Clinical features and treatment results in children with anaplastic large cell lymphoma

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Anaplastic large cell lymphoma (ALCL) tends to have frequent relapse and good response to salvage chemotherapy. The frequency of ALCL among 1486 Non-Hodgkin's lymphoma (NHL) cases followed-up since 1972 was 1.5%, however, the percentage was 9.3% in cases diagnosed after 2000. Event-free survival (EFS) and overall survival (OS) rates for 23 children were 32.2% and 72.8% at 3 years, respectively. Disseminated diseases, no response to first line treatment, anaplastic lymphoma kinase (ALK) negativity were found as significant predictors on survival of ALCL.

The proper diagnosis and early referral is essential in these children for a better survival rate. The children with ALK negative status should be monitored carefully because of the poor prognostic factors, and treated differently. The survival rates in this study are need of further improvement since the survival rates with current protocols are achievable at a level more than 80%. This is mainly related with late referral of those children with advanced disease.

Key words: anaplastic large cell lymphoma, children, treatment.

Lymphomas are the second most common tumors (17.2%) among children in Turkey [1]. Anaplastic large cell lymphoma (ALCL) is a peripheral T-cell lymphoma (WHO 2008) that represents approximately 10% of pediatric NHL and 20-50% of pediatric large cell lymphomas [2-4]. The survival rates for NHLs have increased to 88% for children and 77% for adolescents in recent years [5]. Dramatic improvements in survival have also been achieved for children and adolescents with ALCL. Anaplastic large cell lymphoma has a favorable prognosis and high survival rates in large series[2, 6-8]. The real incidence of ALCL is unknown and there are limited data on treatment outcomes in our country. The aim of this study was to analyze the clinical features and treatment results of pediatric patients with ALCL.

Material and Methods

The demographic and clinical characteristics of 23 consecutively diagnosed ALCL patients younger than 18 years of age were recorded and analyzed among 1486 NHL cases from the files of Department of Pediatric Oncology between 1972 and 2012. Approval for the study was obtained from the Institution Ethics Committee. The Murphy [9] and Société Française d'Oncologie Pédiatrique (SFOP) systems were used for staging or grouping and all cases were classified according to the histopathological classification of tumours of hematopoietic and lymphoid tissues by the World Health Organisation (WHO) [10]. For unknown pathologic subgroup of large cell lymphoma, histologic slides were reviewed in four cases. Immunophenotyping studies such as CD2, CD3, CD8, CD15, CD19, CD20, CD30, CD45RO, CD56, CD79a, TdT, EMA, LCA, granzym, desmin, clusterin, perphorine, cytokeratin, EBV and anaplastic lymphoma kinase (ALK) were determined. Lymphomas presenting with extranodal organs or only minor lymph node involvement were considered primary

extranodal ALCL. Lymphomas in the clinically dominant lymph node involvement category, as well as those presenting in the spleen, thymus and Waldeyer's ring involvement categories, were considered as primary nodal ALCL. Lymphomas with extensive disease involving both nodal and extranodal sites were considered nodal ALCL. The lymphoma spread throughout more than one area of the body was considered as disseminated disease.

Patients were stratified in three groups according to Bergeron et al.[11] before deciding on the treatment in cases treated with SFOP LMT-89 regimens. Patients with ALCL have been treated with the SFOP protocol since 1994. The children were treated by LMT89 in 14 cases, LMB89 in 5 cases, NHL-BFM-90 in 2 cases, NHL-BFM-95 in 1 case and LSA2L2 in 1 case.

The International Prognostic Index (IPI) and Age-adjusted International Prognostic Index (AAIPI) were originally used to evaluate the prognosis to predict the survival of patients with ALCL. IPI incorporates the patient's age, serum lactate dehydrogenase (LDH) level, Eastern Cooperative Oncology Group (ECOG) performance status, Ann Arbor clinical stage, and the number of involved extranodal sites. Patients were then divided based on these factors into four risk groups (0-1: low risk, 2: low-intermediate risk, 3: high-intermediate risk, 4-5: high risk) with significantly different outcomes. AAIPI was calculated after exclusion of age and number of involved extranodal sites from IPI. AAIPI were divided into four risk groups (0: low risk, 1: low-intermediate risk, 2: high-intermediate risk, 3: high risk) [12].

Statistical analyses were performed by using the SPSS software version 15. The Kaplan-Meier survival estimates were calculated. The log rank test was used for the statistical comparisons [13]. Definitions used for survival terms were the following: 1. Overall survival (OS) was calculated from the start of the treatment to death from any cause; 2. Event-free survival (EFS) was calculated from the start of the treatment into the date of first event (failure to achieve CR, relapse or death from any cause). The possible factors identified with univariate analyses were further entered into the Cox regression analysis, with backward selection, to determine independent predictors of survival [14]. A 5% type-I error level was used to infer statistical significance.

Results

The frequency of ALCL among 1486 NHL cases was 1.5%, the percentage was 9.3% in 235 cases diagnosed after 2000. The median age was 11.4 years (range 3.6-17.8) and male/female ratio was 14/9=1.5. The primary tumor localizations were disseminated in 9 (39.1%), cervical lymph nodes in 3 (13.1%), mediastinal in 3 (13.1%), abdominal in 2 (8.7%), bone in 2 (8.7%), skin in 2 (8.7%) cases, and primary intestinal in 1 (4.3%), axillary lymph node in 1 (4.3%) case. Approximately, fifty percent of children had nodal (47.8%) and the rest had extranodal diseases (52.2%). Bone, skin, lung, pleura, kidney, pancreas, and omentum were the extranodal sites of cases. One case also had ataxia-telengiectasia. All of the cases were CD30 positive. T cell phenotype in 10 cases and null-cell (NC) phenotype in 13 cases were evaluated according to immunochemical staining and flow cytometry. Epstein Barr virus (EBV) staining was performed by pathology in 3 of 23 cases. All of them were negative for EBV. ALK expression was determined as positive in 14 cases, and negative in 7 cases. ALK expression was not determined in two cases. Bone marrow involvement in 2 cases (8.7%) and cerebrospinal fluid involvement in 2 cases (8.7%) were detected. The stage distribution were stage II in 5 (21.8%) cases, stage III in 14 (60.8%) cases and stage IV in 4 (17.4%) cases. The children were treated by LMT89 in 14 (60.8%) cases, LMB89 in 5 (21.8%) cases, and other protocols such as LSA2L2, NHL-BFM-95, and NHL-BFM-90 in 4 (17.4%) cases. Complete responses (CR) were obtained in 16 patients (69.6%) after the end of the first-line chemotherapy. Seven of 16 cases with CR were relapsed (43.8%), and CR was obtained again in five of seven cases with second-line treatment (71.4%). ALLREZ-BFM, DICE, LSA2L2, LSA4, BFM95, BFM 90, ABVD, and LMT89 CNS positive were used as a second line treatment in relapsed cases. Two of seven (28.6%) relapsed cases died due to progressive disease and sepsis. Two of 23 cases (8.6%) were relapsed in or during the first-line chemotherapy, and CR was obtained in two of them (100%) with the second line chemotherapy ± stem cell

Table I. Clinical features and first-line treatment in children with Anaplastic Large Cell Lymphoma

Patient	Gender	Age	Primary	Nodal/ Ekstranodal	Organ involvement	Associated condition	CD30	ALK	Bone marrow	CSF	Stage	CT	Status at first-line CT	Primary RT	RT localisation
1	M	14	Disseminated	E	B		+	-	+	-	IV	BFM90	PD	YES	Spinal mass
2	F	16	Skin	E	S, L	AT	+	-	-	-	III	LSA2L2	CR	NO	
3	M	11	Mediastinum	E	L, P		+	-	-	-	III	LMT89	SD	NO	
4	F	12	Disseminated	E	S,L,K,PN		+	+	-	+	IV	LMT89	RLPS	NO	
5	M	10	Bowel	E	O, K		+	-	-	+	IV	LMT89	PD	NO	
6	M	16	Disseminated	E	S		+	-	-	-	III	LMT89	PD	NO	
7	M	10	Axillary LN	N			+	+	-	-	II	LMT89	CR	NO	
8	M	17	Abdominal	N			+	+	-	-	III	LMT89	CR	NO	
9	F	14	Mediastinum	N			+	+	-	-	III	LMT89	CR	YES	Mediastinum
10	M	14	Abdominal	N			+	+	-	-	III	LMT89	CR	NO	
11	M	11	Bone	E	B		+	+	-	-	II	LMT89	CR	YES	Femur
12	F	3	Disseminated	N			+	+	-	-	III	LMT89	CR	NO	
13	M	5	Disseminated	N			+	+	-	-	III	LMT89	CR	NO	
14	M	15	Skin	E	S		+	-	-	-	II	LMT89	CR	NO	
15	M	14	Bone	E	B		+	+	-	-	II	LMT89	RLPS	NO	
16	F	9	Cervical LN	N			+	+	-	-	III	LMT89	CR	NO	
17	F	11	Mediastinum	E	S, L		+	?	-	-	III	BFM95	CR	NO	
18	M	13	Disseminated	E	S, B, P		+	+	+	-	IV	BFM95	CR	NO	
19	M	6	Disseminated	N			+	?	-	-	III	LMB89B	CR	NO	
20	F	4	Cervical LN	N			+	+	-	-	III	LMB89B	CR	NO	
21	F	15	Disseminated	E	L		+	-	-	-	III	LMB89B	PD	NO	
22	F	5	Disseminated	N			+	+	-	-	III	LMB89B	CR	NO	
23	M	8	Cervical LN	N			+	+	-	-	II	LMB89B	CR	NO	

ALK: Anaplastic lymphoma kinase, AT: Ataxia telengiectasia, B: Bone, BFM: Berlin-Frankfurt-Munster, CD: Cluster of differentiation, CNS: Central nervous system, CSF: Cerebrospinal fluid, CT: Chemotherapy, E: Extranodal, F: Female, K: Kidney, L: Lung, LMB: Lymphoma malign B, LMT: Lymphoma malign T, LN: Lymph node, M: Male, N: Nodal, O: Omentum, P: Pleura, PN: Pancreas, RLPS: Relapse, RT: Radiotherapy, S: Skin, ?: Unknown-: Negative, +: Positive

Table II. Treatment in children with Anaplastic Large Cell Lymphoma after relapse

Patient	Relaps localisation	Relaps CT	Relaps RT	Relaps RT localisation	Response to salvage	Stem cell transplant	EFS status	EFS months	OS status	Reason of exitus	OS months
1	Primary	LSA2L2	YES	CS	PD		Event	2.5	Exitus	PD	6
2			NO				Lost	6	Lost		6
3			NO				Event	8.5	Exitus	Se	8.5
4	Skin	LSA4	YES	CS	CR		Event	8.5	Lost		46
5			NO				Event	0.5	Exitus	PD, B	0.5
6			NO				Event	2.5	Exitus	PD, Se	2.5
7	CSF	LMT89 CNS +	YES	CS	CR		Event	3	Alive		117.5
8			NO				Follow-up	97.5	Alive		97.5
9			NO				Follow-up	89	Alive		89
10			NO				Follow-up	75.5	Alive		75.5
11	Maxillary sinus	BFM95	YES	O	CR		Event	29	Alive		77
12	Primary	BFM95	YES	C, S, M, Sp, P	CR		Event	15	Lost		34
13	Primary	BFM90	NO		CR	AUT	Event	13	Alive		53
14			NO				Follow-up	35.5	Alive		35.5
15	Primary	ALLREZBFM2002	NO		CR	AUT	Event	10	Alive		24
16			NO				Follow-up	10	Alive		10
17	Primary	LMT89	YES	M, L	PD		Event	17	Exitus	PD	53.5
18	Primary	DICE	NO		VGPR		Event	15	Exitus	Se	18
19			NO				Follow-up	165	Alive		165
20			NO				Follow-up	90.5	Alive		90.5
21	Primary	ABVD	NO		PD		Event	1	Exitus	PD	1
22	Primary	BFM90	NO		CR	AUT	Event	8	Alive		57.5
23			NO				Lost	9.5	Lost		9.5

ABVD: Adriamycin, bleomycin, vinblastine, dacarbazine, ALLREZ: Rezidive einer akuten lymphoblastischen leukämie, AUT:Autologous, B: Bleeding, BFM: Berlin-Frankfurt-Munster, C: Cervical, CNS: Central nervous system, CR: Complete response, CS:Cranio-spinal, CSF: Cerebrospinal fluid, CT: Chemotherapy, DICE: Dexamethasone, iphosphamide, cisplatin, etoposide, EFS: Event free survival, LMB: Lymphoma malign B, L: Lung, LMT: Lymphoma malign T, M: Mediastinum, O: Orbita, OS:Overall survival, P: Paraaortic, PD: Progressive disease, RT: Radiotherapy, S: Supraclavicular, Ss: Sepsis, Sp: Spleen, VGPR: Very good partial response, +: Positive

transplantation. One case (4.4%) was evaluated as stabile disease, and four cases (17.4%) were evaluated as progressive disease in the first-line chemotherapy. All of these cases died due to progressive disease (Table I,II).

Median follow-up time was 36 months, and event-free survival (EFS) and overall survival (OS) rates for 23 children were 32.2% and 72.8% at 3 years, respectively (Fig. 1). When survival rates were analyzed according to ALK status for 21 children, EFS and OS rates were 34.9% and 91.7% in ALK positive and 21.4% and 21.4% in ALK negative cases (EFS;

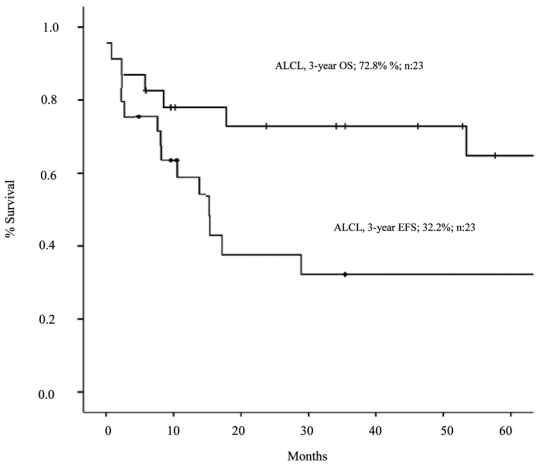

Fig. 1. Overall survival (OS) and event-free survival (EFS) in 23 children with ALCL.

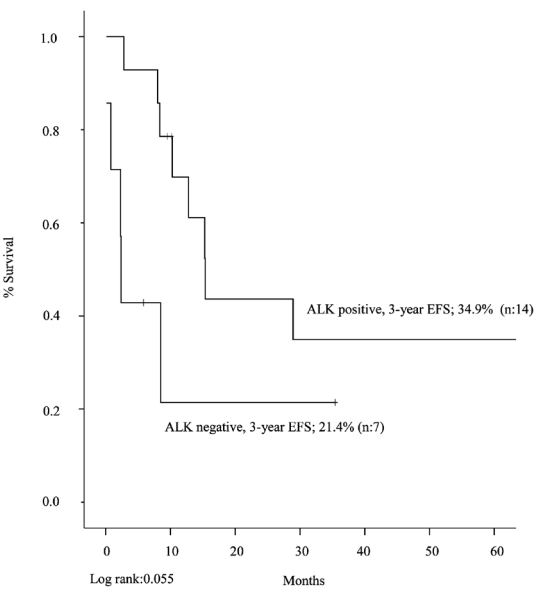

Fig. 2. Event-free survival (EFS) according to the ALK expression.

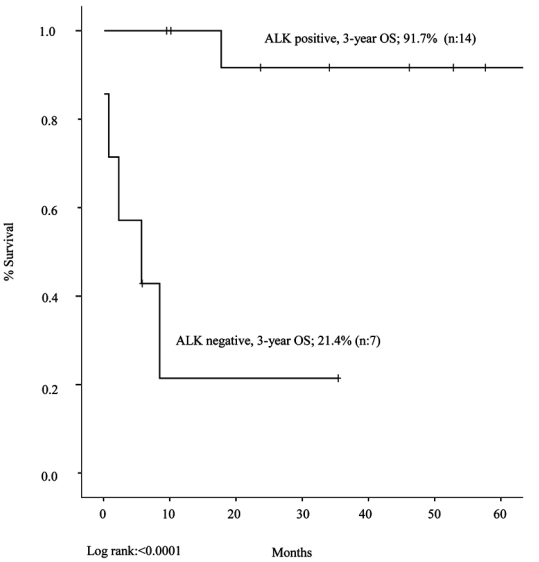

Fig. 3. Overall survival (OS) according to the ALK expression.

p=0.055, OS; p<0.0001) (Figs. 2 and 3). The survival rates according to T-cell or Null- cell phonotype were not significant, respectively at 3 -year (EFS: 21.4% vs 40%, p=0.957; OS: 81.5% vs 60%, p=0.378). Three-year EFS was 42.9% for children younger than 10 years and 27.5% for patients aged 10 years and older, p= 0.327).

The OS and EFS were not significantly different between early (Stage I-II, n=5) and advanced stage (Stage III-IV, n=18) disease (OS; 100% vs 55.9%, p=0.134, EFS; 26.7% vs 33.2%, p=0.832). The OS and EFS of LMB89 (n=5) protocol were 80% and 60% at 36 months. The OS and EFS of LMT89 (n=14) protocol were 78.6% and 32.1 at 36 months.

Radiotherapy was used for local control of mediastinal residue, femur involvement, and spinal mass in 3 of 23 children with ALCL in primary treatment, and one of them who received RT to femur was alive and in remission. One child with femur localization had an event at the orbital bone. The last one died due to progressive disease. Six of 23 children had undergone radiotherapy after relapse. Four of them were in remission. However, 2 of them died due to progressive disease.

Disseminated disease (p=0.036, HR=3.2), no response to first line treatment (p=0.001,HR=16.2), AAIPI (p=0.003, HR=24.1), IPI (p=0.004, HR=3.4), extranodal

involvement (p=0.031, HR=3.6), and cerebrospinal fluid positivity (p=0.025, HR=6.6) were significant for EFS in univariate analysis. After multivariate analysis, disseminated disease (p=0.044, HR=3.2) and no response to first line treatment (p=0.001, HR=17.6) were the significant parameters. Bone marrow involvement (p=0.047, HR=5.6), no response to first line treatment (p=0.007, HR=19.3), ALK negativity (p=0.006, HR=22.6) were the effective parameters in the univariate analysis for OS. Anaplastic lymphoma kinase negativity was a significant prognostic factor on survival in a multivariate analysis (ALK; p=0.036, HR=16.9) (Table III).

According to survival rates of AAIPI and IPI, EFS, and OS rates were found significantly different at 3 years (EFS of AAIPI: 1=85.7%, 2=12.5%, 3=0%, p<0.0001; EFS of IPI: 1=85.7%, 2=20%, 3=0%, p=0.005; OS of AAIPI: 1=100%, 2=87.5%, 3=0%, p<0.0001; OS of IPI: 1=100% 2=100%, 3=33%, p<0.0001)

Discussion

Anaplastic large cell lymphoma in the pediatric population is a second common type of large cell NHL. The previous large scale clinical studies indicate that it constitutes about 10 to 20% of pediatric NHL[2,15,16], as well as it is approximately one-thirds of large cell lymphomas [4]. To our knowledge this is the first report of ALCL in Turkey.

The relative frequency was 9.3% in the last decade and it was on a comparable level with international studies owing to improvement in pathology. This rate may increase in the future with the use of best available technique for the diagnosis of ALCL in Turkey.

Anaplastic large cell lymphoma occurs more frequently during the second decade[4]. Male predominance has been observed with 57% of large cell lymphomas[6]. Incidence increases after 10-years old, and the incidence of ALCL is higher at the age of 10-14 and 15-19 than other age groups, respectively (4.3 and 7.8 cases/million person-years in males, 2.8 and 3.4 cases/million person-years in females) [17]. We found similar findings in this study, nearly 70% of patients were over 10 years of age with a median age of 11.3 and a male predominance with a ratio of 1.5. Being more common in males and being seen at an early age than in industrialized countries are epidemiological features of NHL in our country [18]. However, age (≥ 10 years) was not an independent risk factor for inferior outcome, with 3-year EFS of 42.9% for children younger than 10 years and

Table III. Prognostic factors of anaplastic large cell lymphoma in uni-multivariate analysis.

	Prognostic factors	Category	Univariate analysis			Multivariate analysis		
			HR	95% CI	p	HR	95% CI	p
Overall survival	BMI	Yes/No	5.6	1.1-30.9	0.047			
	RFLT	CR/Others	19.3	2.2-168.2	0.007			
	ALK (-)	(-)/(+)	22.6	2.4-208.8	0.006	16.9	1.2-238.6	0.036
Event-free survival	DD	Yes/No	3.2	1.1-9.4	0.036	3.2	1.1-10.4	0.044
	RFLT	CR/Others	16.2	3.2-80.4	0.001	17.6	3.3-94.5	0.001
	EI	Yes/No	3.6	1.2-11.6	0.031			
	CSFI	Yes/No	6.6	1.2-34.4	0.025			
	IPI	L/LI/HI	3.4	1.5-7.8	0.004			
	AAIPI	LI/HI/H	24.1	3.1-191.7	0.003			

p <0.05 is significant, AAIPI: Age-adjusted international prognostic index, ALK:Anaplastic lymphoma kinase, BMI: Bone marrow involvement, CI: Confidence interval, CSFI: Cerebrospinal fluid involvment, CR: Complete remission, DD: Disseminated disease, EI: Extranodal involvement, HI: High intermediate risk, HR: Hazard ratio, IPI: International prognostic index, L: Low risk, LI: Low intermediate risk, RFLT: Response to first-line treatment, (-): Negative, (+): Positive

27.5% for patients aged 10 years and older. This was the same as adolescent age (≥ 15 years).

Pediatric ALCL is more often localized and less often involves the bone marrow or cerebro spinal liquid[19]. The most common primary sites of ALCL are the mediastinum (40-42%), the peripheral lymph nodes (42-85%), skin (18-25%) and visceral involvement (32%) [4, 6]. The primary tumor localizations were disseminated in 9 (39.1%), cervical lymph nodes in 3 (13.1%), mediastinal in 3 (13.1%), abdominal in 2 (8.7%), bone in 2 (8.7%), skin in 2 (8.7%) cases, and primary intestinal in 1 (4.3%), axillary lymph node in 1 (4.3%) case. Peripheral lymph node involvement was the most common site in our study. Approximately, fifty percent of children had nodal (47.8%) and the rest had extranodal diseases (52.2%). Bone, skin, lung, pleura, kidney, pancreas, omentum were the extranodal sites of cases. ALCL was prone to involve extranodal and visceral site. Localized, low rate bone marrow-cerebrospinal and high rate extranodal and visceral involvement of our cases were compatible with general clinical features of ALCL.

Patients with ALCL have a favorable prognosis[2]. Despite advances in diagnosis of lymphoma, the patients still present with advanced-stage (Stage III-IV) of disease[4, 20]. For low-stage ALCL, EFS is about 79-88%[8, 21, 22]. It is about 60-75% for advanced stage ALCL [16, 19, 23, 24].

In our study, the stage distributions were low-stage (Stage I-II) in 5 (21.8%) cases, and advanced- stage (Stage III-IV) in 18 (78.2%) cases. The EFS rates in patients with early and advanced stage disease were 26.7% and 33.2% in our study, which were lower than other studies (79-88% and 60-75%) [8, 16, 19, 21-24] . These rates showed us ALCL was prone to relapse in treatment or after stopping the treatment. All of the relapses occurred in patients with advanced disease.

Stages II-III-IV are worse than stage I clinically according to studies[25-28]. Survival rates were higher in patients with early -stage disease (5 patients only). However, there were no differences on survival rates between early and advanced stage disease. The major reason for our findings was that ALCL predominantly presents as advanced stage disease with low infiltration of the bone marrow in 8.7% and cerebro spinal fluid infiltration in 8.7% cases. Early diagnosis is very critical to get a high survival rate. To improve the survival rates in children with ALCL in our country, we have to invest on early diagnosis, using updated protocols for the treatment, proper diagnosis and follow-up.

Mediastinal, visceral (defined as lung, liver, or spleen), skin and bone marrow involvement, and noncommon variant of histology, high LDH, ALK status, minimal residuel disease are reported as prognostic factors in some studies [7, 25, 29-31] . A number of factors were found significant on survival rates by multivariate analysis. These are ALK negativity for OS rate (HR=16.9), disseminated disease (HR=3.2), and response to first line treatment (HR=17.6) for EFS rate. We had ALK negative patients in our study, and negative impact on overall survival rate was found in multivariate analysis, although this was not significant on EFS. However, ALK status was not found as prognostic factor on event. We have to evaluate patients with negative prognostic factors in treatment schedule.

The treatment protocols showed the variation in our center and in the world. The most appropriate treatment protocols for ALCL are unknown. Previous studies have shown satisfactory effects for T type or sometimes B type protocol like Lymphoma malignant T (LMT), Lymphomamalignant B (LMB) and Berlin-Frankfurt-Munster (BFM) for the treatment of ALCL [8, 11, 33] . Following the international recommendations for the NHL treatment in children, patients with ALCL have been mostly treated with the LMT89 since 1994 [11] as a standard protocol in our center. Also, we used the other protocol as LMB89, LSA2-L2, BFM 90-95 before LMT89. In the results of LMT89 protocol for lymphoblastic lymphoma is reported the rate of EFS as 69% [11]. Also, Brugieres et al. [31] reported the EFS rates of 54% and 76% for ALCL in HM89 and HM91, respectively[34]. The survival rates are significantly higher in ALK positive and Stage I than in ALK negative and Stage II-III-IV [35], and compatible with our results. Our patients with ALK positive had a high overall survival rate. It was the effective predictor on survival in our study (HR=16.9). Different second line treatment was used in this study such as ALLREZBFM, DICE, LSA2L2, LSA4, BFM95,

BFM 90, ABVD, and LMT89. In conclusion, the prognosis of children with ALCL have significantly improved over the years in high income countries but still needs investigation and investment in the rest of the World. The level of care for pediatric cancer patients is improving in Turkey. The overall survival rates for pediatric cancer patients has increased to 67% [1]. More focus is needed to improve survival.

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