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Original Article

The Survival of Childhood Leukemia and its Related factors in Kerman, Iran

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Abstract

Background and Purpose: Leukemia is the most prevalent type of cancer in children and its prognostic factors vary in different geographic locations. The aim of this study was to estimate the 5 years survival rate of children suffering from leukemia in Kerman, Iran and to investigate the factors which might influence it.

Materials and Methods: This was a cohort study conducted on patients with acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML). Cases were all younger than 15 years old admitted to Afzalipour Hospital, Kerman, Iran between 1998 and 2009, and included 219 patients. Survival rates were estimated by applying the Kaplan–Meier method. Log-rank test was used to estimate the statistical difference in survival probability and the effect of independent variables on survival was examined using Cox regression. All analyses were performed using STATA-12.

Results: The cumulative 5 years rate of survival in this study was 58% and 43% for ALL and AML, respectively, and the difference was statistically significant (P = 0.0030). Multivariate Cox regression analysis showed that white blood cell (WBC) ≥ 50,000 µl (P = 0.0100) and relapse (P = 0.0060) of ALL patients has a significant effect on survival. In AML due to the small number of patients significant results were not achieved. The cumulative survival rate at the end of 1 year for low, medium and high-risk patients were estimated 97%, 94%, and 78%.

Conclusion: Leukemia patients with and WBC ≥ 50,000 µl and a history of relapse had less survival.

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1. Introduction

Cancer is currently one of the most common causes of death in the world, and 8.2 million deaths in the world were related to cancer in 2012 (1). According to the first national study about the burden of disease and injury in Iran, cancers lead to 662.4 years loss in hundred thousand person in 2003 and was the tenth cause for the years of life loss (2). Less than 1% of cancers occur between ages 0 and 14 years; but, after non-intentional injuries, cancer is the second most common cause of mortality in this age group (3-5). In the USA, the annual incidence rate of cancer in children is 186.6 a 1 million children aged birth to 19 years (6). Although progress has been made in treating childhood cancers including leukemia, it is still one of the main reasons for childhood mortality (7). Leukemia has a low incidence, but is the most common type of cancer diagnosed in children (8-10), and accounts for around 32% of childhood cancers (11). Studies have shown that the incidences of leukemia among girls and boys are 12-62 and 9-24 cases a million (12). Leukemia is characterized as an increase in the immature bone marrow, blood, and other tissue cells and therefore jeopardizes blood cell formation and immune systems function (13). Leukemia is classifies as “myeloid” and “lymphoid” types according to cell types and, as acute and chronic based on the clinical course (14). Acute lymphoblastic leukemia (ALL) is the most common form of childhood leukemia and includes 80% of the cases diagnosed in developed countries (15,16). Acute myeloblastic leukemia (AML) includes about 15% of leukemia cases and has a poorer prognosis in comparison to ALL (16). In recent decades, the survival rate of children with leukemia has dramatically increased because of improvements in diagnostic tools and therapeutic protocols (17). In the USA, the 5 years survival rate increased from about 30% in the mid-1970s to approximately 60% in the late 1990s (18). In northern England, the 5 years survival rate for ALL diagnosed between 1991 and 2000 was 87%, and for all European children, diagnosed between 1995 and 2002, it was 85% (19). Moreover, in a study conducted by Goubin et al., the survival rate increased from 77% (between 1990 and 1992) to 85% (between 1997 and 2000) for ALL and from 47% to 61% for AML in French patients (20). Clinical and laboratory symptoms can be used as determinants of prognosis at the time of diagnosis (13). Identifying factors affecting survival (e.g. age, sex, white cell count) is one of the major approaches used to improve the survival of patients with cancer and reduce the overall burden resulting from it (21). Currently, the results of cytogenetic and molecular methods are used to determine prognoses in developed countries. However, in other countries, there is no possibility of performing large-scale tests. Therefore, accurate determination of the impact of primary factors can be important. There is considerable variation in prognostic factors between countries (22). Consequently, the objective of the present study was to estimate the 5 years survival rate in children with ALL and AML and determine the effects of these prognostic factors.

2. Materials and Methods

In this cohort study, 219 patients under 15 years old with acute leukemia (ALL and AML) admitted at Afzalipour Hospital, Kerman, Iran, from 1998 to 2009 were reviewed. The exact time of diagnosis (based on history and immunophenotyping) was considered as the initial event and the exact date of death as the end point event. Cases in which the final event did not happen due to termination of the study were impossible to follow-up for reasons, such as immigration, unwillingness to cooperate or death due to reason other than the acute leukemia types ALL and AML were known as censored data. Final event dates and variables such as age,

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sex, place of residence, parents' education level, parents' job, type of insurance, treatment, type of tumor, a history of relapse, location and number of relapses, hemoglobin, platelet and white blood cells (WBCs), as well as hepatosplenomegaly, were inquired from the patients' medical records, physician reports, communication with their family, cancer registry or insurance agency records. All laboratory data was from the time of diagnosis. The study was approved by the Kerman Medical University Standing Committee on Ethics in Research. Survival rates were estimated by applying the Kaplan–Meier method. Log-rank test was used to compare survival probability between groups. Before using Cox regression, the proportionality assumption was checked for all variables. The variables that showed $P < 0.200$, and satisfied the proportionality assumption were included in the Cox regression analysis. The ultimate Cox model was used to define three (low, moderate, high) risk groups. All analyses were performed using STATA-12 (Stata Corp LP, USA) and $P < 0.050$ were considered statistically significant.

3. Results

Of the 219 patients, 205 (93.6%) cases were followed until the end of the study. Of these, 189 patients (86.3%) were diagnosed with ALL and 29 patients (13/24%) were diagnosed with AML. The mean age of patients with ALL was 5.9 ± 3.5 (and 60.8% were male and 39.2% female). The mean age of patients with AML was 8.27 ± 4.3 years old (and 37.9% were male and 62.1% female). The other demographic and clinical characteristics of patients are shown in table 1. The mean ± standard deviation of the observation period was around 30.65 ± 22.87 months. During this period, 55 (27.4%) patients (41 with ALL and 13 with AML) passed away. The cumulative 5 years survival rate in patients with AML and ALL was 58% and 43%, respectively, and the difference between the two groups was statistically significant ($P = 0.004$). The results of Cox regressions is shown in table 2. Univariate Cox regressions showed that relapse history, the number of relapses and WBC ≥ 50,000 µl were significant survival predictors for patients with ALL. Meanwhile significant predictors for patients with AML, included sex, relapse history and a number of relapses. Overall, the survival of leukemia (including both ALL and AML) represented a statistically significant association with relapse history, the number of relapses and WBC ≥ 50,000 µl. After adjusting for other variables WBC ≥ 50,000 µl and relapse had a significant effect on leukemia survival rate. A survival model was built according to the significant predicting factors. According to the final model the cumulative survival rate at the end of the 1st year for low risk, medium risk and high-risk patients were estimated 97, 94, and 78 percent, respectively. By the end of 5 years, the survival rates were estimated 71, 57, and 43 percent.

4. Discussion

Despite remarkable advances in the treatment of pediatric cancer, blood cancers are still one of the most common causes of childhood deaths (7). Determining prognostic factors can help in making therapeutic decisions. In this paper, some of the factors affecting the prognosis of patients with ALL and AML have been investigated.

The 5 years survival rate in this study was the same as the rates reported from other developing countries but is much lower than developed countries. In this study, the survival rate for patient with ALL and AML was 58 and 43%, respectively, compared to 59.8% in India (23), and 65.2% in Egypt (24), while this value was reported 85% in Europe (25). There are several reasons for this difference which include differences in medical care, lower

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compliance with follow-up or treatment due to economic and cultural problems and insufficient knowledge about the treatment of the disease in developing countries. It seems that the other reason for this difference can be attributed to the variety of clinical and biological characteristics affecting survival in developing and developed countries.

About 27% of patients in this study were in the high-risk age group (less than 1 year or 10 or more years). Results reported by Gaynon et al. (26) in USA, Canada and Australia and Schrappe et al. (27) in Germany, Austria and Switzerland showed that had 24.2 and 20.4% of their patients were in the high-risk age group, respectively.

Table 1. Demographic and biological characteristics of patients with acute lymphoblastic leukemia and acute myeloid leukemia

Variables	Subgroups	All patients	ALL (%)	AML (%)
Age groups (Years)	Less than 5	93 (42.47)	86 (45.5)	7 (24.14)
	5-9.99	76 (34.70)	68 (35.98)	8 (27.59)
	10-14.99	50 (22.83)	35 (18.52)	14 (48.28)
Sex	Male	86 (39.27)	74 (39.20)	11 (37.90)
	Female	133 (60.73)	115 (60.80)	18 (62.10)
Father's education level	Illiterate	15 (9.26)	13 (9.35)	2 (9.09)
	Literate	147 (90.76)	126 (90.65)	20 (90.91)
Mother's education level	Illiterate	27 (16.46)	21 (14.89)	6 (27.27)
	Literate	137 (83.54)	120 (85.11)	16 (72.73)
Father's job	Unemployed	127 (76.97)	108 (76.00)	18 (81.90)
	Employee	38 (23.03)	34 (23.90)	4 (18.10)
Mother's job	Housekeeper	144 (87.70)	124 (87.90)	19 (86.40)
	Employee	20 (12.20)	17 (12.10)	3 (13.60)
Insurance	No	176 (90.72)	123 (90.38)	25 (92.60)
	Yes	18 (9.18)	16 (9.62)	2 (0.00)
WBC	< 10,000 µl	122 (64.50)	109 (64.50)	13 (61.90)
	10,000-50,000 µl	43 (22.63)	40 (23.70)	3 (14.30)
	> 50,000 µl	25 (13.16)	20 (11.80)	5 (23.80)
Hemoglobin	Abnormal	129 (67.89)	115 (68.05)	14 (66.67)
	Normal	61 (32.11)	54 (31.59)	7 (33.33)
Platelet	Thrombocytopenia	137 (72.11)	122 (72.19)	15 (71.43)
	Normal	49 (25.79)	44 (26.04)	5 (32.81)
	Thrombocytosis	4 (2.11)	3 (1.78)	1 (4.76)
Relapse	Yes	75 (38.66)	65 (38.20)	10 (41.70)
	No	119 (61.34)	105 (62.50)	14 (58.30)
Number of relapses	0	119 (61.66)	105 (62.50)	14 (58.30)
	1	54 (27.98)	44 (26.20)	9 (37.50)
	≥ 2	20 (10.36)	19 (11.3)	1 (4.20)
Place of relapses	BM	63 (86.30)	54 (85.70)	-
	CNS	8 (10.96)	8 (12.70)	9 (100.00)
	BM-CNS	2 (2.74)	1 (1.60)	-
Splenomegaly	Yes	97 (51.60)	86 (52.80)	10 (41.70)
	No	91 (48.40)	77 (47.20)	14 (58.30)
Hepatomegaly	Yes	90 (45.00)	8 (46.20)	10 (38.50)
	No	110 (55.00)	93 (53.80)	16 (61.50)
Treatment	Chemotherapy	139 (70.56)	118 (67.80)	21 (91.30)
	Chemotherapy-radiotherapy	55 (27.92)	54 (31.00)	1 (4.30)
	Chemotherapy-bone marrow transplantation	1 (0.51)	1 (0.60)	1 (4.30)
	Chemotherapy- hormone therapy	2 (1.02)	1 (0.60)	-
Status	Censored	164 (74.89)	148 (78.31)	16 (55.17)
	Dead	55 (25.11)	41 (21.69)	13 (44.83)
Total cases		219	189	29

WBC: White blood cells, BM: Bone marrow, CNS: Central nervous system, AML: Acute myeloid leukemia, ALL: Acute lymphoblastic leukemia

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Table 2. The modeling of risk factors which are effective in the leukemia survival rate by using Cox regression model

Leukemia type	Variables		Crude hazard rate			Adjusted hazard rate		
			HR	CI 95%	P	HR	CI 95%	P
Total (219 cases)	Tumor	ALL	Ref	0.21-0.76	0.005	-	-	-
		AML	0.40					
	Relapse	No	Ref	1.21-4.04	0.010	-	-	-
		Yes	2.20					
	Number of relapses	0	Ref	-	-			
		1	2.09	1.06-4.11	0.030	-	-	-
		≥ 2	2.49	1.13-5.47	0.020			
	White blood cells (µl)	< 10,000	Ref	-	-	-	-	-
		10,000-50,000	1.30	0.39-2.19	0.870	1.16	0.42-3.15	0.770
		> 50,000	3.08	1.16-8.21	0.020	3.36	1.05-10.76	0.040
ALL (189 cases)	Relapse	No	Ref	1.99-9.3	< 0.001	3.68	0.44-9.39	0.006
		Yes	4.31					
	Number of relapses	0	Ref	-	-			
		1	4.07	1.73-9.6	0.001	-	-	-
		≥ 2	4.30	1.67-11.11	0.003			
	White blood cells (µl)	< 10,000	0.99	0.38-2.52	0.980	1.52	0.46-5.04	0.480
		10,000-50,000	Ref	-	-	-	-	-
		> 50,000	3.48	1.17-10.28	0.020	6.25	1.55-25.13	0.010
AML (29 cases)	Gender	Male	Ref	0.04-0.89	0.030	-	-	-
		Female	0.19					
	Relapse	No	Ref	0.03-0.85	0.030	-	-	-
		Yes	0.17					
	Number of relapses	0	Ref	-	-			
		1	0.20	0.04-0.98	0.040	-	-	-
		≥ 2	0.44	0.2-0.88	0.030			

AML: Acute myeloid leukemia, ALL: Acute lymphoblastic leukemia, HR: Hazard Ratio, CI: Confidence interval

The percentage of patients within WBC ≥ 50,000 µl in the present study (13%) was lower than other studies. In study of Gaynon, et al it was 21% (26) and in study of Schrappe et al was 19% (27). Central nervous system involvement in the present study was seen in 11% of patients, compared with only 2.4-5.3% in western studies (26,27).

The percent of patients with relapse, as one of the main predicting factors, was 38.2 and 41.7% in ALL and AML cases, respectively, which is comparable to the study in Shiraz, Iran, with 34.1 and 31.2%, respectively (11). This percent is in the 23.4-41.1 range in many developing countries (23,24,28,29), In Turkey (30), this rate was 19.7%, which was comparable with Moricke et al.' study in which this percent was 16.2% (31). The main reason for these differences can be the lack of advanced detection methods and the shortage of transplant centers (stem cell and bone marrow) in developing countries.

In the recent years, the survival rate of children diagnosed with ALL increased dramatically (26), while the recovery rate of patients with AML has been lower, with a worse prognosis (32,33). In the present study, similar to Zareifar et al. in Shiraz (11), the survival rate of ALL patients was higher. However, after adjusting for other variables, there was no significant difference between these two groups. It seems like the higher occurrence of relapse in patients with AML compared to ALL (41/67% vs. 37/87%) is one reason for their low survival rate.

Despite many reports (34,35), in this study age had no significant relationship with survival. The likely reason is that the majority of patients (72.6%) were in the 2-9 years age group, which as described in other studies was

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the group with higher survival (36,37). Several studies showed age had a significant effect on survival (9,11).

Although a higher survival rate in female patients was seen in other studies (37,38).

Our study showed that the survival rate was similar for both males and females, which is in line with the results of studies conducted by Swaminathan et al. (5) and Hazar et al. (30) that showed sex had a significant effect on survival.

In this study, 68.05% of ALL and 66.67% of AML cases had abnormal hemoglobin. As found in other studies (11,34), the difference in survival rate between normal and abnormal patients was not significant.

In this study, the platelet count in patients with leukemia was not a prognostic factor for survival, and this was similar to the results of previous studies (18,40,41). Furthermore as stated in other studies, hepatosplenomegaly had no significant relationship with survival in this study and other studies (23,30).

Our results showed that the occurrence of relapse and the number of relapses have a significant association with survival rates for ALL and AML patients. Researchers showed relapse in the central nervous system and its involvement in patients with ALL is an important prognostic factor for survival (26). However, CNS relapse occurs rarely in patients with AML (42) and in this study it was not observed in with AML patients. In the present study, the site of recurrence had no significant effect on survival.

It seems like the socioeconomic level of families, and their place of residence affects their survival rates. Socioeconomic status probably affects timely referral for treatment, medical costs, insurance and duration of follow-up. However result showed parents' educational level, job or type of insurance was not significantly effective on survival rate.

Currently chemotherapy and if required radiotherapy and bone marrow transplantation are used for the treatment of leukemia patients. Although due to the lack of funding for transplantation, often chemotherapy was used alone. In this study the 5 years survival rate in patients treated with chemotherapy was 60% and shows the effect of chemotherapy in increasing patients' survival. This effect was also seen other studies (43-45).

In this study due to the small number of patients receiving transplants, we were not able to assess its impact on patient survival. It is recommended that other researchers evaluate the effect of different types of chemotherapy and bone marrow transplantation on the survival of leukemia patients.

Although this study was done in the referral center for childhood leukemia in Kerman Province, generalizing the results to other populations should be done with caution. Furthermore, some patients might have traveled to other provinces for treatment.

In conclusion we can say that child leukemia patients with higher white cell counts at diagnosis and a history of relapse have less survival.

Conflict of Interests

The Authors have no conflict of interest.

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