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The outcome of chemotherapeutic regimen by high-risk pre-B-cell protocol in ALL children

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ABSTRACT

Objective: *The aim of this study was to investigate the outcome of chemotherapeutic regimen by high-risk pre-B-cell potocol in ALL children.*

Methods: *The cross-sectional study was conducted on 55 children who were treated with the Children Oncology Group (COG) protocol from September 2010 to February 2015 to evaluate the chemotherapeutic regimen results.*

Results: *There was a complete recovery rate of 76.4% during the first week after treatment. Three-year overall survival was 85.5% and five-year overall survival was 81%. Relapse rate after first remission was 20% and death after relapse was 50%. Thirty percent of total deaths were at the induction period. All of the deceased cases died due to sepsis.*

Conclusion: *Results showed that the survival rate increased. By choosing the COG protocol and by controlling infection in patients without considering the risk group we can improve survival rates.*

Key words: acute lymphoblastic leukemia, pediatrics, survival, chemotherapy

INTRODUCTION

Leukemia is one of the most common types of malignancy in children, with an incidence of approximately 40 per million people, and accounting for about 30% of all cancers in children less than 15 years of age. Leukemia is the leading cause of death in children of the United States (Kim et al., 2006; Belson et al., 2007). Age-Standardized Incidence Rates (ASRs) of leukemia in men and women in Iran were reported as 6.4 and 4.8 respectively (Mesdaghinia et al., 2013) and 4.3 and 2.9 in boys and girls (Khazaei et al., 2019).

AUTHOR NOTES

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The most common type of leukemia in children is Acute Lymphoblastic Leukemia (ALL), which accounts for about 78% of all cases. In most cases its cause is unknown. However, many genetic and environmental factors are associated with childhood leukemia (Podvin et al., 2006; Shu et al., 2002). Diagnostic radiation exposure during both intrauterine life and childhood is associated with an increased incidence of ALL. In addition, according to research and studies published from different geographical areas, the possibility of environmental factors is associated with increasing incidence of ALL, which is on the increase (Winick et al., 2004; Kadan-Lottick et al., 2003).

The diagnosis of ALL is strongly supported by the findings of peripheral blood, which indicates bone marrow failure. Leukemic cells are not seen in routine tests. In many patients with ALL the complete leukocyte count is less than 10,000 µl. In such cases, leukemic cells are often initially reported as atypical lymphocytes and only further evaluation reveals that these cells are part of a defective colony. When the results of a peripheral blood test suggest leukemia, a bone marrow test should be performed immediately to confirm the diagnosis. Bone marrow aspiration alone is usually sufficient, but sometimes a bone marrow biopsy is needed to prepare enough tissue to study or rule out other causes of bone marrow failure (Winick et al., 2004; Kadan-Lottick et al, 2003). The disease is diagnosed when, as seen in the evaluation of the bone marrow, more than 25% of the total bone marrow cells have formed a uniform population of lymphoblasts.

Part of ALL staging is based on cerebrospinal fluid (CSF) test. If lymphoblasts are found in the CSF and the CSF leukocyte count is elevated, then there is a clear CSF (or meningeal) leukemia. These findings indicate a worsening of the disease stage and additional systemic treatment actions and CSF are necessary. If the diagnosis of leukemia has already been confirmed by bone marrow evaluation, then staging the disease with lumbar puncture is performed with the first spinal dose injection (Winick et al., 2004; Kadan-Lottick et al., 2003).

The highest incidence of leukemia occurs between the ages of two and five years. In less than 5% of ALL cases, central nervous system involvement is seen first (Shu et al., 2002). The French-American-British (FAB) system define three different types of lymphoblasts, with 85% of children with ALL having predominantly L1 morphology, 14% L2, and 1% L3 (Farhangi, Badiee, & Bani-Hashem, 2018). Patients between the ages of one to nine years with a white blood cell count (WBC) of less than 50,000 mm^3 are defined as standard risk (Farhangi et al., 2018).

The literature describes different treatment protocols for the treatment of patients with ALL which have been introduced based on the individual condition of each patient, as well as the conditions of different treatment centres. These have been mainly similar in general treatment methods and principles,

but the details of the executive method are different in each centre. According to the patients' conditions and the available facilities, a special treatment method is selected and the patients are treated according to it. The aim of this study was to investigate the outcome of chemotherapeutic regime by high-risk pre-B-cell protocol in ALL children admitted to our hospital.

METHODS

Design and sample

In this cross-sectional study of survival analysis, 80 patients with ALL who were diagnosed and confirmed pathologically in Ardabil City Hospital from September 2010 to February 2015 were included in the study. Information on sex, age, initial complaint, initial clinical manifestations, primary white blood count (WBC), primary hemoglobin (HG), primary platelet count (PLT), FAB grade and histological type were recorded on all patients. In addition, and after starting treatment with the high-risk pre-B-cell (COG) method, treatment results such as time of first recovery; recurrence, time and location of disease recurrence, and death, including in the case of death concurrence, time and cause of death. Survival at three and five years of age for all patients was evaluated.

Treatment approach

In this treatment method, patients were treated in three phases of induction, consolidation and maintenance, which lasted a total of 2.5 to 3 years and was based on prednisolone, vincristine, daunomycin, peg-asparaginase, cytarabine and methotrexate. Also, in the times before the start of treatment and during the treatment, several stages of CSF sampling, diagnostic bone marrow aspiration, intrathecal injection of drug to prevent CNS recurrence, as well as treatment of patients were performed. Following completion of treatment and discontinuation of interventions to control side effects, the patients continued to be followed; they underwent monthly clinical examinations and blood cell counts for at least five years and the results were recorded. Collected data were entered into SPSS version 21 and analyzed by using descriptive statistical methods in the form of number, percentage and table. To evaluate three -and five-year survival in this study, only the survival or death of samples during three and five years after the start of treatment were evaluated. Survival models were not used in this study due to the lack of survival analysis conditions.

The study was conducted after obtaining a license from the Biomedical Ethics Committee of Ardabil University of Medical Sciences with the number IR.ARUMS.REC.1398.439.

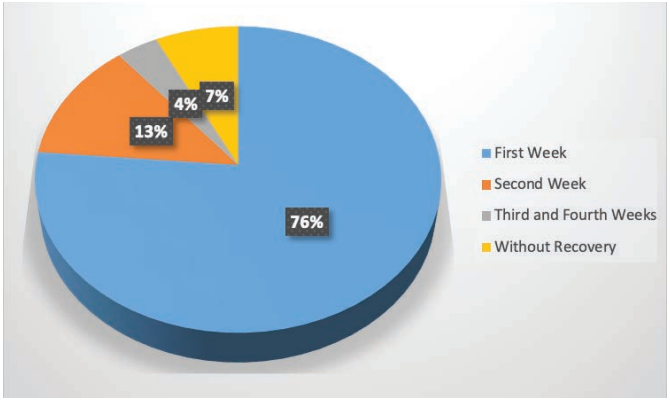

Figure 1. Frequency of the time of recovery in patients treated with the COG protocol

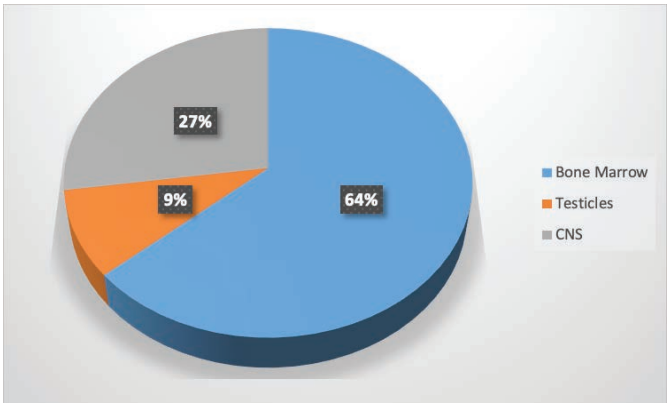

Figure 2. The rate of relapse in all patients treated with COG method

RESULTS

Demographics

In this study, 55 patients were treated with the high-risk pre-B-cell (COG) method. The majority of cases ($n = 51$, 92.7%) were in the age group of 1 to 9 years. Of all patients, 30 (54.5%) were boys and the rest were girls. The most common type of histology was B-cell with 52 patients (94.5%). Most of the initial complaints were related to weakness and lethargy with 25 patients (45.5%) and then related to bone pain with 16 patients (29.1%). Of all patients, 32 (58.2%) were without clinical symptoms and 11 (20%) had hepatosplenomegaly. The initial WBC count was less than 10,000 with 24 patients (43.6%). The highest initial hemoglobin level was about 7 to 11 which was seen in 30 patients (54.5%). The highest primary platelet count was related to the platelet count of 20,000 to 100,000 with 31 patients (56.4%). The highest FAB stage was L1 type with 34 patients (61.8%).

Patient outcomes

Among patients treated with high-risk pre-B-cell (COG) method, 42 patients (76.4%) had recovery in the first week, and 7(12.7%) after the second week. Only 4 (7.3%) patients failed treatment and never recovered; 3 of these 4 cases (75%) died in the induction phase (Figure 1). Among patients treated with the high-risk pre-B-cell (COG) method, 10 patients (18.2%) died; 5 of the 10 patients (50%) died during relapse, 3 (30%) during the time of induction, and 2 (20%) after induction. The cause of death in all of them was sepsis.

Among patients treated with high-risk pre-B-cell (COG) method, 11 cases (20%) had relapse after the first recovery and 80% had no relapse. Among patients treated with high-risk pre-B-cell (COG) method who had relapse after the first recovery, 6 cases (54.5%) had a recurrence 18 months after the first recovery. Among patients treated with high risk pre B-cell (COG) method who had recurrence after the first recovery, 7 of the 11 cases (63.6%) had recurrence in the bone marrow (Figure 2).

Out of 55 patients treated with high-risk pre-B-cell (COG), 47 (85.5%) had a three year survival. Out of 47 patients who had three year survival, 37 patients have passed five years of life, of which 30 patients (81%) had five year survival (Figure 3).

DISCUSSION

In this study, slightly more than half of patients were male (n = 43, 53.8%) and was similar to other studies where most of the cases were related to males (Draper et al., 1994; Gurney et al., 1996). According to the results of this study, the highest number of cases in this centre occurred in the age group of one to nine years. In the study of Pedram, Fathi, and Hiradfar (2010), 75% of the patients were in the age range of 1 to 10 years. In this study, the most frequent type of histology was B-cell with 52 patients (94.5%) was seen in most patients, which in the study of Hashemi et al. (2009) and Pedram et al. (2010), this rate was reported to be 60%. The overall prevalence of B-cell type includes adult or precursor B-cell type and is higher than other types (Hashemi et al., 2009; Pedram et al., 2010). Also, the most primary complaints were related to weakness and lethargy with 25 patients (45.5%). In the Hashemi et al. (2009) study, after fever (68%), weakness and lethargy were in the second place. Most patients (58.2%) had no positive findings on examination at the beginning of diagnosis. Twenty percent of the patients had hepatosplenomegaly on initial examination, which was higher than other studies and in most studies, patients had initial symptoms in favor of enlarged liver and spleen (Hashemi et al., 2009; Pedram et al., 2010).

Regarding laboratory symptoms, the highest number of primary WBC was less than 10,000 with 24 patients (43.6%). In the Hashemi et al. (2009) study, 48% of the patients had the same characteristic and in the Pedram et al. (2010) study conducted in Ahvaz, 80.4% of patients had WBC less than 50,000 at diagnosis time. The highest level of primary hemoglobin was related to hemoglobin level 7 to 11 with 30 patients (54.5%). In the Pedram et al. (2010) study, most (73%) had hemoglobin less than 10 and in the Hashemi et al. (2009) study, 90% of patients had anemia with 48% with hemoglobin less than 7 (Greaves, 1997; Hashemi et al., 2009). The highest platelet count was related to the platelet count of 20,000 to 100,000 with 31 people (56.4%). In other studies, the same pattern was observed for the initial platelet count (Greaves, 1997; Hashemi et al., 2009). The highest FAB rate was related to type L1 with 34 patients (61.8%), while in the Children Oncology Group this rate was reported to be 82%. In another study, the L1 rate was 86% (Hjalgrim et al., 1999) and in another study, the L3 rate was 1% (Ishii et al., 2001) In our study, this rate was 7.5%.

Of all patients treated with High risk pre B-cell (COG) method, 42 patients (76.4%) had recovery in the first week of treatment and only 4 (7.3%) patients failed treatment and never recovered. This rate in patients treated in the same way in the study of Goodarzi et al. (2018) in the hospital of Mazandaran, was 5.9%. In general, failure of induction therapy in ALL rarely occurs, i.e., less than 5% of patients (Draper et al., 1994). In our study, this percent is close to this stated percent. It is

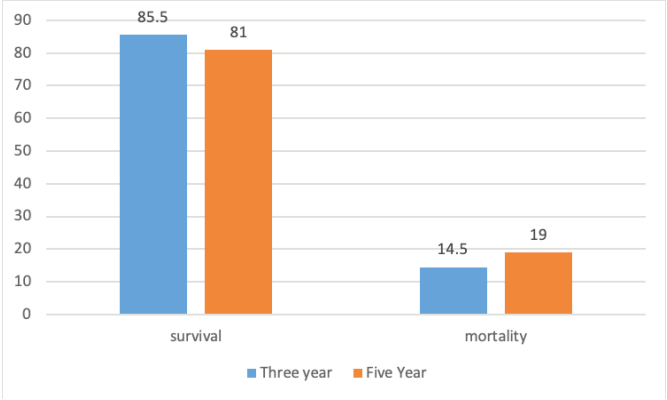

Figure 3. The rate of survival in treated patients with COG method

also similar to the results of the Pedram et al. (2010) study in Ahvaz (5%) and the Silverman et al. (1999) study performed on the UKCCSG method.

In our study, the rate of bone marrow relapse in all relapsed patients was 63.6%, which was lower than a study done by Goodaarzi et al. (2018). In total, the rate of bone marrow recurrence among all treated patients was 12.7%, which was lower than reported rates of about 25%-30% in all children with ALL worldwide (Draper et al., 1994). In the UKCCSG method used in the Pedram et al. (2010) study, this rate was 17.3%. These rates indicate that treatment with high-risk pre-B-cell method reduces the recurrence rate (Eden et al., 1991; Kaiserová et al., 2011; Research Council Leukemia Trial, 1985).

Of the 55 patients treated with high-risk pre-B-cell method, 47 (85.5%) had a three-year survival. Out of the 37 patients who passed five years after diagnosis, 30 patients (81%) had five-year survival. The five-year survival rate was 54% in the Chali et al. study between 2000 and 2009 (Research Council Leukemia Trial, 1985) and 17.7% in patients treated in Slovakia (Stiller & Eatokk, 1999) and 80.3% in the Friedman and Weinstein (2000) study, which was lower than our study. This can be related to the type of treatment, as well as the treatment of T-cell leukemia and B-cell leukemia together in those studies. While treatment was in the same way in Mazandaran, the five year survival of about 96.1%, was due to the lower rate of sepsis in that centre (31.5%) (Pedram et al., 2010). We can say that the reason for the lower survival in our centre compared to Mazandaran could be due to either less observance of the principles of isolation of chemotherapy patients or exclusion of high-risk patients from the study. However, regarding the survival rate according to four-year survival sources in B-cell ALL patients, 80% was expressed among the standard risk group (Farhangi et al., 2018).

Lack of long-term follow-up and consistency of visits of parents, which has made it difficult to follow these patients, can be solved to some extent by building trust and explaining the course of research to parents. Due to the high cost of tests and measures related to parental follow-up after ensuring the primary improvement, they often refuse to continue the follow-up process. To eliminate this limitation, the financial assistance of NGO can be used.

CONCLUSION

From the results of this study, it can be concluded that the choice of high-risk pre-B cell (COG) treatment at the diagnosis of ALL has increased patient survival; the bone marrow, testicular and CNS recurrence rates were decreased in our study in comparison with other studies worldwide. The rate of decreases in bone marrow relapse was more than both. Therefore, CNS therapy should be strengthened in this treatment method. Regarding the survival rate with this treatment method, when we compared our results with other methods used, as well as the rate expressed in scientific sources, the survival rate of three and five years by choosing the high-risk pre-B-cell (COG) method and controlling infection in patients without considering the risk group have increased in all patients. Also, when we consider that all deaths in this study occurred due to sepsis, it is possible to reduce the mortality rate and increase the survival rate of patients by controlling the infectious agents, including strict observance of isolation and anti-sepsis precautions for chemotherapy patients in the hospital and at home by improvement of the nursing system. Also, the issue of patients' migration causes them to become inaccessible, which is overcome by increasing estimated sample size, but also by working with other health facilities to ensure long-term follow-up.

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