Frequency of Cytogenetic Findings and its Effect on the Outcome of Pediatric Acute Lymphoblastic Leukemia

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ABSTRACT

Introduction: Acute lymphoblastic leukemia (ALL) is one of the most common cancers in children and accounts for about ½ of cancers in children. The annual incidence of ALL is 4 patients per 100,000 children. Their peak age is between 2-5 years. One of the most important prognostic factors is cytogenetic abnormalities which are very effective in determining treatment policy. Aim: To determine the frequency of cytogenetic findings and its effect on the outcome of children with ALL. Materials and Methods: This retrospective cross-sectional analytical study was conducted on children with ALL who their disease was diagnosed between 2001 and 2009. Furthermore, 206 patients with ALL were examined by referring to Clinic of Ali Asghar Hospital in Tehran. Data was collected from medical records and analyzed by SPSS16 software. Results: 206 children with ALL were enrolled in the study. The estimated event-free survival rate of all enrolled patients was more than 70%. There was a significant relationship between type of cytogenetic disorder and clinical outcome of patients (P<0.001), where the highest mortality was observed in patients with t(9;22) and t(4;11). There was no significant correlation between the sex and age with the clinical outcome of the patient (P=0.064; p=0.322). There was a statistically significant relationship between mediastinal mass and clinical outcome (P=0.002), indicating that the presence of cells growth in an involuntary way can be cause of the cancer. A significant association was found between the clinical outcome of patients and radiotherapy (P=0.043), indicating that radiotherapy is effective in improving cancer. Conclusion: The findings demonstrated that the average survival rate without recurrence in children was at level of the European countries. However, the strong chemotherapy weakened the role of many prognostic factors in ALL patients, but some translocations are prognostic factors in predicting death in patients with ALL. Therefore, patients with this factor need to receive more confident treatment policy. Comprehensive studies are required by focusing on more samples because of low number of relapses and deaths in the present study.

Keywords: Acute lymphoblastic leukemia, Children, Cytogenetics, Child.

1. INTRODUCTION

Cancer is an uncontrolled growth of the body’s cells, the most common form of which is in children as hematologic malignancies, accounting for 44% of the cancers diagnosed in children (33% leukemia and 11% lymphoma) (1). Acute Lymphoblastic Leukemia (ALL) accounts for about 75% of leukemia cases, and is considered as a clonal malignancy of bone marrow in which early lymphoid precursors proliferates, leading to replacement of them with normal hematopoietic cells in the bone marrow (2).

The annual ALL incidence is estimated to be 4 case per 100,000 children aged 2 to 5 years old (3). Despite the high prevalence of ALL in children, the percentage of complete remission has increased from 10% in the years before 1970 to about 100% (4-5). Clinical suspicion of leukemia can be increased via clinical symptoms such as fatigue, fever, petechiae, ecchymosis, nose and gum bleeding, bone pain, and distributed lymphadenopathy, as well as central nervous system symptoms such as headache, vomiting and paralysis (6). The prognosis of patients with ALL is evaluated based on several factors. One of these factors is cytogenetic findings. The relationship between prognosis and karyotype at diagnosis time of ALL is first introduced by Sedker Walker in the year 1978 and continues until today (7).

In diagnosis, a cytogenetic evaluation, including chromosomal trans-
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location, and hyperdiploidy, is performed simultaneously
with patient sampling.

Chromosomal abnormalities are found in most pa-
tients with ALL. These abnormalities may show abnor-
mal number of chromosomes, chromosomal transloca-
tion and chromosomal removal, which provides valuable
information about the prognosis of the disease (8, 9).

Despite the low prevalence of leukemia in children of
Iran in comparison with Western countries, but ALL is
the most common malignancy in Iranian children (10).
Considering the above evaluations, there is no compre-
hensive data on other cytogenetic disorders. Moreover,
studies on acute lymphatic leukemia in children in Iran
are very limited.

2. AIM

Aim of this study was to evaluate the cytogenetic find-
ings and its effect on prognosis ALL patients to evalu-
ate the relationship between recurrence and cytogenetic
disorders and other biological data and to determine the
factors affecting the prognosis of the disease for provid-
ing new therapies.

3. MATERIALS AND METHODS

This retrospective cross-sectional study was conduct-
ed on children with ALL who their disease was diag-
nosed between 2001 and 2009. The medical records of
these patients were selected by referring to the archives
of Ali Asghar Hospital Tehran-Iran. Demographic data
(age and gender), karyotype, cytogenetic information,
therapeutic regimen and clinical outcome of patients
were extracted and then recorded in the relevant check-
list.

The data were analyzed using SPSS 16 software; de-
ographic data were analyzed descriptively and Chi-
square, Log-Rank and Kaplan–Meier tests were used for
survival analysis. P-value less than 0.05 was statistically
significant.

Ethical approval was obtained from Ali-Asghar Chil-
dren Hospital, Tehran, Iran.

4. RESULTS

Total amount of 206 children with ALL were included
in the study. Based on the age range, 7 (3.4%) patients
belonged to the age group of less than one year, followed
by one to ten years (171, 83%) and more than 10 years
(28 people, 13.6%). Of the 206 children enrolled in the
study, 116 cases (56.3%) were boys and 90 (43.7%) were

Morphologically, 1 patient (0.5%) belonged to type
L3. For FAB classification, 95 cases (46.1%) were classi-
fied in the Early pre B group, followed by pre-B (79 cases,
38.8%), T Cell (27 cases, 12.7%) pro B Cell, (4 cases, 1.9%)
and Mature B cell (1 case, 0.5%).

The frequency of types of markers was evaluated in
Table 1. CD19 (73.8%) was the most frequent marker,
and both CD4 and CD22 had the least frequency among
markers (6.3%).

The findings showed that 10 (4.85%) had mediastinal
mass breast and 196 (95.15%) had no mass. In terms of
white blood cell count, at the beginning of the study,

Flow cytometric findings Frequency Frequency percentage
CD10 139 67.5%
CD19 152 73.8%
CD20 55 26.7%
CD22 13 6.3%
CD5 22 10.7%
CD2 30 14.6%
CD3 30 14.6%
CD7 31 15%
CD34 63 30.6%
CD45 84 40.8%
HLADR 124 60.2%
CD4 13 6.3%
CD8 15 7.3%

Table 1. Frequency of markers

Primary LDH Frequency Frequency percentage
> 500 84 40.8%
1000-500 101 49%
1500-1000 16 7.3%
< 1500 6 2.9%

Table 2. Prevalence of primary LDH in patients

Cytology type Frequency Frequency percentage
normal 122 59.2%
t(9;22) 6 2.9%
t(4;11) 8 3.9%
t(1;19) 7 3.4%
t(12;21) 3 1.5%
Hyperdiploidy 34 16.5%
Other cases* 23 11.2%
Down syndrome 3 1.5%

Table 3. Cytogenetic disorders t(9;7), t(2;16), t(14;20), t(19,14), t(2;4),
t(2;16), t(8;14), t(10;11)*

172 patients (83.5%) showed WBC < 50,000, followed
by WBC between 50000-100,000 (17 patients, 8.3%) and
WBC <100,000 (17 patients, 8.3%). Table 2 shows the
level of primary LDH in patients.

Cytogenetic disorders of patients are shown in Table 3.
Out of 206 patients, 122 cases (59.2%) were normal for
genetic disorders, and 84 patients (40.8%) had a variety
of cytogenetic disorders.

According to the treatment protocol, the most

172 patients (83.5%) showed WBC < 50,000, followed
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of cytogenetic disorders.

According to the treatment protocol, the most

treatments were related to the BFMIC 2002 protocol (106
cases, 51.9%), followed by Conventional BFM (74 cases,
35.9%) and NY-1 (26 cases, 12.2%). Of course, children
with T-cell ALL were treated. The median duration of

treatment was determined as 48 months with a standard
deviation of 31.6.

Of the 206 patients under study, 148 patients (71.8%)
survived for 48 months. In this period, 58 cases of relapse
were reported, of which 12 (5.9%) were related to the
deaths, and 46 (22.3% for other factors. BM relapse was
observed in 41 patients, followed by relapse in CNS (16
cases) and 1 patient relapse in the testes.

The median time of relapse rate in this study was 41.15
with a standard deviation of 26.6 months. Regarding
the location of the second relapse in the patients, 5
cases (33.3%) showed relapse in BM, followed by 6 cases (40%) of recurrence in CNS and 4 cases of (26.6%) tests recurrence. The third relapse was reported in CNS (1 case) and testes (one case). Furthermore, 37 patients (18%) had radiotherapy in this study, of which 21 were alive, 14 were relapsed and 2 were died.

In Table 4, the clinical outcome of patients was evaluated based on cytogenetic type. There was a statistically significant relationship between cytogenetic disorder and clinical outcome of patients (P-value=0.0001), with the highest death rate in patients with t (9,22) and t (4,11). In addition, only three patients had t (12,21), which recurred all three cases until the end of the study and one of them died.

There was no significant relationship between the cause of death and the type of cytogenetic impairment (P = 0.682), indicating that the presence of cells growth in an involuntary way can be cause of the cancer.

There was no significant relationship between morphological and clinical outcome (P = 0.14). A significant correlation was found between clinical outcome and radiotherapy (P = 0.043), indicating that radiotherapy was effective in improving cancer, but there was no significant relationship between the early levels of LDH and the clinical outcome of the patients (P = 0.80).

Clinical outcome based on cytogenetic markers are presented on Table 4. Patient survival is shown in Figures 1 and 2, based on the type of cytogenetic.

5. DISCUSSION

Leukemia refers to a group of types of cancers that usually originate from bone marrow and cause the formation of a large number of abnormal white blood cells. These white blood cells are not completely formed and they are called blast or leukemia cells (11). Symptoms include bleeding and bruising, severe fatigue, fever, and increased risk of infection. Diagnosis is performed using blood tests and bone marrow biopsy (12). Like many other cancers, children's leukemia is due to several factors that arise from interactions between various aspects of the human environment and human genetics. The largest
subgroup of leukemia is ALL, which accounts for 75% to 80% of children’s leukemia (13). To investigate the effect of prognostic factors on outcomes of patients with ALL, mediastinal involvement, age, sex, type of ALL, according to cytological markers, were included in the study.

The findings of our study showed a significant relationship of translocation T (22;9) and translocation t (11;4) with the clinical outcome of patients, so that there was a significant relationship between the two translocation with death. On the other hand, translocation t (21;12) was associated with relapse of the disease, which was consistent with the study conducted by Conter et al in 2004 on ALL. In their study, 2% of the patients had t (9;22), 3.2% had t (1;19), 2.4% had t (4;11), and 38.8% had t (12;21) and hyperdiploid, which are known as the most common cytologic marker that these markers showed good prognosis and higher survival than other markers (14). Josep-Mar et al also concluded in 2002 that patients with translocation (22;9) had a poor prognosis (15), which was consistent with our findings.

In the present study, there was a significant relationship between the mediastinal mass (P = 0.002) and radiotherapy (P = 0.04) with the clinical outcome of the patient. On the other hand, no significant relationship between white blood cell levels at the time of diagnosis and the clinical outcome. Contrary findings by Hashemi et al. indicated that the WBC count of more than 50,000 was a prognostic factor in determining the prognosis of patients (16). Advani et al. in India reported an age group of 9-2 years old (63%) and male gender (64.8%) as involved groups that were consistent with our findings (17). In our study, the WBC evaluation was divided into three groups (less than 10,000, from 10,000 to 50,000 and more than 50,000), with the highest levels of WBC in the first and second groups. While Chen and colleagues demonstrated that the WBC >50,000 is the most important factor in patients suffering from ALL by Multivariate Analysis (18).

Another study in Egypt, conducted by Hussein et al on 154 ALL children, showed that central nervous system involvement, high-risk group, and slow early response to treatment are of great importance in prognosis of disease via multivariate analysis. In this study, the frequency of LDH level holders between 500 and 1000 was the highest value. On the other hand, unlike other studies, Bulky Extramedullary Disease has been identified as an important risk factor and concludes that prognostic factors in different regions of the world can be very different. Also, in this study, a significant relationship of the level of WBC, LDH, platelet, and hemoglobin level with clinical outcome was found (19).

6. CONCLUSION

The results of this study showed that the average survival rate in children with ALL was at level of the European countries. However, the strong chemotherapy weakened the role of many prognostic factors in ALL patients, but some translocations are prognostic factors in predicting death in patients with ALL. Therefore, patients with this factor need to receive more confident treatment policy.

Comprehensive study is needed by focusing on more patients due to the low number of relapses and deaths.

- Declaration of patient consent: The authors certify that they have obtained all appropriate patient consent forms
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