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RESEARCH ARTICLE

Prognostic factors, lines of treatment, and outcome of relapsed pediatric lymphoblastic lymphoma in Children Cancer Hospital Egypt

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ABSTRACT

Background: Pediatric patients with relapsed lymphoblastic lymphoma (LBL) have poor prognoses. **Aim:** This study aims to evaluate the prognostic factors, chemotherapy used, the role of hematopoietic stem cell transplantation (HSCT), and the survival outcome of relapsed pediatric LBL. **Materials and Subjects:** This retrospective study included 38 relapsed pediatric patients out of 295 patients (12.8%) with LBL in CCHE from July 2007 till July 2020. The median follow-up period was 59.4 months. Males were 68.4% of the study patients, with a median age of 9.3 years. All patients received acute lymphoblastic leukemia St. Jude total XV protocol. **Results:** Initially, patient's gender, pathological subtype, initial stage, central nervous system or bone marrow infiltration, and early response to induction treatment did not have an impact on relapse-free survival. Early relapse was documented in 89.47% of patients with 3y OS 5.8% and was 75% for late relapsed patients with a P-value of 0.01. Hematological or CNS relapse did not affect the outcome of the patients. Seventeen (44.7%) patients received FLAG-M as a salvage protocol with 3y OS 0%, and re-induction R16 was given to 17 (44.7%) patients with 3y OS 17.6%, with significant P-value. Sixteen (42%) patients had complete response post 2nd line therapy with 3y OS 31.2%, but 34.4% developed 2nd relapse, then 84.4% of patients died of active disease. Allogenic BMT was done for only 2 patients with a P-value of 0.1. **Conclusion**: Early relapse and poor response to salvage chemotherapy worsen the outcome of relapsed pediatric LBL; giving re-induction R16 protocol, followed by allogeneic HSCT, improves the outcome.

Keywords: Acute lymphoblastic leukemia Hematopoietic Stem Cell Transplantation, lymphoma, pediatric, protocol, refractory disease, relapse total XV

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INTRODUCTION

The treatment of children with T-cell and B-cell lymphoblastic lymphoma mimics the treatment of acute lymphoblastic leukemia with 5 years overall survival rate of 80-90%, pediatric patients with relapsed or refractory lymphoblastic lymphoma still have a poor prognosis (Mitsui et al., 2009). Several chemotherapy regimens are used as a treatment of relapsed lymphoblastic lymphoma followed by hematopoietic stem cell transplantation (HSCT) post-second complete remission (CR2). The incidence of relapse in pediatric patients with lymphoblastic lymphoma is 10%. T cell subtype in pediatric age

is initially more common than the precursor B cell subtype and has a higher relapse rate. Evaluation of the prognostic factors; chemotherapy used as a second line post relapse, role of hematopoietic stem cell transplantation, and overall survival of relapsed pediatric T cell or precursor B cell lymphoblastic lymphoma is important.

The outcome post-second relapse after HSCT has a much worse survival. New immune therapies such as chimeric antigen receptor-redirected (CAR) T cells may change with more benefit (Sandlund JT et al.,2015). The role of immunotherapies including blinatumomab, inotuzumab ozogamicin, and CAR-T cells are under research (Maude SL et al.,2018) (Horton TM et al.,2019).

AIM OF THE WORK

This is to evaluate the prognostic factors; chemotherapy used as a second line post relapse, role of hematopoietic stem cell transplantation, and overall survival of relapsed pediatric T cell or precursor B cell lymphoblastic lymphoma in Children Cancer Hospital Egypt.

PATIENTS AND METHODS

It is a retrospective study including all relapsed pediatric patients with T cell or precursor B cell lymphoblastic lymphoma received initially St. Jude total XV protocol as a first line of treatment in Children Cancer Hospital Egypt during the period between July 2007 and the end of July 2020.

Age under 18 years, with established pathological diagnosis as T or B lymphoblastic lymphoma, were included. All patients received St. Jude total XV of acute lymphoblastic leukemia protocol as first-line chemotherapy; all patients underwent a physical examination, imaging for staging according to the St. Jude staging system using computed tomography, biopsy for pathology, bone marrow aspirate, bilateral bone marrow biopsy, cerebrospinal fluid analysis. Response assessment was done according to St. Jude protocol, by CT, or MRI evaluation for extramedullary lesions, and morphologic evidence of disease in BM or CSF if present at diagnosis; it was done at the end of induction to assess early response to treatment.

Time to relapse was evaluated by 3 years relapse-free survival (RFS) to assess the prognostic factors for relapse as age, sex, stage at initial diagnosis, initial CNS or/BM infiltration, initial pathological subtype B or T-cell precursor, the early response at the end of induction ALL like chemotherapy, evaluation of the early response of CNS or BM if present. Data from relapsed patients was collected as the time of relapse early or late, presence of BM or CNS infiltration at the time of relapse, type, and response to second-line salvage chemotherapy, Allogeneic or autologous stem cell transplantation offered to the relapsed patient, and the overall survival and comparison between early or late relapse, good and poor responder, and between patients with or without BMT.

Definitions

Complete Remission (CR): Disappearance of all disease (three designations), CT or MRI reveals no residual disease or new lesions, in bone marrow infiltration, the reduction of blasts below a specific threshold in the bone marrow and extramedullary sites, incorporating minimal residual disease (MRD) techniques for marrow evaluations (Sandlund et al., 2015).

Partial response (PR): refers to a state where the tumor has shrunk in size by at least 50% after treatment but still has some remaining cancerous cells (Sandlund et al, 2015).

Minor response (MR): Decrease in SPD > 25% but <50% on CT or MRI; no new and/or PD; morphologic evidence of disease may be present in BM or CSF if present at diagnosis; however, there should be a 25–50% reduction in the percentage of lymphoma cells (Sandlund et al., 2015).

Good response: For those who meet CR, or PR criteria at the time of evaluation as per treatment protocol.

Poor response: For those who do not meet CR, PR, or MR criteria at the time of evaluation as per treatment protocol.

Progressive disease: For those with >25% increase in SPD on CT or MRI, Deauville scores 4 or 5 on FDG-PET with an increase in lesional uptake from baseline or development of new morphologic evidence of disease in BM or CSF (Sandlund et al., 2015).

Early relapse: Relapse or recurrence can be defined as the reappearance of disease in the site of prior disease and/or new sites within 6 months post end of 1st line of treatment in complete response (Maude et al., 2018).

Late relapse: Relapse or recurrence can be defined as the reappearance of disease in the site of prior disease and/or new sites after 6 months post end of 1st line of treatment in CR (Horton et al., 2019)

Overall Survival: Was defined as the time from date of relapse till the end of the study or death (Jourdain A et al., 2015).

Relapse-free survival (RFS); time until recurrence (Jourdain A et al., 2015)

Statistical analysis

Nominal data is calculated as frequencies and percentages, continuous data defined with means and standard deviations or medians with interquartile ranges according to the normality of distribution. Descriptive measurements, frequency distributions, and percentages estimated for the study baseline characteristics, result variables, and other covariates of interest. Unpaired comparisons of categorical results were performed with the Chi-square test. A two-sided probability of $P < 0.05$ reflected statistics significant.

Kaplan-Meier test for 3 years (3y) relapse-free survival (RFS) is measured from the date of diagnosis to the date of relapse, and 3 years (3y) overall survival (OS) is measured from the date of relapse to the date of death or date of last contact. Statistical analysis was accomplished using Statistical Package for SPSS, version 20.

RESULTS

Initial data

Two hundred and ninety-five pediatric patients were diagnosed with lymphoblastic lymphoma during the period between July 2007 and the end of July 2020 in Children Cancer Hospital Egypt. The median follow-up period was 59.4 months, ranging from 8-144 months. Thirty-eight patients out of a total of 295 (12.8%) patients relapsed and were included in the current study. The non-relapsed group was 257 (87.1%) patients. In the non-relapsed group, male gender accounted for about 178 (69.2%) patients, and most relapsed patients were males (65.6%), with no significant P-value of 0.9, table 1. With a median age of 9.3 years, a range= of 0.4 to 17.8, a mean of 9.1, SD 4.046.

According to Modified Murphy Staging, in the relapsed group, stage III accounted for 76.3% of patients, and stage IV accounted for 21.0%, 15 (46.9%) patients initially presented with enlarged mediastinal lymph nodes which do not differ from the non-relapsed group as stage III was detected in 63.4% of patients, and stage IV was diagnosed in 22.5% of patients with no significant P- value 0.2, table 1. Central nervous system metastasis detected by positive craniospinal fluid, presence of radiological finding as an intracranial or paraspinal extension or cranial nerve affection was diagnosed in only 3 (7.9%) patients in the relapsed group, and also was detected in 15 (5.8%) in a non-relapsed group with no significance as P- value was of 0.6 (Table 1).

Bone Marrow Biopsy was infiltrated initially with a cut-off value of blasts less than 20% (Minimal Disseminated Disease) in one relapsed patient (2.6%), and was infiltrated in 22 (8.5%) non-relapsed patients with P-value 0.2 (Table 1).

In the non-relapsed group (257 (87.1%) patients) there were about 237(92.2) T cells and 58 precursor B cell lymphoblastic lymphoma, on the other hand, in the relapsed group, there were 34 (89.5%) patients had T-cell subtype, and 4 (10.5%) patients had the precursor B-cell subtype, with no significant P-value, 0.1 (Table 1).

All patients received total XV protocol (Acute Lymphoblastic Leukemia (ALL) like treatment) as the first line of treatment; evaluation was done post-induction phase. Good response to treatment was detected in 36 (94.7%) patients in relapsed patients, and in 245 (95.3%) patients in the non-relapsed group with no significant P-value, 0.8 (Table 1).

Data of relapse

Early relapse was documented in 89.5% of patients with 3 years' overall survival (3y OS) 5.8%, on the other hand, late relapse was detected in 4 (10.5%) patients with 3y OS 75% with a significant P-value of 0.01 (Table 2 and Figure 1).

Table 1. Initial data of pediatric lymphoblastic lymphoma(relapsed and non-relapsed groups) according to time to relapse and relapse-free survival.

Characteristics		Time to relapse		P value	Number	Event Number	3 y RFS	P value
		relapsed	Not relapsed					
Gender	Female	12	79	0.9	91	12	86.8%	0.9
	Male	26	178		204	26	87.2%	
Stage	1	0	9	0.2	9	0	100%	0.2
	2	1	27		28	1	96.4%	
	3	29	163		192	29	84.9%	
	4	8	58		66	8	87.9%	
Initial CNS infiltration	Free	35	242	0.6	277	35	87.4%	0.6
	Positive	3	15		18	3	83.3%	
initial BMB	Free	34	227	0.2	261	34	86.9%	0.2
	Positive	1	22		23	1	95.7%	
Pathology subtype	B	4	54	0.1	58	4	93.1%	0.1
	T	34	203		237	34	85.6%	
Response at end of induction	Regressive course(CR, PR)	36	245	0.8	281	36	87.2%	0.8
	Stationary course	2	12		14	2	85.7%	

Table 2. Data of relapsed patients according to survival status and 3 years overall survival.

		Survival status		P value	Number	Events	3y OS	P value
		Alive	Dead					
Time of relapse	Early	2	32	0.000	34	32	5.8%	0.01
	Late	3	1		4	1	75%	
Site group	Multiple	0	6	0.2	6	6	0%	0.4
	Single	5	27		32	27	37.5%	
Bone marrow biopsy relapse	Free	4	22	0.9	26	22	42.3%	0.6
	Positive	1	6		7	6	14.3%	
Bone marrow aspirate infiltration at relapse	Negative	4	23	0.6	27	23	44.4%	0.4
	Positive	1	10		11	10	18.2%	
CNS relapse	Positive	0	4	0.4	4	4	0%	0.2
	negative	5	29		34	29	38.2%	
Chemotherapy	FLAG/M	0	17	0.07	17	17	0%	0.00
	R 16 PROTOCOL REINDUCTION	3	14		17	14	17.6%	
Response post salvage	CR	5	11	0.00	16	11	31.2%	0.00
	No response	0	22		22	22	0%	
Transplant	NO	4	32	0.1	36	32	11.1%	0.2
	Yes	1	1		2	1	50%	

Median fu period is 59.4 months, Median age 9.3 years, range: 0.4:17.8, Mean age: 9.1

Eleven (28.9%) patients had hematological relapse diagnosed by bone marrow aspirate infiltration, three (7.9%) cases relapsed with myeloid elements, one case had ambiguous (myeloid and B cell), the rest of the cases (7 cases) relapsed with T cell infiltration to bone marrow with no significant P- value 0.6, bilateral bone marrow biopsy was done, and 7 (18.4%) patients had positive infiltration with no significant P-value, 0.9, table 2. Central Nervous System relapse was detected in 4 (10.5%) patients with a P-value 0.4, with 3y OS 0% with no significant P-value, 0.2 (Table 2).

In most cases received relapsing ALL protocol, 17 (44.7%) patients received FLAG-M, and re-induction R16 was given to 17 (44.7%) patients, with P- value 0.07, 3y OS for patients who received re-induction R16 protocol was in 17.6%, and unfortunately, the patients who received FLAG-M regimen had 3y OS 0% with highly significant P-value, 0.00 (Table 2, Figure 2). Sixteen (42%) patients had complete response post first salvage therapy with a significant P-value of 0.00, table 2, 3y OS for good responders post salvage chemotherapy was 31.2%, and for poor responders was 0% with a significant P-value of 0.00 (Table 2, Figure 3).

Unfortunately, 26.3% of relapsed patients had 2nd relapse, and 84.2% of patients died of active disease from the whole cohort. There were 26 (68.4%) patients died from DRM (disease-related mortality), And about 7 patients died from TRM (treatment-related mortality). Allogeneic Bone Marrow Transplantation (allo BMT) was done for only 2 patients with a P-value of 0.1 (Table 2). Three years' overall survival for patients with relapsed lymphoblastic lymphoma treated with salvage chemotherapy not followed by allo BMT was 11.1% and was 50% for patients who received salvage chemotherapy followed by allo BMT with a P-value 0.2.

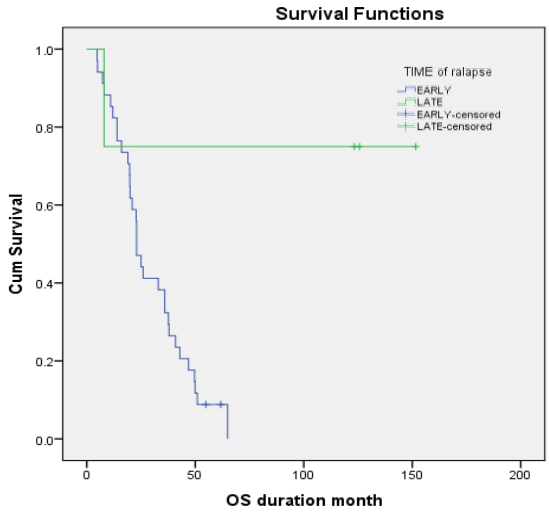

Figure 1. 3 years overall survival of relapsed patients according to time of relapse (early/late), 5.8%, 75% with significant P-value, 0.01

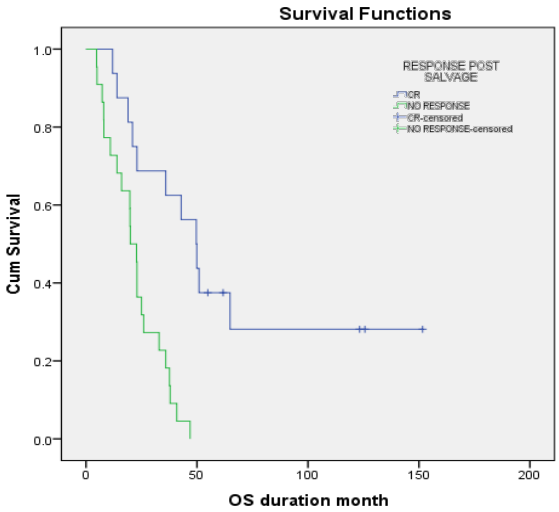

Figure 3. 3y OS for good responder , and poor responders post salvage chemotherapy were 31.2%, 0% with significant P-value 0.00

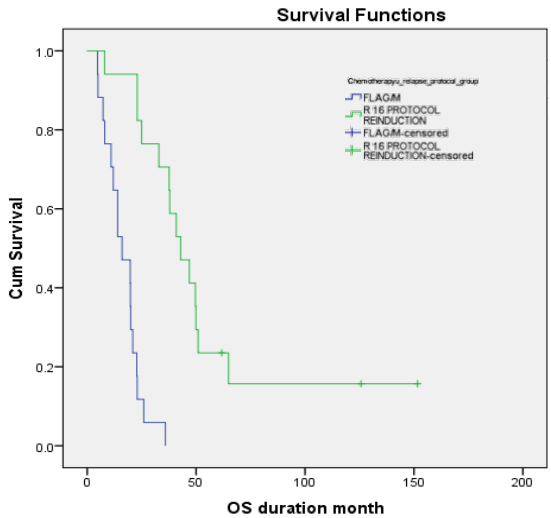

Figure 2. 3y OS for patients who received re-induction R16 protocol, who received FLAG-M regimen was 17.6%, 0%, respectively, with highly significant P-value, 0.00

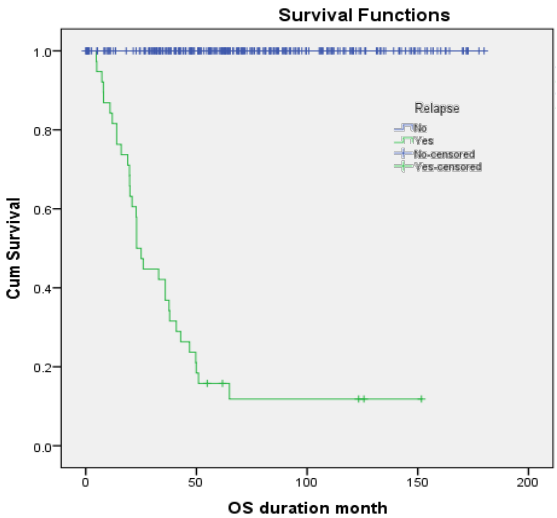

Figure 4. Three years overall survival for relapsed and non-relapsed pediatric lymphoblastic lymphoma were 36.8% and 100% respectively, with P-value, 0.00.

Three years of overall survival for relapsed and non-relapsed pediatric lymphoblastic lymphoma were 36.8% and 100% respectively, with a P-value, of 0.00 (Figure 4).

DISCUSSION

Lymphoblastic Lymphoma (LBL) is the second most common subtype of NHL in children (Thomas DA et al., 2004) (Rizzari et al., 2004) The treatment of children with T-cell and B-cell lymphoblastic lymphoma mimics the treatment of acute lymphoblastic leukemia with 5 years overall survival rate of 80-90% (Mitsui et al., 2009).

In the literature, only small percentages, about 8-16%, have a disease refractory to initial treatment or relapses (Hunger et al., 2012) (Pui et al., 2015) with a dismal prognosis. In the current study, the relapse rate of pediatric patients with lymphoblastic lymphoma is 12.8%, as seen in the literature. The T cell subtype in pediatric age is more common than the precursor B cell subtype, which accounts for about 80.3% of the total number of pediatric patients with lymphoblastic lymphoma in our center, as in (Burkhardt et al., 2005), as the T cell subtype accounts about 77.5% of pediatric LBL. The relapse rate in T cell LBL is higher than that in precursor B cell LBL, which accounts 89.5% of relapsed patients.

T-LBL affects males 2.5 times more often than females; the median age of T-LBL diagnosis is around 9 years (Burkhardt et al., 2005), as in our study, as male: female ratio is 2.25:1, with a median age of 9.3 years. Most patients with T-LBL present with disseminated disease (Murphy stage III or IV) (Burkhardt et al., 2005). In the current study, according to Modified Murphy Staging, stage III was diagnosed in 65% of patients, stage IV was diagnosed in 22.0%, and about half of patients initially presented with enlarged mediastinal mass, as in Patel et al., 2012, T-LBL arise in the vast majority of patients in the mediastinum and cervical nodes. About 15–20% of patients exhibit bone marrow (BM) infiltration. Less than 5% show central nervous system involvement (Burkhardt et al ., 2005) concomitant with our study as central nervous system metastasis detected by positive craniospinal fluid, presence of radiological finding as intracranial or paraspinal extension, or cranial nerve affection was diagnosed in only 18 (6.1%) patients, Bone Marrow Aspirate, Bone Marrow Biopsy was done initially and was infiltrated initially with cut off value of blasts less than 20% (Minimal Disseminated Disease) in 23 patients (7.8%).

In pediatric LBL Using ALL-type treatment regimens, EFS rates of 75–90% have been achieved (Gao et al., 2010); in the current study, we are using St. Jude total XV of acute lymphoblastic leukemia protocol as first-line chemotherapy for pediatric LBL, evaluation was done post-induction phase, good response to treatment was detected in 281/295 (95.25%) patients, but the gender of the patient, pathological subtype T cell or precursor B cell, stage of the disease, central nervous system or bone marrow infiltration, early response to induction treatment did not affect the time to relapse and relapse-free survival of this group of patients, may be due to favorable remission and cure rates in the initial line of treatment, as well as a small number of relapsing patients, then detection of initial risk factors is difficult.

Relapsed or refractory T- and pB-LBL continue to have dismal outcomes, with survival rates of 10–30% (Schmidt et al., 2016). In the current study, the rate of relapse is 12.9%, and the overall survival is 13.1% worse in the early relapse with a significant P- value of 0.01. The rate of relapse/refractory was 18%; an allogeneic hematopoietic stem cell transplant (HSCT) was done for 19 patients; six of them suffered from relapse, three of them died out of treatment-related mortality (TRM), while ten survived without further progression (Mitsui et al., 2009). On the other hand, autologous HSCT was done for six patients; four suffered from relapse and died, while two survived (Mitsui et al 2009). The event-free survival for 39 patients treated with allogeneic HSCT was 40% and 4% in patients treated with autologous HSCT (Gross et al., 2009). In the current study, Allo BMT was done for only 2 patients with a P-value of 0.2.

The available data on relapsed LBL is limited and shows that patients without high-dose treatment followed by autologous or allogeneic HSCT have an almost low chance of cure. In the current study, most cases received relapsing ALL protocol in the form of FLAG-M in 17 (44.7%)

patients. Re-induction R16 protocol was given to 17 (44.7%) patients, with a significant P- value of 0.00 for giving re-induction R16, as all patients who received FLAG-M protocol died with 3 y overall survival 0%. In comparison, 70.6% of patients who received re-induction R16 protocol may be due to less toxicity starting with re-induction R16 than starting with a more intensive FLAG-M regimen and increased treatment-related mortality. Sixteen (42.1%) patients had complete response post-first salvage therapy with a significant P- value of 0.00, but not all patients had a chance for allogeneic HSCT, then 34.4% achieved 2nd relapse, then 84.4% of patients died in active disease. Allogeneic HSCT is superior but associated with higher Treatment-Related Mortality. Different studies showed a higher probability of disease-free survival after allogeneic HSCT than autologous SCT, but in the current study, small numbers of the study's patients and the unavailability of immune therapies such as chimeric antigen receptor-redirected (CAR) T cells, blinatumomab, inotuzumab, and ozogamicin in developing countries to assess their role in relapsing pediatric patients with LBL.

CONCLUSION

In Children Cancer Hospital Egypt, the 3 years overall survival rate for pediatric patients with lymphoblastic lymphoma is of 87.1%, with relapse rate 12.9%. Patients' gender, pathological subtype T cell or precursor B cell, initial stage, central nervous system or bone marrow infiltration, and early response to induction ALL-like treatment did not affect the time to relapse or relapse-free survival of pediatric LBL. The 3-year overall survival of relapsing patients is 13% worse in the early relapse with a significant P-value of 0.01. Most of the cases received relapsing ALL protocol, with a significant P- value of 0.00 for giving re-induction R16 instead of FLAG-M protocol. Patients had complete response post first salvage therapy with a significant P- value of 0.00, Three years' overall survival for good responder post salvage chemotherapy were 31.2%, and for poor responders were 0%, and a higher probability of Disease-Free Survival after allogeneic HSCT.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interests

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