

Childhood acute lymphoblastic leukemia: refusal and abandonment of treatment in the southeast of Iran

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Background/aim: Acute lymphoblastic leukemia (ALL) accounts for 25% of all malignancies in children. ALL treatment has standard protocols, and treatment abandonment is a main cause of treatment failure. Therefore, this study aimed to assess the relationship between socioeconomic status and rate as well as cause of abandoned treatment in children with ALL in the southeast of Iran.

Materials and methods: This retrospective, descriptive cohort study was conducted with ALL patients at the Ali Asghar Hospital in the city of Zahedan. The study population included 22 children with different subtypes of ALL who had abandoned their treatment. A structural questionnaire was filled out by patients or their parents. Results were assessed using descriptive and analytical tests.

Results: The rate of treatment abandonment was 24.4% (22 patients). We had 18 ALL-L1 (78.3%) and four ALL-L2 (17.4%) patients. Reasons for treatment abandonment were low family income, transportation difficulties, the father's education status, conviction about ALL's incurability, and reference to spiritual means, respectively.

Conclusion: Low family income, transportation difficulties, the father's education status, belief about ALL's incurability, and reference to spiritual means were the most common associations with ALL treatment abandonment in that order. Financial problems in this part of the country can impose high costs to the healthcare system.

Key words: Acute lymphoblastic leukemia, treatment abandonment, socioeconomic status

1. Introduction

Acute lymphoblastic leukemia (ALL) accounts for one-fourth of all malignancies in children (1). ALL treatment is based on standard protocols (2). With the existing improved therapies, about a quarter of children affected by ALL suffer from relapse, which is higher than in other childhood malignancies (3–5). Treatment abandonment is the main cause of treatment failure in childhood cancer treatment in developing countries (6). According to previous studies, financial and transportation difficulties and the lack of essential drugs and local medical facilities are the main reasons for ALL treatment refusal in these countries (2,7,8). Adherence to treatment protocol by children or their parents as well as physicians is an important point (9). Different factors affect survival rates in children with ALL, including treatment regimen, socioeconomic status (SES), and individual features like

age, sex, white blood cell (WBC) count at diagnosis, and subtype of disease (10). SES measures parents' income and education, access to healthcare, and lifestyle (11,12). There is limited and inconsistent information on the correlation between SES and survival as well as relapse rate of ALL (10,12–14). This study was performed to assess the relationship of SES with the rate and causes of abandoned treatment in children with ALL in the southeast of Iran.

2. Materials and methods

2.1. Characteristics of study patients

This is a retrospective, descriptive cohort study, conducted in Sistan and Baluchestan Province in the southeast of Iran from 2011 to 2013. The study was approved by the ethical committee of Zahedan University of Medical Sciences and informed consent was signed by patients or their parents in the case that patients were younger than 18 years old.

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Zahedan is the capital of this province, which includes 31 cities. The majority of health services are available in the city of Zahedan, and patients throughout the province refer to this city in order to receive basic health services and facilities. The study population included 22 children with different subtypes of ALL who received remission induction regimens typically include a glucocorticoid (prednisone, prednisolone, or dexamethasone), vincristine, and asparaginase, with or without one or more additional drugs (e.g., an anthracycline, cyclophosphamide) (15) and achieved complete remission but did not refer again for complementary treatments or regular physical and laboratory examinations by a hematologist. All patients or their parents completed a structural questionnaire consisting of questions about demographic data. The items included age group, sex, race, city of residence, parents' income, etc. Other data included WBC count at diagnosis, ALL subtype, chromosomal abnormalities, and so on.

According to this questionnaire, leukocyte count was divided in three categories: 1) <50,000 μL 2) 50,000–100,000 μL 3) $\geq 100,000$ μL .

2.2. Diagnosis of ALL

ALL was diagnosed by morphological characteristics under a light microscope, immunophenotyping using a multicolor flow cytometer (Becton-Dickinson, San Jose, CA), and genetic characterizations. Initial WBC and differential counts were calculated by Sysmex KX21N (Sysmex Corporation, Kobe, Japan). Other variables in leukemic cells leading to better understanding of the pathogenesis and prognosis of ALL and its genetic subtypes show different frequencies in children and adults (16,17).

All our patients were treated with standard protocols by an expert hemato-oncologist in the field of leukemia after admission to hospital. A few hours after confirmation of disease, patients' parents were aware of their child's illness, and all treatment steps were explained for them. Treatment was started after receiving informed consent.

2.3. Charity and financial support

In our hospital, two charity services are provided for those with financial problems. Upon entry, each patient can register for receiving charity. The first charity service is the hospital charity that covers each patient with financial problems. This type of hospital charity service offers hospital services free of charge but does not cover any costs outside the hospital. The second one is the national charity service for pediatric patients known as Mahak, an abbreviation of the Persian phrase Moassesse Hemaia Az Kodakane Saratani, which means an institute for support of children with cancer. This institute covers all kinds of patients' costs and undertakes an appropriate percentage of costs, but not all, based on patients' economic status. Also, in our hospital, each patient was daily visited by physicians. If the patient was unable to communicate with

the physician due to verbal communication problems, an interpreter was recruited simultaneously with parents.

2.4. Assessment of SES of patients

Social and economic statuses of patients were assessed based on several items: 1) family income was divided in two categories of <99.34 and >99.34 USD; 2) parental education was designated as illiterate, primary school, intermediate (high school), and higher education (university); 3) city distance to Zahedan was divided into three categories of <200 km, 200–400 km, and >400 km. Because of the high rate of spiritual beliefs in this region, we also made a choice for reference to clergymen as a cause of treatment abandonment.

2.5. Statistical analysis

Results were reported as mean \pm standard deviation (SD) for quantitative variables and percentage for categorical variables. For categorical data, the chi-square test and, when appropriate, Fisher's exact test were used. The Kruskal-Wallis and Monte Carlo tests were also used as appropriate. Statistical significance was based on two-sided design-based tests evaluated at the $P = 0.05$ level of significance. All the statistical analyses were performed using SPSS.

3. Results

3.1. Characteristics of study patients

From August 2011 to April 2014, we had 90 patients with established ALL in the Ali Asghar Hospital in Zahedan in the southeast of Iran. Out of these 90 patients, 22 children (24.4%) abandoned their treatment during the study period. Most of our study population included boys ($n = 14$, 60.9%). With regard to ethnicity, the majority of the patients ($n = 20$, 90.9%) were Baluch, and we had only one Fars and one Afghan patient (Table 1). The mean period of ALL relapse was 5.3 ± 1.6 months, and there were 21 (95.5) cases of bone marrow relapse and one case (4.5%) of central nervous system relapse (Table 1). The relationship between sex and site ($P = 1$) as well as time of relapse were not significant ($P = 1$) by Fisher's exact test.

3.2. Diagnosis and type of ALL

The characteristics of patients' phenotypes are summarized in Table 2. Based on the French-American-British (FAB) classification system, we had 18 ALL-L1 (78.3%) and 4 (17.4%) ALL-L2 patients (Table 2). This classification of disease is based on morphology and cytochemistry of patient lymphoblasts (18). The relationship between immunophenotype and time of relapse was close to significance ($P = 0.053$) but the relationship between cytochrome and time of relapse was not significant ($P = 0.521$). The relationship between cytochrome and location of relapse was not significant ($P = 0.771$) and neither was the relationship between FAB classification and time of relapse ($P = 0.712$).

Table 1. Demographic and clinical data of patients.

Age (years)	6.4 ± 4.12
Sex number (%)	
Male	14 (60.9)
Female	8 (34.8)
WBC count (number/mL)	
<50,000	18 (81.8)
50,000 –100,000	0
>100,000	4 (18.2)
Cytochrome	
Uncertain	17 (73.9)
Ph+: t (9 ; 22)	2 (8.7)
t (1 ; 19)	1 (4.3)
t (8 ; 21)	1 (4.3)
t (4 ; 11)	1 (4.3)
Morphology (FAB classification)	
L1	18(78.3)
L2	4(17.4)
Time of relapse (months)	5.3 ± 1.6
Location of relapse	
B.	21 (95.5)
CNS	1 (4.5)

BM = Bone marrow, CNS = central nervous system.

3.3. Financial support

Eight patients (36.4%) used the financial support of the hospital. The relationship between using hospital support and time of relapse was not significant ($P = 0.402$). Twenty of 22 patients (90.9%) were covered by the Mahak Institute for reducing treatment costs. The relationship between the Mahak Institute's financial support and time of relapse ($P = 0.312$) was not significant.

3.4. SES of patients

Patients' SES is given in Table 3. Among these 22 patients, just one (4.5%) of their fathers had a regular job and seven (31.8%) parents were jobless (Table 3). Other parents were ranchers and farmers with a mean monthly income of 66.23 USD while all patients' mothers were housewives with no income. The first reason of abandoned treatment was low income, such that 21 (95.5%) patients had monthly household incomes of <99.34 USD. The third reason for leaving treatment was educational status, such that 16 (72.7%) of patients' fathers were illiterate (Table 3).

Belief in the curability of ALL with reference to clerics was the fourth reason to abandon treatment, and 10 patients (45.5%) were referred to spiritual clerics for treatment of ALL.

The distance between different cities of Sistan and Baluchestan Province from the capital of Zahedan as the only place for receiving medical facilities was too long and 18 patients (81.8%) had parents who did not own a vehicle, and this was one of the most important reasons to abandon treatment. Three (13%) of our patients lived in cities within 200–400 km of distance from Zahedan. Five of them (21.7%) lived in cities within >400 km of distance from the capital of Sistan and Baluchestan Province (Table 3). However, we did not find a significant correlation between patients' residence with time of ALL relapse ($P = 0.549$). We did not have any variable for assessing the treatment abandonment, so we assessed our variables using time of relapse. Furthermore, 68.2% of our patients' parents had given a wrong telephone number, probably due to the fathers' very low education levels, among whom 16 (72.7%) had no education and were illiterate.

4. Discussion

In the present study, we observed a 24.4% rate of treatment abandonment (22 out of 90 patients) during the study time in pediatric patients with ALL in the city of Zahedan. There are various reasons for treatment abandonment in different studies; however, in our study, the most common reasons included poor family income, transportation difficulties, father's education status, belief about ALL's incurability, and reference to spiritual means, in that order (6,8,19,20).

The first and most common reason for treatment abandonment in our study population was financial difficulties, which was similar to the findings of Njuguna et al. and Sitaresmi et al. (6,8). We found that 95.5% of our patients' fathers had an income of less than 99.34 USD per month and just one of them, a teacher, received more than 99.34 USD, which is low in Iran. The rest of patients' fathers were unemployed and received subsidies from the government, which was not sufficient to support their children's treatment costs. There was no significant correlation between the father's profession and his income ($P = 0.926$).

Sistan and Baluchestan Province is the largest province of Iran with a surface area of 181,785 km². The city of Chabahar in the south of the province has the longest distance from the capital (692 km). In general, distances of most cities of the province from Zahedan are long and this is a big problem for patients to attend Zahedan for regular checkups and treatment. Therefore, transportation difficulty was the second most common reason for

Table 2. The characteristics of patients' phenotypes.

	WBC count	FAB classification	Immunophenotype	Cytogenetics
1	2500	L1	pB	Uncertain
2	18,000	L1	pB	Uncertain
3	35,000	L1	pB	Uncertain
4	3100	L2	pB	Uncertain
5	150,000	L1	pB	t(9:22)
6	20,000	L1	Tc	Uncertain
7	2200	L2	pB	t(1:19)
8	5500	L1	pB	Uncertain
9	2000	L1	Tc	Uncertain
10	33,000	L1	pB	t(8:21)
11	110,000	L1	pB	Uncertain
12	17,500	L2	pB	Uncertain
13	1500	L1	pB	Uncertain
14	4500	L1	pB	t(9:22)
15	300,000	L1	pB	Uncertain
16	5500	L1	Tc	Uncertain
17	2300	L1	pB	Uncertain
18	14,000	L1	pB	Uncertain
19	3000	L1	pB	Uncertain
20	200	L1	pB	t(4:11)
21	220,000	L1	pB	Uncertain
22	10,000	L2	pB	Uncertain

pB: pre B-cell, Tc: T-cell.

treatment abandonment, since 81.8% of patients' fathers did not have any vehicle to go to Zahedan. We think that long distances from health facilities might lead to abandoned treatment and relapse of disease.

The third reason for treatment abandonment in our study was lack of fathers' education, which was 72.7% in our cohort. This was supported by the correlation between giving a wrong phone number and education level ($P = 0.001$). We suppose that fathers were not able to give us the correct telephone number because of their illiteracy. Moreover, low level of education among patients' parents can be a significant reason for sensing no need for further treatment after remission and thus treatment abandonment.

The fourth reason for treatment abandonment was belief about the incurability of ALL with current medical therapies, as 45.5% mentioned reference to spiritual means as the reason for treatment abandonment. Spiritual and religious issues are undeniably important in boosting the morale of patients, but these affairs should be combined with medical care and treatment.

The other reason for treatment abandonment in our study was access to charity service. Our hospital has a charity institute, and patients with financial insufficiency were introduced to the charity institute incognito for financial supports. We found that 36.4% of patients who stated financial problems used the charity service upon admission to hospital. We think that according to fathers'

Table 3. Socioeconomic status in patients with treatment abandonment.

Socioeconomic status	Number (%)
Father's education level	
No education	16 (72.7)
Primary school	6 (27.3)
Intermediate (high school)	0
Higher education (university)	0
Father's profession	
Unemployed	7 (31.8)
Farmer	8 (36.4)
Rancher	6 (27.3)
Regular job	1 (4.5)
Total number of household members (mean ± SD)	4.2±1.5
Vehicle	
Motorcycle	1 (4.5)
Automobile	3 (13.6)
No vehicle	18 (81.8)
Phone number as given	
Correct	7 (31.8)
Incorrect	15 (68.2)
Distance from hospital	
<200 km	14 (60.9)
200–400	3 (13)
>400	5 (21.7)
Income (USD)	
<99.34	21 (95.5)
>99.34	1 (4.5)
Reason of treatment abandonment	
Spiritual	10 (45.5)
Financial difficulty	12 (54.5)

low income, they did not tell the truth because of their shame and embarrassment, but 90.9% of our patients used Mahak Institute charity.

Although a considerable number of patients were registered with both the Mahak Institute and the hospital charity, it seems that these financial aids were not sufficient for patients to continue their treatment. Because of the low income and long distance of patients' residence, even travel to Zahedan and paying for hotel and additional treatments not fully supported by any institute were expensive for patients.

We also assessed the satisfaction rate of patients' parents with their physicians, and we found that they were

all satisfied with their child's doctors. This was not a reason for treatment abandonment.

In our study, poor family income, transportation difficulties, father's education status, belief about ALL's incurability, and reference to spiritual means were the most common associations with ALL treatment abandonment, respectively. We did not find a significant relationship between Mahak and financial supports from the hospital and time as well as site of relapse for the low sample size in our study, which is a limitation of our study. We could not find logical relationships between our different variables in this regard. Financial problems in this part of Iran can impose high costs to the healthcare system of the country.

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