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Clinic Analysis of Adult Patients with Acute Lymphoblastic Leukemia

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ABSTRACT

Objectives: In this study, it was aimed to evaluate the demographic and clinical characteristics, prognostic factors, response to different treatment options, side effects caused by changing treatment choices, and overall survival rates of adult Acute Lymphoblastic Leukemia (ALL) patients.

Methods: Our study included 44 patients aged 18 and over, who were followed up with the diagnosis of ALL in our hematology clinic, and treated with treatment protocols containing hyperCVAD (cyclophosphamide, vincristine, Adriamycin, dexamethasone) chemotherapy regimen. Patients were classified according to their clinical findings, organ involvement, and demographic data at the time of diagnosis. The treatment response rates and treatment complications were compared.

Results: The median age of 44 patients included in the study was 34, 72.2% were male, and 27.7% were female. It was determined that 61% of the patients had B cell immunophenotype, and 6 (13.6%) had Philadelphia (+). The rate of the high-risk patient group was 81.8%. The complete remission rate was 72.7%, and the overall survival rate was 43.1%. It was observed that treatment-related sepsis and death rates increased, and complete remission rates and total survival time decreased in patients who added L-asparaginase to the HyperCVAD treatment regimen.

Conclusion: It was observed that the results obtained in our study were similar to other studies. It has been concluded that the current treatment options are not sufficient for adult ALL patients with a total survival rate of 27%, and new treatment protocols are required.

Acute lymphoblastic leukemia (ALL) is a malignant disease characterized by clonal proliferation of lymphocyte precursors (consisting of 80-85% B cell precursors, 15-20% T cell precursors) [1, 2]. It constitutes approximately 85% of childhood acute leukemias and approximately 15% of adult leukemias [3, 4]. In addition to being more common in men, it is known that diseases such as Down syndrome, Bloom's syndrome, Fanconi anemia, and ataxia-telangiectasia are hereditary disorders that predispose to ALL, and the risk of ALL increases after exposure to ionizing radiation [5].

Signs and symptoms in ALL occur

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with bone marrow infiltration and suppression of normal hematopoiesis. The most common signs and symptoms are pallors, fatigue, fever, bone, and joint pain, organomegaly, and lymphadenopathy [3]. The FAB (French-American-British) classification is basically based on morphological features and has limited significance in terms of prognosis and guiding treatment. The WHO (World Health Organization) classification system has started to be used more widely. The treatment of ALL consists of chemotherapy regimens with a combination of cytotoxic drugs [5].

Clinical parameters, immunophenotyping, cytogenetic analysis, treatment response, and minimal residual disease are the primary indicators used in risk stratification in ALL patients today [6].

It was aimed to evaluate the demographic and clinical characteristics, prognostic factors, response to different treatment options, side effects caused by changing treatment choices, and overall survival rates of adult ALL patients in this study.

METHODS

Our study, which was planned in accordance with the Helsinki Declaration decisions, the patient rights regulation, and ethical rules, started after the approval of Medical Research Ethics Committee with the decision numbered 2015-19/19.

A total of 44 patients diagnosed with ALL that received the hyperCVAD chemotherapy protocol, including regimens as a remission induction therapy in Hematology Department outpatient clinic, were included in this study. The data of the patients were obtained from the electronic medical records and follow-up files. Patients older than 18 years of age, diagnosed with ALL by histopathology and flow cytometry, and receiving hyperCVAD included chemotherapy protocol were included in the study.

All patients' symptoms at the time of diagnosis, medical histories, and physical examination information were retrospectively scanned from

Table 1. Characteristics of the patients at the time of diagnosis

Age, median (min-max)	34 (20-62)
Gender, n(%)	
Male	32 (72.2)
Female	12 (27.7)
ECOG performance status, median(min-max)	1.27 (0-4)
Patients with B symptoms, (%)	93
Involvements, (%)	
Hepatomegaly	15.9
Splenomegaly	47.7
Lymphadenopathy	43
Mediastinal mass	4
Central nervous system leukemia	9
Testicular involvement	0
Pericardium	4
Pleura	2
Skin	2
Immunophenotype, n (%)	
Mature T Cell ALL	12, (27.2)
Precursor T-Cell ALL	1, (2.2)
Mature B-Cell ALL	19, (43.1)
Precursor B Cell ALL Calla (+)	5, (11.3)
Precursor B Cell ALL Calla (+) (Myeloid Expression+)	1, (2.2)
CML Transformed Precursor B-Cell ALL	2, (4.5)
Biphenotypic ALL	2, (4.5)
Lymphoma in T Cell Leukemia Form	1, (2.2)
Lymphoma in Precursor T-Cell Leukemic Form	1, (2.2)

ECOG: Eastern Cooperative Oncology Group

their files. Complete blood count, peripheral smear, serum electrolyte measurements, kidney function tests, hepatic enzymes, coagulation tests, and Lactate dehydrogenase value of the patients were noted. The results of chest X-ray, cranial imaging, and cerebrospinal fluid examination performed to evaluate systemic involvement were recorded. Cytogenetic, immunophenotypic, and morphological evaluations studied from bone marrow aspiration and biopsy were filed.

Descriptive statistics for categorical variables were given as frequency and percentage, and continuous variables were given as median (minimum-maximum). Fischer's exact chi-square test was used to compare categorical variables between groups, and the Mann-Whitney U test was used for intergroup comparison of continuous variables. Median survival values, standard errors, confidence intervals, and survival graphs were obtained by using the Kaplan-Meier method. Analyzes were made in IBM SPSS v.21 software. $P < 0.05$ was considered statistically significant.

RESULTS

Of the 44 patients included in the study, 42 were diagnosed with ALL, one with T-cell lymphoma in the leukemic form, and one with lymphoma in the Precursor T-cell leukemic form. The median age of the patients was 34 (20-62), 32 patients (72.2%) were male, and 12 patients (27.7%) were female. (Table-1)

While 39 (88.6%) of the patients were in the high-risk group, 5 (11.3%) were in the standard-risk group. Of the patients with a mean ECOG performance of 1.27 (0-4) at the time of diagnosis, 15.9% had hepatomegaly, 47.7% splenomegaly, 43% lymphadenopathy, 4% mediastinal mass, and 9% central nervous system involvement was observed. No patient with testicular involvement was detected at the time of diagnosis. When evaluated in terms of other organ involvement, pericardial involvement, pleural involvement, skin involvement, and myometrial involvement were observed in 2,1,1 and 1 patients, respectively (Table 1).

While the number of patients with L1, L2, and L3 morphology was 2 (4.5%), 23 (52.2%), and 3 (6.8%), respectively, morphological typing information of 16 patients could not be reached. In the immunophenotypic evaluation, It was determined that 27.2% of the patients had mature T-cell ALL, 2.2% had precursor T-cell ALL, 43.1% had mature B-cell ALL, 11.3% had precursor B-cell ALL Calla(+), 2.2% precursor B-cell ALL Calla(+) with myeloid expression, 4.5% CML-transformed precursor B-cell ALL, 4.5% bi-phenotypic ALL, 2.2% T-cell ALL lymphoma in the leukemic form and 2.2% of them were lymphoma in the precursor T-cell leukemic form (Table 1).

At the time of diagnosis, the median leukocyte count was 73,967 (1,500-662,000), the neutrophil count was 6,268 (0-53,300), the platelet count was 106,481 (6,000-677,000), hemoglobin level was 9.35(4-15.2), lactate dehydrogenase (LDH) level was 1.625 (79-7,500). While the blast rate was 86.69% in the bone marrow, it was 60.3% in the peripheral blood (Table 2). No cytogenetic anomaly was detected in 38 (87%) of the patients, while Ph(+) was detected in 6 (13%) patients (Table 2).

The degree of toxicity developed with remission induction therapy, including a hyperCVAD chemotherapy regimen, is shown in the table (Table 3). After remission induction therapy, 32 (72.7%) of the patients were in complete remission, but relapse was observed in half of them (16 patients) during the follow-up period. Twenty-five (56.8%) of the patients included in the study died during the follow-up period. Of the 9 (20.4%) patients who died during remission induction therapy, six died due to sepsis and related complications, and three died due to bleeding.

It was found that the rate of achieving complete remission was not related to the gender distribution of the patients (81.3% male vs. 18.8% female, $p = 0.213$). It was observed that the presence of hepatomegaly,

Table 2. Laboratory characteristics of the patients at the time of diagnosis

	Median (min-max)
White Blood Cells (K/µL)	73,967 (1,500-662,000)
Neutrophil (K/µL)	6,268 (0-53,300)
Hemoglobin (g/dl)	9.35 (4-15.2)
Platelet (K/µL)	106,481 (6,000-677,000)
Lactate dehydrogenase (IU/L)	1,625 (79-7,500)
Blast rate in bone marrow, (%)	86.69
Blast rate in peripheral blood, (%)	60.3

Table 3. Chemotherapy toxicities					
	Grade 0	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Gastrointestinal	59.0	29.5	4.5	4.5	2.2
Hematological	2.2				97.7
Renal	90.9	6.8	2.2		
Neuromuscular		2.2			
Cardiovascular		2.2		2.2	
Dermatological		6.8		2.2	
Hepatic	72.7	4.5	15.9	2.2	4.5
All parameters are given as a percentage.					

splenomegaly, and mediastinal mass did not affect the rate of complete remission in the patients (p = 1.00). Although complete remission was achieved in 4 of 6 patients with Philadelphia (+), it was observed that this did not affect the complete remission rate (p = 0.616). It was observed that 32 (72.7%) of the 42 patients with risk scoring were in the high-risk category, 87.5% of the patients in complete remission were in the high-risk group, and 12.5% of them were in the standard-risk group. No significant relationship was observed between the risk scoring of the patients and the rates of achieving complete remission (Table 4).

A comparison of complete remission rates in terms of immunophenotype and morphological type could not be made due to the insufficient number of patients in the subgroups. The proportional evaluations of these variables and their subgroups are given in Table 5.

When the effects of risk scoring, treatment regimen difference, and presence of cytogenetic anomaly on the recurrence rates of patients in complete remission after remission induction therapy were examined, no statistically significant difference was observed between the presence of recurrence and cytogenetic anomaly (Table 6, p = 1.00).

ALL patients in our study received four different treatment regimens (hyperCVAD, HyperCVAD + L-asparaginase, hyperCVAD + dasatinib, and hyperCVAD + dasatinib + L-asparaginase) as remission induction therapy (7-10). Statistical analyzes were performed on effects, side effects, mortality, and survival among these treatment regimens. Patients who received remission induction therapy with hyperCVAD + dasatinib and hyperCVAD + dasatinib + L-asparaginase combination regimens were not included in the statistical comparisons due to insufficient data. Significant differences were observed in the treatment-related sepsis frequency,

Table 4. Comparisons made about achieving complete remission			
	Complete Remission (+) n = 10	**Complete Remission (–) n = 32**	***P***
Gender, n (%)			
Male	6 (60)	26 (81.3)	0.213
Female	4 (40)	6 (18.8)	
Hepatomegaly, n (%)			
Exist	1 (10)	6 (18.8)	1.000
None	9 (90)	26 (81.3)	
Splenomegaly, n (%)			
Exist	4 (40)	15 (46.9)	1.000
None	6 (60)	17 (53.1)	
Mediastinal Mass, n (%)			
Exist	0 (0)	2 (6.3)	1.000
None	10 (100)	30 (93.8)	
Cytogenetic anomaly, n (%)			
t(9.22) Positive	2 (20)	4 (12.5)	0.616
t(9.22) negative	8 (80)	28 (87.5)	
Risk score, n (%)			
Standard risk	2 (20)	4 (12.50)	0.616
High risk	8 (80)	28 (87.50)	

Table 5. Distribution of variables related to complete remission achieving		
	Complete Remission (+) n = 10	**Complete Remission (–) n = 32**
Immunophenotype, n (%)		
Mature T Cell ALL	4 (40)	7 (21.90)
Precursor T-Cell ALL	0 (0)	1 (100)
Mature B-Cell ALL	4 (40)	14 (43.80)
Precursor B Cell ALL Calla(+)	1 (10)	4 (12.50)
Precursor B Cell ALL Calla(+)(Myeloid Expression+)	0 (0)	1 (3.10)
CML Transformed Precursor B-Cell ALL	0 (0)	2 (100)
Biphenotypic ALL	1 (10)	1 (3.10)
Lymphoma in T Cell Leukemia Form	0 (0)	1 (3.10)
Lymphoma in Precursor T-Cell Leukemic Form	0 (0)	1 (3.10)
Morphological type, n (%)		
L1	1 (16.70)	1 (4.50)
L2	5 (83.30)	17 (77.30)
L3	0 (0)	3 (13.60)

death during treatment, and complete remission rates with the treatment regimen applied. Comparing HyperCVAD with HyperCVAD + L-Asparaginase treatment, sepsis rates (5 (15.2%) vs. 4 (57.1%), p = 0.034), the mortality rate (5 (15.2%) vs. 4 (57.1%), p = 0.034) It was observed that the rate of complete remission (26 (81.3%) vs. 2 (33.3%), p = 0.031) was lower (Table 7).

The applied treatment regimen and achieving complete remission were found to be effective in overall survival. The total survival time of all patients who received a treatment protocol, including the HyperCVAD chemotherapy regimen, was calculated as 530 ± 106.10 days. It was observed that the total survival time was longer in patients with complete remission (1021.23 ± 174.72 days vs. 70.11 ± 20.42 days, $p < 0.001$). While total survival was observed as 603 ± 75 days in patients receiving the HyperCVAD chemotherapy regimen, total survival time was found to be 17 ± 4.9 days in patients receiving HyperCVAD + L-asparaginase combined therapy (Table 8).

The disease-free survival time of all patients was determined as 499 ± 117.68 days. There was no effect of hepatomegaly, splenomegaly, and cytogenetic abnormality on disease-free survival (Table 9).

DISCUSSION

The prognosis of ALL patients varies according to patient and disease characteristics. Age, performance status, organ functions, immunophenotype, karyotype, accompanying cytogenetic anomaly, leukocyte count at diagnosis, time to complete remission, and presence of minimal residual disease are shown as risk factors affecting prognostic indicators in adult patients [1, 3, 11-13]. According to these characteristics, patients are divided into groups low-risk (standard-good-risk) and high-risk (poor-risk) patients [12]. While the disease-free survival rate was 50-60% in the standard-good-risk patient group, this rate was found to be 20% or less in the high-poor-risk patient group. High-risk patients are seen in 75% of adult ALL patients [11-13]. In the current study, the rate of high-risk patients was found to be 81.8%.

ALL constitutes approximately 20% of adult acute

Table 6. Comparisons of recurrence rate			
	No Recurrence n = 15	**Recurrence n = 16**	***p***
Cytogenetic anomaly, n (%)			1.000
t(9.22) Positive	2 (3.30)	2 (12.50)	
t(9.22) negative	13 (86.70)	14 (87.50)	

Table 7. Comparisons with the applied treatment regimen			
	HyperCVAD n = 33	**HyperCVAD + L-Asparaginaz n = 7**	***p***
Frequency of treatment-related FEN			
Exist	23 (%69.70)	6 (%85.70)	0.650
None	10 (%30.30)	1 (%14.30)	
Frequency of treatment-related sepsis			
Exist	5 (%15.20)	4 (%57.10)	**0.034**
None	28 (%84.80)	3 (%42.90)	
Side Effects			
Gastrointestinal	0 (0-3)	1 (0-3)	0.382
Hematological	4 (0-4)	4 (4-4)	0.917
Renal	0 (0-0)	0 (0-1)	0.081
Neuromuscular	0 (0-2)	0 (0-0)	0.917
Cardiovascular	0 (0-0)	0 (0-4)	0.577
Dermatological	0 (0-3)	0 (0-0)	0.626
Hepatic	0 (0-3)	0 (0-4)	0.382
Mortality during treatment			
Excitus	5 (%15.20)	4 (%57.10)	**0.034**
Alive	28 (%84.80)	3 (%42.90)	
Complete remission			
No Remission	6 (%18.80)	4 (%66.70)	**0.031**
Remission	26 (%81.30)	2 (%33.30)	
Recurrence rate			
Exist	14 (%56)	0(%0)	0.222
None	11 (%44)	2(%100)	
FEN: Febrile neutropenia			

leukemia. The most common B cell immunophenotype is seen in adult patients with ALL [5, 6]. In our study, it was observed that 61% of the patients had B cell immunophenotype.

While there is no difference in the incidence of ALL in childhood, the male gender comes to the fore in adulthood [4]. It was found to be more common in males, with a rate of 72.2% in the current study. Approximately 2/3 of childhood ALL cases are cured after treatment. This rate decreases to 1/3 in adulthood [4].

Cytogenetic anomaly is seen in 80% and 60-70% of childhood and adult ALL cases, respectively [6]. In our study, in which t(9:22) mutation was observed to be positive in 6 (13.6%) of the 44 patients included in the study, the most common cytogenetic disorder was found to be Philadelphia (+) in accordance with the literature.

In patients with ALL, the overall survival rate has been reported to be between 27 and 48% [10, 13]. Similarly, in our presented study, this rate was found to be 43.1%. It was observed in our study that the risk scoring at the time of diagnosis and the presence of cytogenetic anomaly did not have a significant effect on the rate of complete remission, and the immunophenotypic and morphological diagnosis did not affect the rates of achieving complete remission. This situation may be associated with the insufficient number of patients included in the study.

It was reported that gender, lymphadenomegaly, bone marrow blast rate, splenomegaly, and presence of mediastinal mass at the time of diagnosis were not effective in complete remission after treatment which was in line with our study [2, 3]. Consistent with the literature (complete remission rates have been reported to be between 74-93%), the rate of complete remission was observed as 72.7%. In studies, it has been shown that while the total survival rate is 5% in patients who cannot achieve complete remission, it increases to 45% in patients with complete remission [12]. It was shown in the current study that the total survival time was longer in patients with complete

Table 8. Determination of factors affecting overall survival				
	n	**Survival time (days)**	**%95 CI**	***p***
Hepatomegaly				
Exist	8	491 ± 81.57	331.14-650.89	0.799
None	36	530 ± 132.10	271.09-788.91	
Splenomegaly				
Exist	21	530 ± 89.53	354.52-705.48	0.715
None	23	603 ± 167.51	274.68-931.32	
Leukocyte count at diagnosis				
< 30,000 K/µL	25	661 ± 131.33	403.60-918.405	0.224
≥ 30,000 K/µL	19	426 ± 208.30	17.74-834.26	
Age				
< 35	27	603 ± 62.75	480-725	0.217
≥ 35	17	407 ± 263.76	0-923.96	
Cytogenetic Anomaly				
t(9;22) positive	6	100 ± 108.27	0-312.20	0.092
t(9;22) negative	38	603 ± 63.55	478.45-727.56	
Risk scoring				
Standard risk	6	661 ± 605.78	0-1848.33	0.929
High risk	38	527 ± 93.62	343.50-710.50	
Applied treatment regimen.				
HyperCVAD	33	603 ± 63.75	478.05-727.96	**0.009**
HyperCVAD + L-Asp	7	17 ± 4.90	7.40-26.60	
Complete remission				
No Remission	10	70.11 ± 20.42	30.08-110.14	***p* < 0.001**
Remission	32	1021.23 ± 174.72	678.77-1363.68	

L-Asp: L-Asparaginaz

Table 9. Determination of factors affecting disease-free survival				
	n	**Survival time (days)**	**%95 CI**	***p***
Hepatomegaly				
Exist	6	609 ± 132.11	350.07-867.93	0.424
None	25	359 ± 187.77	0-727.02	
Splenomegaly				
Exist	15	443 ± 153.67	141.80-744.20	0.181
None	16	567 ± 202.99	169.15-964.86	
Cytogenetic Anomaly				
t(9:22) positive	4	212.67 ± 69.67	76.12-349.24	0.167
None	27	772.57 ± 184.99	410-1135.15	

remission ($p < 0.001$).

In our study, in the HyperCVAD + L-asparaginase group, it was observed that the rates of treatment-related sepsis and treatment-induced excitus increased while the rates of achieving complete remission and total survival decreased.

CONCLUSION

It has seen that the general characteristics, response to treatment, and complications of adult ALL patients included in our study were similar to those in the literature. There is a need for new targeted treatment protocols for adult ALL patients with a total survival rate of up to 27%.

Authorship Contributions:

Conception: V.O., F.Ö., F.C. Design: V.O., F.Ö., F.C. Supervision: V.O., F.Ö. Funding: None, Data Collection or Processing: F.C., Analysis or Interpretation: V.O., F.Ö., F.C. Literature Review: F.C., V.O., N.K., Writer: F.C, V.O., N.K., Critical

Review: N.K.

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Conflict of Interest

No conflict of interest was declared by the authors.

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