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Survival Rate of Childhood Leukemia in Shiraz, Southern Iran

Amir Almasi-Hashiani[1], MSc; Soheil Zareifar[2], MD; Mehran Karimi[2], MD; Esmaeil Khedmati[3], MSc; Abolfazl Mohammadbeigi[4*], PhD

1. Department of Public Health, School of Health, Arak University of Medical Sciences, Arak, Iran
2. Hematology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran
3. Center for Research on Social Determinants of Health, University of Social Welfare and Rehabilitation Sciences, Tehran, Iran
4. Department of Public Health, School of Health, Qom University of Medical Sciences, Qom, Iran

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Abstract

Objective: Leukemia is the most prevalent type of cancer in children. The aim of this study was to estimate the 5-year survival rates of Acute Lymphoblastic Leukemia (ALL) and Acute Myeloblastic Leukemia (AML) as well as factors influencing them.

Methods: This is a nonrandomized retrospective study conducted on 280 patients with ALL and AML. They were all below 15 years old children admitted to Shahid Faghihi hospital, Shiraz, Iran from 2004 to 2008.The survival rates were estimated by applying the Kaplan-Meier method. In addition, the log rank test was used to estimate the statistical significance of differences in the survival probability. Cox regression model was applied to conduct multivariate analysis for adjusting confounding variable. All analyses were performed in SPSS statistical software (version 16). *P*-values less than 0.05 were considered as statistically significant.

Findings: The mean (± standard deviation) of the observation period was 28.2±16.1 months. In this period, 60 (24.7%) patients (47 ALL and 15 AML) passed away. The cumulative rate of survival in this study was 53.3±0.1 percent. This probability was 56.6±0.1% and 44.2±0.1% for ALL and AML patients, respectively, which indicates no statistically significant difference between them (*P*=0.8). According to Cox model, there was a significant relationship among the variables of platelet count and relapse with the survival rate.

Conclusion: Platelet count was identified as a positive prognostic factor of the survival rate in ALL patients. However, on the base of our results and other studies, incidence of relapse and the number of relapses are significant factors of survival rates of leukemia.

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Key Words: Lymphoblastic Leukemia; Myeloblastic Leukemia; Survival Rate; Relapse

Introduction

Cancer, after non-intentional injuries, is ranked as the second most common cause of mortality in under 14 year old children (e.g. by rate of 0.41 deaths per 10,000, in Italy)[1]. Despite the low rate of overall incidence, leukemia is the most prevalent type of cancer in children[2-8], in a way that almost 32% of pediatric cancers consist of leukemia[9]. The most common type of leukemia in children under 19 years is Acute Lymphoblastic Leukemia (ALL), and its incidence in 1-4 year-old children is over nine times more than in 20-24 year-old individuals[10]. In developed countries, ALL is also responsible for almost 80% of childhood leukemia cases[3,11], and its incidence rate reaches to 34.3 cases per one million[3]. Far differently, Acute Myeloblastic Leukemia (AML)

*** Corresponding Author;**
Address: Department of Public Health, Health School, Rohallah Sq., Qom, Iran
E-mail: beigi60@gamil.com

cases in children are very rare, and its annual incidence in Europe is limited to 4 to 9 cases per million. Moreover, only 20-25% of all newly-diagnosed leukemia cases in children under 15 years are of AML and CML (ranging from 300 to 350 annual new cases in European Union)[12], and its incidence rate reaches hardly 7.1 to 8.9 cases per million[3]. The survival rates of childhood cancers have significantly improved in recent decades[1,13]. In America, for instance, advances in cancer therapeutic procedures and supportive cares have resulted in elevation of the five-year survival rate from less than 30% in 1960 to over 70% in 1990[13].

The survival rate of all childhood cancers has been investigated in many studies. In a study carried out by Sankila and colleagues[14], starting 1988 to 1997 in Europe, the five-year survival rate was estimated as 37%, while this rate was calculated as 74% in American patients who were diagnosed between 1985 and 1999. In the study conducted in Shiraz in 2002, from 75 ALL patients diagnosed during 1995-2000, five-year survival rate was estimated as 72.5%[4].

Considering the soaring trend in incidences and prevalence rates of leukemia, in this study we intended to estimate the five-year survival rates of AML and ALL leukemia as well as their influencing factors in children under 15 years who were referred to Shahid Faghihi hospital, Shiraz, Iran from 2004 to 2008.

Subjects and Methods

The subjects of this retrospective study were AML and ALL patients under 15 years who had been hospitalized in Shahid Faghihi hospital from autumn 2004 to autumn 2008. Diagnosis was based on the international coding diseases (ICD-10) with codes C-92 and C-95. Totally 280 patients had been hospitalized during this time. The exact date of the diagnosis - based on immune-phenotyping results - and the exact date of death were considered as the initial event and the end point event, respectively. In cases in which the end point event did not occur due to termination of the study, missed follows, or the patient's death by reasons other than AML or ALL, data was considered as censored.

The required data was gathered from archived profiles of Shiraz Shahid Motahari Clinic, and the information needed for determining the patients' survival status was gathered from physician reports, existing profiles, and in some cases, by communicating parents using the recorded phone numbers in the patients' profiles. Since the required information was obtained from the patients' profiles which were supplied for research tasks, there were no ethical predicaments in this project. However, the study protocol was approved by ethical committee of Shiraz University of Medical Sciences. Kaplan-Meier method and Log rank test were used to determine the survival rate and to compare the survival curves, respectively. Cox regression model was used to conduct the data modeling (Control of confounding variable). The proportionality assumption (as one of the Cox regression model assumptions) was also studied and confirmed in the variables of interest. The variables with *P*-values below 0.25 in univariate analysis and a satisfying proportionality assumption, were qualified to be included in the Cox regression model analysis. Data analysis was performed applying the SPSS statistical software (version 16), and the proportionality assumption was investigated by using the STATA software (version 9). *P*-values less than 0.05 were considered as statistically significant.

Findings

From 280 hospitalized patients, 243 (86.7%) cases were successfully followed up until the end of the study. From these successfully followed-up patients, 179 (73.7%) cases were diagnosed as ALL patients and 64 (26.3%) as AML patients. Demographic characteristics of the patients- based on age, gender, residency, and hematologic data - are shown in Table 1. The mean age of ALL patients was 6.8±3.5 years (9.8% males and 40.2% females). Also, the mean age of AML patients was 8.5±3.6 years (53.1% males and 49.6% females). In addition, the mean±SD (median) of the following period was about 28.2±16.1 (22.9) ranging from 6.4 to 67.4 months. During this

Table 1: Demographic characteristics of ALL and AML patients based on age, gender, residency, and hematologic data

Variables	Subgroups	ALL (%)	AML (%)
Age groups	1>	1(0.6)	1(1.6)
	1-4.99 yrs	65 (36.3)	11 (17.2)
	5-9.99 yrs	58(38.8)	23 (35.9)
	10-14.99 yrs	45(25.1)	29 (45.3)
Sex	Male	107 (59.8)	34 (53.1)
	Female	72 (40.2)	30 (46.9)
Residency	Shiraz city	63 (35.2)	22 (34.4)
	Fars except Shiraz	68 (38)	23 (35.9)
	Other provinces	48 (26.8)	19 (29.7)
White blood cell	<25000	170(95)	59(92.2)
	25000-49999	3(1.7)	2(3.1)
	50000-99999	3(1.7)	-
	>100000	2(1.1)	3(4.7)
Hemoglobin	Abnormal	128 (71.5)	54 (84.4)
	Normal	51 (28.5)	10 (15.6)
Platelet	Thrombocytopenia	103 (57.5)	52 (81.2)
	Normal	63 (35.2)	11 (17.2)
	Thrombocytosis	13 (7.3)	1 (1.6)
Relapse	Yes	61 (34.1)	20 (31.2)
	No	118 (56.9)	44 (68.8)
Number of relapses	0	118 (65.9)	44 (68.8)
	1	36 (20.1)	9 (14.1)
	≥ 2	25 (14)	11 (17.2)
Immunophenotype	Pre B-Cell	73 (40.8)	-
	Common	89 (49.7)	-
	AML	-	64 (100)
	T-Cell	17 (9.5)	-
Status	Censored	132 (73.7)	49 (76.6)
	Death	47 (26.3)	15 (23.4)
Total cases		179 (73.7)	64 (26.3)
Follow up duration (month) (mean±SD)		28.5(16.3)	27.4(15.7)

ALL: Acute lymphoblastic leukemia; AML: Acute myeloblastic leukemia

period, 60 (24.7%) cases passed away (47 ALL and 15 AML patients). In this study, the cumulative probability of five-year survival rate of cancer was 53.3±0.1% and as Fig. 1 shows, this probability was 56.6±0.1% and 44.2±0.1% for ALL and AML patients, respectively, which indicates no statistically significant differences between them (P=0.8).

According to the log rank test results – shown in Table 2 – in ALL patients, the variables of blood platelet count, relapse history of the disease, and the number of relapses showed a significant relationship with the cancer survival rate; while in AML patients, the survival rate only showed a significant relationship with the relapse history of the disease and the number of relapses. Overall, the survival rate of leukemia (including both ALL and AML subtypes) showed a statistically significant relationship with the platelet count, the relapse history, and the number of relapses.

The results of multivariate analysis, carried out by Cox regression model, are shown in Table 3. As this table illustrates, in ALL patients, variables of platelet count and the number of relapses showed a significant relationship with the cancer survival rate. Moreover, taking both subtypes of leukemia into account, Cox regression model showed a significant relationship among variables of platelet count, number of relapses, and the survival rate.

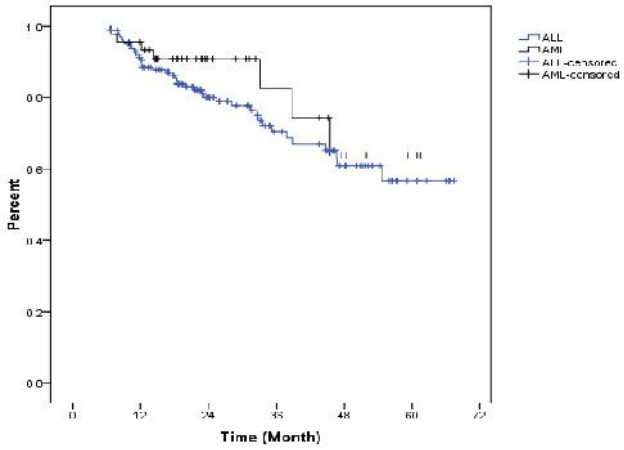

Fig. 1: Cumulative probability of five-year survival rate in ALL and AML patients
ALL: Acute lymphoblastic leukemia; AML: Acute myeloblastic leukemia

Discussion

During recent decades, salient advances have been achieved in childhood cancer therapy. Nonetheless, childhood cancers – especially blood cancers – have already been ranked as one of the most common causes of childhood mortality[15]. In this study, we tried to investigate some factors including age, gender, immunophenotype, WBC count, platelet count, and relapse history, which affect ALL and AML patients' five-year survival rate. In this study, there was no significant relationship between age and survival rate whereas in a study which was conducted by Pastore and colleagues in Italy, children belonging to the 5-9 year-old and the 10-14 year-old groups had, respectively, 30% and 50% risk of death in comparison to the children of the 1-4 year-old

Table 2: The mean of survival rates for ALL, AML, and all patients

Variables		ALL	*P* value	AML	*P* value
Age groups	1-4 yrs	51.4	0.2	37	0.09
	5-9 yrs	46.5		48.6	
	10-14 yrs	48.7		54.3	
Sex	Male	49.7	0.8	46.4	0.9
	Female	49.9		47.6	
Residency	Shiraz city	46.9	0.4	43.9	0.4
	Fars except Shiraz	51.9		52.4	
	Other province	46.6		46.5	
Initial white blood cell	Leukopenia	49.1	0.4	46.8	0.8
	Normal	55.8		51.5	
	Leukocytosis	40.3		47.3	
Initial Hemoglobin	Abnormal	47.5	0.2	45.6	0.1
	Normal	56.4		57	
Initial Platelet	Thrombocytopenia	44.7	0.004	48.3	0.9
	Normal	59.8		45.7	
	Thrombocytosis	34.7		-	
Relapse	Yes	37.9	<0.001	37.1	0.002
	No	58.6		54.2	
Number of relapses	0	58.6	<0.001	54.2	<0.001
	1	44.7		46.3	
	≥ 2	28.2		30.5	
Immuno-phenotype	Pre B-Cell	40.8	0.19	-	
	Common	54.1		-	
	AML	-		-	
	T-Cell	45.1		-	

ALL: Acute lymphoblastic leukemia; AML: Acute myeloblastic leukemia

Table 3: The modeling of risk factors which are effective in the leukemia survival rate by using Cox regression model

Leukemia type	Variables	Sub groups	Hazard ratio(HR)	95% CI for HR	*P*-value
Total (243 cases)	Initial Platelet	Normal	1	-	-
		Thrombocytopenia	2.41	1.1-4.9	0.016
		Thrombocytosis	4.54	1.4-13.9	0.008
	Number of relapses	0	1	-	-
		1	2.9	1.4-5.7	0.002
		≥ 2	7.9	4.3-14.5	0.001
ALL (179 cases)	Initial Platelet	Normal	1	-	-
		Thrombocytopenia	2.8	1.2-6.4	0.012
		Thrombocytosis	4.01	1.14-14.1	0.03
	Number of relapses	0	1	-	-
		1	2.93	1.37-6.29	0.006
		≥ 2	7.53	3.71-15.25	0.001
AML (64 cases)	Relapses	No	1	-	-
		Yes	5.18	1.6-16.5	0.005

ALL: Acute lymphoblastic leukemia; AML: Acute myeloblastic leukemia; CI: Confidence interval

group[16].

Although a higher survival rate is expected to be observed in females compared to males, our study showed similar rates for both sexes which were in line with the results of the study by Pastore and colleagues[16]. Immunophenotyping results in ALL patients revealed enhanced survival rates for Common ALL patients compared to other patients; however, the differences were not statistically significant.

It has been demonstrated by numerous studies that WBC count has an effective role in survival rate of leukemia, especially ALL patients, in a way that WBC count less than 10,000 is associated with a better prognosis[17]. In our study, although the patients (especially ALL patients) with high levels of leukocytosis, compared to the control group or the patients with leukopenia, showed low rates of survival rates (40.3 months vs. 55.8 and 49.1 months), this difference was not statistically significant. This matter might be due to gathering the WBC count results in the middle of the chemotherapy or other therapies.

As we expected, the incidence of relapse and the number of relapses showed a significant relationship with survival rates for ALL and for AML. In this regard, frequent relapses and nervous system involvement are emphasized as important prognostic factors of survival rate in ALL patients[15,18]. Furthermore, in this study, the variable of platelet count was identified as a positive prognostic factor of the survival rate in ALL patients.

Conclusion

Regardless of some differences between effective factors in prognosis and survival rates of childhood leukemia in different regions of the world, it can be concluded that – according to many studies – indicators such as the disease relapse and the number of relapses as well as factors such as WBC primary count, gender, and immunophenotype play major role in determining the survival rate of leukemia patients. Platelet count was identified as a positive prognostic factor of the survival rate in ALL patients. On the base of our results and other studies, incidence of relapse and the number of relapses are significant factors in survival rate of leukemia.

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Conflict of Interest: None

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