Risk Factors of Leukemia Relapse among Iranian Under-15 Year's Children (2004-2009)

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Abstract: Leukemia is the most common cancer among children that its relapse leads to major reduction in survival of patients. This study aimed to identify determinant risk factors of leukemia relapse among patients under 15 years who had visited Shahid Faghihi hospital in Shiraz city during 2004 to 2009. In a retrospective cohort study 280 patients with acute lymphoblastic leukemia (ALL) and acute myeloblastic leukemia (AML) were followed. To identify the determinant risk factors of leukemia relapse, Chi-square, Fisher's exact test and Logistic regression were used. All of the analysis was done in SPSS software (version 16) and $P< 0.05$ was considered as significance level of study. The logistic regression revealed that age had a significant relation with leukemia relapse (OR= 0.35, 95% confidence interval= 0.15-0.82), so that the chance of relapse among children of 5-10 years old were 0.35 times of under five children (P= 0.01). As under-five year's children had higher chance of relapse, this group should receive more attention and care in order to increase survival and decrease leukemia consequences.

Key words: Acute Lymphoblastic Leukemia · Acute Myeloblastic Leukemia · Relapse · Risk Factors

INTRODUCTION

Cancer ranks second among major causes of death in some countries [1, 2] and it considered as main public health problem throughout the world [3-6]. In Iran, however, following cardiovascular diseases and accidents it stands in third rank of death major causes [7]. Cancer also can be found among children, although they are very rare in this group [8-13] and account only for 1 % of all cancer cases [8, 10, 12]. In spite of this, cancer is among the main causes of death in children [13, 14] so that, after unintentional injuries, cancer is the second cause of under-15 children death in US [15-18].

Leukemia is the most common cancer among children [19-22] and is responsible for 32% of childhood cancers [23]. Acute lymphoblastic Leukemia (ALL) is the most prevalent form of leukemia among children [24] that accounts for 80% of leukemia cases in developed countries [25]. Although there has been notable therapeutic progress in three past decades, yet ALL is the most prevalent cancer among children and those who experience the relapse of ALL make up a major proportion of cancer cases [26]. In comparison with new cases of cancer, the relapse cases are more defiant to treatment and there is no identified therapeutic protocol for them and their survival rate is considerably low [27]. The present study aimed to identify determinant risk factors of relapse among leukemia cases (under-15 years old) who had visited Shahid Faghihi hospital in Shiraz city during 2004 to 2009.

MATERIALS AND METHODS

This work was a retrospective cohort study in which the units of study were all of ALL and AML (Acute myeloblastic leukemia) patients (280 cases) who were under-15 years old and had visited Shahid Faghihi hospital in Shiraz city during 2004 to 2009. Due to some

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defects, data of 37 patients out of 280 cases were not entered into final analysis. The required data such as age, gender, place of residence, immune phenotype, type of tumor, count of white blood cells, platelets, hemoglobin and the relapse history were gathered from Shahid Motahari clinic archived files.

As the required data were gathered from archived files and these files are set up for research purposes, there was no ethical predicament to be considered in present study. To identify the determinant risk factors of relapse, Chi-square and Fisher's exact test were used. Also, to control for confounding factors logistic regression modeling was used. All of analysis was done in SPSS (version 16) and $P < 0.05$ was determined as significant level of study.

RESULTS

Of all studied patients, 81 ones (33%) were identified as with-relapse cases and 162 ones (67%) as without-relapse cases. Of all with-relapse cases, 45 cases (55.5%) had experienced single-time relapse and 36 cases had multi-time relapses. According to univariate analysis (Table 1) it was revealed that the age ($P=0.001$) and platelet count ($P= 0.03$) were the effective determinants of

relapse whereas gender, weight, place of residence, immune phenotype, type of tumor, count of white blood cells and hemoglobin had no significant relation with relapse. It was interesting that weight had a significant relation with relapse in logistic regression model (OR= 0.97, CI= 0.94-0.99) and platelet that had a significant relation with relapse in Chi-square univariate analysis, showed no such a relation in logistic regression. As the confounding factors were not controlled for in univariate analysis, a statistical modeling that was purged of confounding effects was shown in Table 2. According to this table, age had a significant relation with relapse (OR= 0.35, CI= 0.15-0.82) so that the chance of relapse among children of 5-10 years old was 0.35 times of under five children (P= 0.01).

As shown in Table 3, according to univariate analysis based on ALL and AML, age (p=0.001), platelet count (p=0.04) and weight (p-0.006) have significant relationships with relapse in ALL type and there was no significant relationship between included variables with relapse in AML type. According to Tables 4 and 5 which revealed results of logistic regression model for ALL and AML, age (p=0.01) had a relation with relapse occurrence in AML patients and odds of relapse in 1-5 years old in compare with 10-15 years old was 0.12 (CI=0.02-0.6).

Table 1: Determinants of leukemia relapse's risk factors among Iranian under-15 year's children

Variable		No. & % with relapse	No. & % without relapse	P
Gender	Male	48(59.3)	93(57.4)	0.8
	Female	33(40.7)	69(42.6)	
Place of residence	Shiraz city	29(35.8)	56(34.6)	0.98
	Other cities	30(37)	61(37.7)	
	Other provinces	22(27.2)	45(27.8)	
Age	0-5	16(19.8)	62(38.3)	0.001*
	10-May	43(53.1)	48(29.6)	
	15-Oct	22(27.2)	52(32.1)	
Immune phenotype	Pre B-Cell	21(25.9)	52(32.1)	0.5
	Common	35(43.2)	54(33.3)	
	AML	20(24.7)	44(27.2)	
	T-Cell	5(6.2)	12(7.4)	
Type of tumor	ALL	61(75.3)	118(72.8)	0.7
	AML	20(24.7)	44(27.2)	
Count of white blood cell	Leucopenia	53(65.4)	93(57.4)	0.23
	Normal	14(17.3)	44(27.2)	
	Leukocytosis	14(17.3)	25(15.4)	
Platelet	Thrombocytopenia	59(72.8)	96(59.3)	0.03*
	Normal	16(19.8)	58(35.8)	
	Thrombocytosis	6(7.4)	8(4.9)	
Hemoglobin	Abnormal	64(79)	118(72.8)	0.3
	Normal	17(21)	44(27.2)	
Weight (Mean±St.D)		25.2±14.7	21.9±11.9	0.059
Count of white blood cell (Mean±St.D)		11.5±28.9	8.05±22.3	0.3
Platelet (Mean±St.D)		119±137.2	149±144.6	0.12
Hemoglobin (Mean±St.D)		8.8±3.03	9.4±2.7	0.08
Total		81(33.3)	162(66.7)	-

Table 2: Modeling of leukemia relapse determinants among under-15 year's children (logistic regression)

Variable	Subgroup	Odds Ratio* (95% CI)	P-value	Adjusted Odds Ratio** (95% CI)	P-value
Weight		0.97(0.94-0.99)	0.04*	0.981 (0.962-1.001)	0.06
Age	0-5	1.6 (0.78-3.4)	0.19	0.94 (0.31-2.8)	0.9
	10-May	0.47 (0.2-0.9)	0.02*	0.35 (0.15-0.82)	0.01*
	15-Oct	1	-	1	0.3
Immune phenotype	Pre B-Cell	1.03 (0.32-3.2)	0.9	1.25 (0.36-4.3)	0.72
	Common	0.64 (0.2-1.9)	0.4	0.63 (0.18-2.1)	0.46
	AML	0.9 (0.28-2.9)	0.8	1.26 (0.36-4.3)	0.71
	T-Cell	1	-	1	-
Count of white blood cells	Leucopenia	0.98 (0.47-2)	0.96	1.2 (0.54-2.6)	0.65
	Normal	1.7 (0.72-4.2)	0.2	2.2 (0.8-6)	0.12
	Leukocytosis	1	-	1	-
Platelet	Thrombocytopenia	1.2 (0.4-3.6)	0.72	1.1 (0.32-4.3)	0.79
	Normal	2.7 (0.82-8.9)	0.1	2.6 (0.67-10.1)	0.16
	Thrombocytosis	1	-	1	-
Hemoglobin	Abnormal	0.71 (0.37-1.3)	0.2	1.3 (0.62-3.07)	0.41
	Normal	1	-	1	-

* Results of univariate analysis ** Results of multivariate analysis (logistic regression)

Table 3: Determinants of leukemia relapse's risk factors among Iranian under-15 year's children based on ALL and AML

Variable		ALL			AML		
		No. & % of relapsed cases	No. & % of non relapsed cases	P	Relapsed	No relapsed	P
Gender	Male	38(62.3)	69(58.5)	0.6	10(50)	24(54.5)	0.7
	Female	23(37.7)	49(41.5)		10(50)	20(45.5)	
Place of residence	Shiraz city	23(37.7)	40(33.9)	0.8	6(30)	16(36.4)	0.8
	Other cities	23(37.7)	45(38.1)		7(35)	16(36.4)	
	Other provinces	15(24.6)	33(28)		7(35)	12(27.3)	
Age	0-5	10(16.4)	56(47.5)	0.001*	6(30)	6(13.6)	0.07
	10-May	34(55.7)	34(28.8)		9(45)	14(31.8)	
	15-Oct	17(27.9)	28(23.7)		5(25)	24(54.5)	
WBC	Leucopenia	38(62.3)	61(51.7)	0.2	15(75)	32(72.7)	0.9
	Normal	12(19.7)	38(32.2)		2(10)	6(13.6)	
	Leukocytosis	11(18)	19(16.1)		3(15)	6(13.6)	
Platelet	Thrombocytopenia	41(67.2)	62(52.5)	0.04*	18(90)	34(77.3)	0.4
	Normal	14(23)	49(41.5)		2(10)	9(20.5)	
	Thrombocytosis	6(9.8)	7(5.9)		-	1(2.3)	
Hemoglobin	Abnormal	46(75.4)	82(69.5)	0.4	18(90)	36(81.8)	0.4
	Normal	15(24.6)	36(30.5)		2(10)	8(18.2)	
Weight (Mean±St.D)		25.6±14	20.2±11	0.006*	24.1±15	26.4±13	0.5
Count of white blood cell (Mean±St.D)		9.9±22	7.1±15	0.3	16.1±43	10.4±34	0.5
Platelet (Mean±St.D)		138±148	165±152	0.16	59±65	105±112	0.08
Hemoglobin (Mean±St.D)		9±3	9.7±2.6	0.2	8±2	8.8±2.9	0.2

Table 4: Modeling of ALL relapse's risk factors among under-15 year's children (logistic regression

Variable	Subgroup	Odds Ratio*(95% CI)	P-value	Adjusted Odds Ratio**(95% CI)	P-value
Weight		0.96(0.94-0.99)	0.01*	0.97(0.93-1.008	0.1
Age	0-5	3.4(1.3-8.3)	0.008*	2.2(0.6-8.1)	0.23
	10-May	0.6(0.2-1.3)	0.2	0.42(0.15-1.1)	0.09
	15-Oct	1	-	1	-
Count of WBC	Leucopenia	0.9(0.3-2.1)	0.8	1.2(0.5-3.3)	0.5
	Normal	1.8(0.6-4.9)	0.8	2.7(0.8-8.8)	0.08
	Leukocytosis	1	-	1	-
Platelet	Thrombocytopenia	1.2(0.4-4.1)	0.6	1.3(0.33-5.2)	0.6
	Normal	3(0.8-10.3)	0.08	3.4(0.8-14.3)	0.09
	Thrombocytosis	1	-	1	-
Hemoglobin	Abnormal	0.7(0.3-1.4)	0.4	2.4(0.9-6.6)	0.07
	Normal	1	-	1	-

* Results of univariate analysis   ** Results of multivariate analysis (logistic regression)

Table 5: Modeling of AML relapse's risk factors among under-15 year's children (logistic regression)

Variable	Subgroup	Odds Ratio* (95% CI)	P-value	Adjusted Odds Ratio** (95% CI)	P-value
Age	0-5	0.2(0.04-0.9)	0.03*	0.12(0.02-0.6)	0.01*
	10-May	0.3(0.09-1.16)	0.08	0.2(0.07-1.1)	0.07
	15-Oct	1	-	1	-
Platelet		1.006(0.99-1.01)	0.1	1.006(0.99-1.01)	0.1
Hemoglobin	Abnormal	0.5(0.09-2.6)	0.4	0.25(0.04-1.5)	0.1
	Normal	1	-	1	

* Results of univariate analysis   ** Results of multivariate analysis (logistic regression)

DISCUSSION

In the present study, the findings showed that 33% of leukemia patients had a history of relapse and the age was a significant risk factor for relapse whereas other variables like gender, weight, place of residence, immune phenotype, type of tumor, count of white blood cells and hemoglobin had no such a relation with relapse.

Relapse is a common event in leukemia and as it was showed in present study, 30% of under-15 year's children with leukemia had a relapse experience on average. This rate has been reported to be 20-25% in other studies [28]. For example, in a same study in Turkey the relapse rate was reported to be about 20% [29] that is in line with results of present study. The importance of relapse arises from its role in treatment failure so that among leukemia patients, the relapse is the most prevalent cause of failure in treatment [30]. Indeed, the relapse leads to decrease in leukemia survival rate and increase in its mortality.

In the present study, the weight of patients had a significant relation with relapse in univariate analysis whereas after controlling for confounding factors there was no such a relation. This finding is not in line with the result of a study in which obesity and over-weight were predicting factors of relapse among 181 cases of ALL [31].

Among the studied cohort, even in the case of control for confounders, the age was identified as a risk factor for relapse so that the number of relapse was significantly higher among children of 5-10 years old. In a study that the consequences of leukemia were investigated, the age was proved to be among major predictors of death [28, 29], a result that is consistent with our findings. This is noteworthy that, contrary to our study, Aria and colleagues [32] could not prove any relation between age and relapse of leukemia. However, in their study, gender also had no significant relation with relapse of leukemia.

According to multivariate analysis, the results of the present study showed that there was no significant relation among platelet, hemoglobin, count of white blood cells, immune phenotype and relapse whereas in other studies [28, 29, 32] count of white blood cells and immune phenotype (type of T-cells) were proved to have a significant relation with serious consequences of leukemia.

As the chance of leukemia relapse was significantly related with age so that the number of relapse was higher among under-five children, more attention and care is required to reduce the consequences of leukemia and improve its survival rate among this group of children.

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