23 (SPSS Inc., Chicago, IL) for windows. Qualitative data are expressed by frequency and percentage; quantitative data are expressed by mean± standard deviation and median. *Chi²*-test was used to compare the nominal data of different groups in the study while *Student t test* was used in case of continuous data. P value <0.05 we considered significant. The cutoff point of the study was on 12/2019.

Results:

Table (1) shows the clinical characteristics of the patients with continuous complete remission (CCR) who presented159 (51.2%) and the 309 patients enrolled in this study. Patients treated in total XIIIB (n=190), have better overall event-free than patients treated in BFM 90 study (n=119) (53/44.5% s versus 106/55.7%).

Induction failure:

Table (2) shows the clinical laboratory characteristics and outcome of 66(21.3%) patients who had failure of induction (M2 or M3) in (41%) and (59%) respectively. The majority were males 43(65.1%) with significant P value (0.001**). HR and SR patients were 49(74.3%) and 17 (25.7%) respectively with high significant P value (0.001**). The outcome of patients after consolidation therapy was continuous remission 14(21.2%), 17(25.8%) refractory disease and 35 (53%) patients relapsed shortly after remission, with significant P value (**0.003**).**

Refractory disease:

As mentioned before 17 patients (5.5%) had refractory disease. (53%) of the patients were more than 10 years old and (65%) patients were males. (94%) of them were CNS +ve. The HR patients were (88%). All patients showed disease progression and died. (Table3).

Relapse:

Table (4) shows the clinical laboratory characteristics of 59 relapsed patients. Early relapse (< 36 months) represented in (88%) of patients and late (>36 month) in (12%) patients. The age of most relapsed patients was ≥10 years in 24 (57.6 %). Also, the majority were males (p=0.048). There was no significant difference in the distribution of immunophenotype among relapsed patients. High risk

in early relapse represented (69.2%) and (30.8%) were SR. The outcome of relapse was second remission (CR2) in 16 (27%) with one patient underwent BMT, death in 43 (72.8%) including 5 patients had multiple relapse.

Table (1): The clinical laboratory characteristics of patients in continuous complete remission and all patients enrolled in the study

Variable	Complete continuous remission No (%)	Total No (%)
Patients number	159 (51.4%)	309 (100 %)
Age		
• 2-10 year	122(39.4%)	221(71.5%)
• >10 year	37(12%)	88(28.5%)
Sex		
• Male	97(31.3%)	194(62.8%)
• Female	62(20%)	115(37.5%)
Leukocyte count, × 10^9/L		
• <50	124(40%)	202(65.3%)
• >50	35(11.3%)	107(34.6%)
Immunophenotyping		
• B lineage	135(43.6%)	241(78%)
• T lineage	24(7.7%)	68(22%)
Risk stratification		
• HR	62(20%)	173(55.9%)
• SR	97(31.3%)	136(44%)
CNS Status		
• -Ve	156(50.4%)	276(91.1%)
• +Ve	3(0.9%)	33(8.9%)
Philadelphia chromosome		
• Absent	44(14.2%)	63(20%)
• Present	13(4.2%)	29(9.3%)
BMA post first induction		
• M1	137(44.3%)	194(62.7%)
• M2	22(7.1%)	92(29.7%)
• M3	0(0%)	23(7.4%)
Chemotherapy Protocol		
• BFM 90	53(17%)	110(35.5%)
• Total Therapy studies XIIIB	106(34.4%)	199(64.4%)

Data expressed as frequency (percentage), mean (SD) according to the total number of patients (309). (CNS: central nervous system, HR: high risk, SR: standard risk, BMA: bone marrow aspirate, M1 =<5%, M2 =5-25 %, M3 = >25%)

Treatment and adverse event related mortality

Table (5) shows the clinical laboratory characteristics of the studied106 (34.3%) died patients. Death in remission represented in 25(23.5%) due to infection and sepsis during high dose chemotherapy, while 64 (60.3%) patients died in relapse. Most of the patients (53.1%) were HR also with predominance of male in 63.3%.

Table (2): The clinical laboratory characteristics and outcome of 66 patients with induction failure according to initial features

Variable	Induction failure (n=66)		P-value
	N	%	
Age			
• 2 - 10 year	47	71.2	<0.001**
• > 10 year	19	28.7	
Sex			
• Male	43	65.1	0.001**
• Female	23	34.8	
leucocytes count			
• <50(x109/l)	37	56	0.02
• > 50 (x109/l)	29	43.8	
Immunophenotyping			
• B linage	47	71.2	0.03
• T linage	19	28.7	
Risk stratification			
• HR	49	74.2	<0.001**
• SR	17	25.7	
CNS status			
• - Ve	50	75.7	<0.001**
• + Ve	16	24.3	
Philadelphia chromosome *			
• - Ve	6	9.1	0.762
• + Ve	6	9.1	
Chemotherapy Protocol			
• BFM 90	29	43.9	0.224
• Total XIII protocol	37	56	
Outcome			
• Second Remission	14	21.2	
• Refractory disease	17	25.8	0.003**
• Relapse	35	53.0	

Data expressed as frequency (percentage). *P* value was significant if < 0.05. (TLC: total leucocytic count, CNS: central nervous system, HR: high risk, SR: standard risk, *Philadelphia chromosome was done for only 12 patients)

Table (3): The clinical laboratory characteristics and outcome of 17studied patients with refractory disease according to initial features

Variable	Refractory disease (n=17)	
	No.	%
Age		
• 2-10year	8	47
• >10year	9	53
Sex		
• Male	11	64.7
• Female	6	35.3
TLC		
• <50(x109/l)	4	23.5
• >50(x109/l)	13	76.5
Immunophenotyping		
• B cell	12	70.5
• T cell	5	29.5
Risk stratification		
• HR	15	88
• SR	2	12
CNS		
• -Ve	1	5.8
• +Ve	16	94.2
Philadelphia chromosome*		
• -Ve	2	11.7
• +Ve	6	35.2
BM post reinduction		
• M2	13	76.5
• M3	4	23.5
Chemotherapy Protocol		
• BFM	8	47
• Total XIII protocol	9	53

Data expressed as frequency (percentage). TLC: total leucocytic count, CNS: central nervous system, HR: high risk, SR: standard risk, IPT: immunophenotyping, BMA: bone marrow aspirate, M2 =5-24 %, M3 = >25%, *: Philadelphia chromosome was done for only 8 patients)

Table (4): The clinical laboratory characteristics of 59 patients with relapse according to initial features

Variable	Early relapse (n=52)		Late relapse (n=7)		P-value
	No.	%	No.	%	
Age					
• 2 - 10 year	31	59.6	4	23.5	0.603
• ≥ 10 year	21	40.4	3	17.6	
Sex					
• Male	36	69.2	2	11.8	0.048*
• Female	16	30.8	5	29.4	
leucocytic count					
• <50x109/l)	26	50	3	17.6	0.928
• >50x109/l)	26	50	4	23.5	
immunophenotyping					
• B cell	37	71.2	5	29.4	0.68
• T cell	15	28.8	2	11.8	
Risk stratification					
• HR	36	69	7	41	0.094
• SR	16	30.2	0	0	
CNS status					
• - Ve	47	90	6	35.3	0.548
• + Ve	5	9.6	1	5.9	
Philadelphia chromosome					
• - Ve	9	17.3	1	5.9	0.206
• + Ve	5	9.6	3	17.6	
Previous BM post induction.					
• M1	35	67.2	2	11.8	0.052
• M2	16	30.8	5	29.4	
Chemotherapy protocol					
• BFM 90	21	40.4	2	11.8	0.435
• T XIII	31	59.5	5	29.4	
Site of relapse					
• Isolated BM (61%)	36	69.2	3	42.9	
• Isolated CNS (22%)	11	21.2	2	28.6	0.310
• Combined (10%)	4	7.7	2	28.6	
• Testicular (1.6%)	1	1.9	0	0	
Outcome					
• Remission	13	23.1	3	42.9	0.313
• Deaths	39	75	4	57.1	

Data expressed as frequency (percentage), mean (SD). Chi-square test,* statistically significant difference ($p<0.05$), ** highly statistically significant difference ($p<0.01$). CNS: central nervous system, HR: high risk, SR: standard risk, BMA: bone marrow aspirate, M1 = < 5%, M2 =5-25 %, M3 = >25%.

Table (5): The clinical characteristics of 106 died patients

Clinical characteristic	Number = 106	%	P-value
Sex:			
• Male	67	63.2	0.002**
• Female	39	36.7	
Age:			
• 2-10 years old	60	56.6	0.074
• >10 years old	46	43.4	
Immunophenotyping			
• B.cell	77	72.6	<0.001**
• T.cell	29	27.3	
leucocytic count			
• <50(x109/l)	54	50.9	0.889
• >50(x109/l)	52	49	
CNS status :			
• -VE	85	80	<0.001**
• +VE	21	20	
Philadelphia chromosome			
• -VE	90	84.9	<0.001**
• +VE	16	15	
Risk stratification:			
• SR	33	31.1	<0.001**
• HR	73	68.8	
Chemotherapy Protocol:			
• BFM	44	41.5	0.020*
• Total protocols	62	58.4	
Time of death:			
• Refractory disease	17	16.2	<0.001**
• Remission	25	23.5	
• Relapse	64	60.3	

Data expressed as frequency (percentage), mean (SD). Chi-square test,* statistically significant difference ($p<0.05$), ** highly statistically significant difference ($p<0.01$). TLC: total leucocytic count, CNS: central nervous system, HR: high risk, SR: standard risk

Chemotherapy toxicities:

In Table 6 early toxicity is exhibited in our patients. Bone marrow suppression grade II and III were presented in 45.3% and 25% respectively. Most of patients were presented with attacks of fever neutropenia (FN) that required hospitalization and recurrent attacks of chest infection in 64(20%) {(75%) bacterial infection, (25%) fungal}. Sepsis was presented in 20 (6.5%) and was an important cause of multiple organ failure and deaths in our study. GIT toxicity was common in form of mucositis 29.7% and typhilitis in 3.2% patients. Hepatic toxicity was evident in 37 (11.9%) patients {27 (8.7%) had HCV, 7(2.2%) had HBV and 3 toxic)}. Regarding CNS peripheral neuropathy occurred in 24(7.7%) and encephalopathy in 45(14.5%) patients. Renal toxicity was presented in 26 (8.4%), during high dose methotrexate administration, all of the patients were managed with leucovorine rescue and urine alkalinazation with vigorous hydration and close follow up.

Table (6): The early toxicity in the studied 309 ALL patients

Variable	Number of patients	(%)
1- Bone marrow suppression		
• (grade II)	140	45.3
• (grade III)	80	25
2- Infectious complications		
Chest infections:	64	20
• Sepsis	20	6.5
• Hepatitis	37	2.2
• Skin infection	5	1.6
• Ear infection	6	1.9
• CNS infection	25	8
3-Gastrointestinal complications		
• Mucositis (grade III- IV)	92	29.7
• Typhilitis	10	3.2
• Hepatotoxicity Grade II-III	37	11.9
• Gastroenteritis	62	20
• Pancreatitis	5	1.6
4) Cardiovascular complications		
• Hypertension	50	16
• Cavernous sinus thrombosis	6	1.9
5) Central Nervous System complications		
• Peripheral neuropathy	24	7.7
• Encephalopathy	45	14.5
6) Renal toxicity	26	8.4
7) Hormonal		
• Diabetes Mellitus	5	1.6

Discussion:

ALL is the most common cancer diagnosed in children and confers 25% of pediatric cancer. Multimodal therapy with enhanced supportive care have resulted in 5 year survival rates that approach 90% for those diagnosed at 14 years of age and younger.(16) Unfortunately, ALL patients still facing a lot of adverse events either from the disease itself or from toxic chemotherapy. The most common is relapse which is considered the main cause of treatment failure in pediatric ALL. (17)

Induction failure:

Because of the rarity of IF in recent studies, affected patients have been considered very-high-risk patients and are offered allogeneic hematopoietic stem-cell transplantation as the treatment of choice. (15)

In our study IF occurred in 21.3% patients, that was more than Vora et al., (4) where IF represented 2-3%, the increase number may be explained by the differences in the study populations, the type of treatment administered, the HR group that was much prevalent in our study and irregular treatment during induction phase.

The majority of patients were males which matched with the polish pediatric leukemia and lymphoma study

group experience(18) that males were significantly more prevalent than females in the group of patients with induction failure compared to children who lived in first complete remission (CR1) (68.2% Versus 55%.).

Commonly IF was reported in patients with high risk criteria as High leukocyte count , T-cell phenotype , CNS leukemia and HR patients which matched with Schrappe et al., (15) where IF diagnosed in HR group 64%, male 61%, high TLC 58%, T-cell 38% and +ve BCR/ABL (13%), CNS leukemia (6%). The outcome of the patients was completely different from Schultz et al., (19) where the outcome of IF was 70% achieved complete remission with the salvage therapies and 30% died. The difference due to the varieties in patient's number, treatment protocols and risk assessment.

Relapse:

Despite the fact that relapse is the most common adverse event and cause of treatment failure, it only represented (19%) which was much lower than that reported in a study conducted in Mexico recruited 302 pediatric patients with ALL, and they reported a relapse rate of 26.2% (20) and Jiménez et al.,(21) where a relapse rate of 20.5% was reported.

The site of relapse is considered an important factor in defining risk and prognosis of the patient's. In our study isolated BM was the most occurred followed by combined BM and CNS. These results were comparable with those reported in Abdelmabood et al., (23) .The time of relapse is the strongest individual risk factor for survival. Most of patients with early relapses were stratified as high-risk indicating that clinical and genetic features present at diagnosis affect survival after relapse (24). In this study early relapse was more common than the late relapse.

The clinical characteristics of relapsed patients were mostly near to the study conducted by Abdelmabood et al., (23) where HR was 73.2%, B.cell (65.9%) and male sex (61%).

The outcome in both types of relapse was much lower than reported in Raetz & Bhatla (25) where overall CR2 rates reach 85%, and Tallen et al., (22) where 440 patients (84%) achieved CR 2 from which 246 patients (56%) suffered subsequent relapse. This Discrepancy in the outcome can be attributed to the different treatment protocols the patients were enrolled on as front line therapy and to the lack of supportive care.

Mortality:

Death in the study occurred in (34.3%) that was close to Kiem Hao et al. (26) where it showed (31,1%), and much more the rate in the study conducted by Prucker et al. (27) the mortality rate was 3.4%. The reason for was what we faced from difficulties in providing supportive care, medications and blood product as well as the challenge in health awareness of early detection of the disease and treatment.

This high mortality rate was much prevalent in the HR group , Male was almost 2 times higher than females (63% vs 36%)and age from 2-10 years , that was near to Kiem Hao et al., (26) where HR (67.6%) and SR (32.4%), male: female (73%;27%), age 2-10 (67.5%).

The time of death in the patients was allied to the disease progression and resistance as 16.2% of the patients died in refractory disease and 60% died at the time of relapse. High percent of the patients (23.5%) died in remission which had provoked the importance of continuous modification in treatment protocols and supportive care for our patients. That result was close to Abdelmabood et al., (23) where induction deaths 23%, deaths in remission 18.9% while relapse deaths reached 63.4%.

Toxicity:

In our study, the most observed early toxicities were bone marrow suppression grade II and III, which were the main cause of morbidity and mortality and was close to Badr et al., (28) and Li et al., (29) where morbidity and mortality occurred in 73.5% -64% of cases due to bone marrow suppression. Chest infection occurred in 20% of the patient that closely matched with Hough & Vora (30). Incidence of mucositis was observed in 29.7% of the cases close to Schmiegelow et al., (31) where mucositis represented 40%. Severe liver dysfunction and fatal fulminant hepatitis through virus reactivation have been described in patients with viral hepatitis B and C. The percent of the cases was much lower to the studies by Parrish et al., (32), Schmiegelow et al. (31) and Adrienne & Erzsébet (33) where they found hepatotoxicity in 77%.

Central nervous system toxicities during chemotherapy are infrequent adverse events and occur in 10-15% of ALL patients (31, 34). Peripheral neuropathy was uncommon and completely reversible in most of the cases. It was much lower than Ramachandran & Labib (35) and Diouf et al. (36) where reported 29% in their studies.

Nephrotoxicity is a potentially life-threatening complication of high dose methotrexate. We tracked MTX toxicity and found that the result was 8.4% which was more than Patterson & Lee (37) and Savhan et al., (38) where experienced 3% of their patients. Pancreatitis and thrombosis formation are a common complication of asparaginase therapy with incidence (1.6%) and (1.9%) in our study which matched with that reported in Schmiegelow et al. (31).

List of Abbreviations:

ALL: Acute lymphoblastic leukemia
BMA : Bone marrow aspirate
BFM: Berlin frankfurtmunster
CBC: Complete blood count
CCR: Complete clinical remission
CSF: Cerebrospinal fluid
CR: Complete remission
FN: Fever neutropenia
HBV: Hepatitis B virus
HCV: Hepatitis C virus
IF : Induction failure
IPT: Immunophenotyping
SECI: South Egypt cancer institute

Conclusion:

The incidence of induction failure was high and mostly related to the high risk presentation of the patients in our study and it showed the worst outcome in studied patients. Early relapse was common and showed the worst prognosis in our ALL patients. Childhood ALL management in countries with limited health resources faces multiple challenges including quality improvement, educational and financial supports.

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