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Impact of Chemotherapy on Echocardiography, Uric acid and Lactate Dehydrogenase in Children with Acute lymphoblastic leukemia (ALL)

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Abstract

Background: Acute lymphoblastic leukemia (ALL) is the most prevalent malignancy in pediatrics. ALL blood cancer causes excessive production of immature white blood cells called lymphoblasts or leukemic blasts. Therefore, the present study evaluates the effect of chemotherapy on echocardiography, uric acid (UA) and lactate dehydrogenase (LDH) in ALL children.

Materials and Methods: A quasi-experimental study was designed for 53 ALL patients who referred to Shahid Beqaei 2 in Ahvaz from 2022 to 2023. The inclusion criteria for the studied ALL children aged 2 to 16 years were the maintenance phase of chemotherapy and lack of symptoms of cardiomyopathy. The levels of LDH, UA and echocardiographic parameters were compared before and after chemotherapy through paired sample t-tests. P-values<0.05 were considered significant.

Results: The mean age of the ALL patients was 6.28 ± 4.13 years. Of all the patients, 64% were male. The mean levels of LDH before and after chemotherapy were 1443.36 ± 1373.26 and 534.51 ± 236.61 U/L, and the LDH levels decreased significantly after chemotherapy ($P < 0.001$). The mean U.A levels before and after chemotherapy were 6.67 ± 6.80 and 5.30 ± 6.15 mg/dl, respectively ($P = 0.30$). Abnormal echocardiography before and after chemotherapy was observed in 3.76% and 22.64% of the patients, respectively, but the difference was not markedly significant ($P = 0.44$). The relative risk was estimated to be 0.16, suggesting that the probability of cardiac dysfunction after chemotherapy reduced to approximately 16% of the baseline risk observed before chemotherapy.

Conclusion: The initial evaluation of serum LDH can be beneficial in knowing the response to chemotherapy. So, it is of importance to determine the prognostic value of this biological marker. On the other hand, chemotherapy does not seem to have a significant effect on the mean values of echocardiographic parameters and the level of uric acid.

Keywords: Acute lymphoblastic leukemia (ALL), Chemotherapy, Echocardiography, Lactate dehydrogenase

Introduction

Acute lymphoblastic leukemia (ALL) is the most prevalent cancer in children, accounting for 25-30% of the annual cancer cases among children aged 0-14 years worldwide (1-3). The main cause of ALL is not yet known, but it has been observed that various factors such as environmental factors, viral infections, some syndromes and genetic changes play a role in inducing this disease (4). The treatment of ALL involves high toxicity and is likely to cause the damage or dysfunction of many organs in the body.

In ALL children, the risk of metastasis to other organs and premature death due to various causes, especially cardiac events, is significantly high (5, 6). Elucidating the mechanisms involved in the neuromuscular function of chemotherapy is very difficult because each of the drug classes used in chemotherapy can cause destructive effects through different cellular pathways. Therefore, it is very important to diagnose the long-term side effects of the drugs used in cancer treatment (7, 8). Several studies have reported that multiple signaling pathways

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are the main cause of leukemia cell resistance to chemotherapy. Among these factors, one can mention the signal transducer and activator of transcription 5 (STAT5), which plays an important role in the proliferation of leukemia cells (9). Certain types of cancer treatments are associated with an increased risk of cardiotoxicity. Cardiotoxicity may make it difficult for the heart to pump blood throughout the body, and, in severe cases, it can lead to cardiomyopathy (10). ALL patients may have no symptoms of cardiotoxicity. In this case, echocardiography and the evaluation of serum levels of cardiac enzymes can serve to diagnose cardiotoxicity caused by chemotherapy (11). Biochemical tests including those for serum lactate dehydrogenase (LDH) activity and uric acid (UA) levels have side by side gained importance in monitoring the prognosis of leukemia, especially during the phase of treatment (12). LDH is present in many different cellular systems, and serum LDH levels may increase following tissue or cellular injury (13). It has not been determined whether the elevated levels of serum LDH commonly found in cancer patients reflect the increased production and release of the enzyme by malignant cells. The relationship between neoplasia and increased LDH levels has been reported in human and animal tumors (13, 14). Several investigations have reported the diagnostic value of LDH and UA in children undergoing evaluation for malignancies (3). It is to be noted that UA is strongly associated with the incidence, severity and poor prognosis of cardiovascular diseases (15). Considering the common evidence for destructive cardiomyopathy in patients treated with chemotherapy drugs and the limited research on the causes and mechanisms involved in the occurrence of cardiomyopathy, conducting basic studies is very useful in discovering the mechanism of the disease occurrence and finding suitable ways of preventing it (16). If a significant relationship is found between the increase of uric acid, LDH and echocardiography, it is possible to reduce the fatal outcome of some drugs used in the treatment of ALL. This current study was conducted with the purpose of evaluating the impact of chemotherapy on echocardiography, uric acid and lactate dehydrogenase in ALL children.

Materials and Methods

This quasi-experimental study was conducted on 53 ALL patients who referred to Shahid Beqaei 2 in the city of Ahvaz during 2022 and 2023. ALL was diagnosed by bone marrow (BM) aspirate containing at least 30% blast cells according to the French-American-British classification. The inclusion criteria for the ALL-diagnosed children aged 2 to 16 years were a) being in the maintenance phase of chemotherapy, b) lacking symptoms of cardiomyopathy, and c) having completed echocardiographic, LDH and UA tests before and after chemotherapy. The children with leukemia who already had cardiomyopathy and/or any inflammatory disease were excluded. The treatment of the patients was according to the national standardized guidelines, including the administration of Vincristine, Cyclophosphamide, Cytosar, Pegasparginase, Anthracycline, 6MP, Daunorubicin, Methotrexate and Corticosteroids. The leukemia patients were treated in three stages as follows:

1. Initial induction treatment: The induction lasted for four weeks. At this stage, neuromotor impairments were likely to occur due to the use of vincristine.
2. Consolidation treatment: There were four to six months of weekly treatment.
3. Maintenance treatment: On a monthly basis, the girls took it for two years, and the boys had it for three years.

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For the children with leukemia, two stages of echocardiography were performed, one before treatment and the other in the maintenance phase (after receiving 4 doses of Daunorubicin and 3 doses of doxorubicin). In terms of echocardiography, left ventricular ejection fraction (LVEF) was performed at least with two methods including M mode and LVOT VTI. A drop in LVEF of more than 5% in serial echo was considered positive (17). Echocardiography was used by a cardiologist to examine the heart. This non-invasive method uses sound waves to image the internal structure of the heart and is considered the standard for diagnosing heart disease. The Pars Azmoun LDH kit was used to measure the quantitative levels of serum LDH. Moreover, a Pars kit was used to measure uric acid. The Ethics Committee of Ahvaz Jundishapur University of Medical Sciences approved this study (IR.AJUMS.HGOLESTAN.REC.1402.08.

Statistical analysis

The statistical analysis was performed by the SPSS software Version 22 (IBM, Chicago, USA). Kolmogorov-Smirnov and Shapiro-Wilk tests were also used to test the distributions. The differences were compared through paired sample t-tests. McNemar's Chi-squared test was used to determine the correlation between the qualitative variables. In addition, the relative risk (RR) was estimated to evaluate the impact of chemotherapy on cardiac function. P-values less than 0.05 were considered statistically significant.

Results

The mean age of the patients was 6.28 ± 4.13 years. Of them, 64% were male (34 patients). The mean values of lactate dehydrogenase before and after chemotherapy were 1443.36 ± 1373.26 and 534.51 ± 236.61 U/L, and a significant difference was observed in terms of LDH before and after chemotherapy (P < 0.001). The mean uric acid before and after chemotherapy treatment was 6.67 ± 6.80 and 5.30 ± 6.15 mg/dl, respectively, but there was no significant difference in this regard (P = 0.30). More details are provided in Table I.

Table II shows the comparison of normal and abnormal echocardiography before and after chemotherapy. The percentage of the patients with abnormal echocardiography before and after chemotherapy was 3.76% and 22.64%, respectively, but the difference was not statistically significant (P = 0.44). The relative risk was found estimated to be 0.16, suggesting that the probability of cardiac dysfunction after chemotherapy reduced to approximately 16% of the baseline risk observed before chemotherapy.

Table I: Laboratory findings before and after chemotherapy

Variable	Before chemotherapy	After chemotherapy	P-value*
LDH (U/L)	1443.36 ± 1373.26	534.51 ± 236.61	< 0.001
U.A (mg/dl)	6.67 ± 6.80	5.30 ± 6.15	0.30
LDH: lactate dehydrogenase, U.A: Uric acid, *: T-test analysis was used .P value< 0.05 is significant.			

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Table II: Echocardiography findings before and after chemotherapy

Variable	Abnormal	Normal	P-value*
Before echocardiography	2 (3.76%)	51 (96.24%)	**0.44**
After echocardiography	12 (22.64%)	41 (77.36)	
*** Chi-square analysis was used. P value< 0.05 is significant.**			

Discussion

Treatment of leukemia, such as chemotherapy, or certain cancers with tumors that have rapid cell division may lead to the rapid death of cancer cells and high levels of uric acid in the body. Patients with leukemia may have high levels of uric acid. If a large number of cancer cells die quickly, they release significant amounts of uric acid into the bloodstream, which the kidneys are unable to remove quickly. Therefore, determining uric acid before and after chemotherapy is important (18, 19). This study was conducted with the aim of evaluating the effect of chemotherapy on echocardiography, uric acid and lactate dehydrogenase in children with ALL. According to the results, LDH decreased significantly after chemotherapy. There was no remarkable difference in the level of uric acid before and after chemotherapy. Tsimberidou et al. (20) evaluated the prognostic significance of U.A in 1180 patients with acute myeloid leukemia (AML). In their multivariate analysis, U.A levels higher than the upper limit of normal and lactate dehydrogenase levels higher than 1.5 times the upper limit of normal were identified as the independent adverse factors predicting poorer survival in the patients. Moreover, Yamauchi et al. pointed that a high serum U.A level is associated with poor prognosis in AML patients (21). In another study, reported that serum U.A level has been considered as an independent predictor of the prognosis in some cancer such as leukemia (22). Elevated LDH levels are the product of increased tumor glycolytic activity and tumor necrosis due to hypoxia, the latter being related to high tumor burden. Most previous studies have shown that serum LDH is an independent prognostic factor for patients with AML. The higher the serum LDH level, the shorter the survival time (23, 24). In a study by Oriaifo et al. (25) conducted to determine the diagnostic value of lactate dehydrogenase and uric acid in children with malignancy, the results showed that the level of lactate dehydrogenase after treatment was significantly different from that before treatment. The findings of that study were similar to those of the present study. Similarly, Saharia et al. (12) conducted biochemical tests of serum lactate dehydrogenase activity and uric acid concentration to monitor the prognosis of leukemia, especially in the treatment phase. The levels of LDH and serum uric acid were estimated one month before and after chemotherapy. Based on the results, an increasing level was found in the mean values of serum uric acid concentration and LDH, but the difference was significantly reduced after one month of chemotherapy. That is, the levels of uric acid and lactate dehydrogenase decreased after chemotherapy. Like in the study by Saharia's study, the mean LDH in our patients decreased after chemotherapy. Contrary to Saharia's findings, however, the mean uric acid levels in our patients were not considerably different from those before the treatment. The difference in the sample size may have been the cause of this discrepancy. In another study by Al-Saadoon et al. (26), the mean LDH levels in patients with acute lymphoblastic leukemia were significantly higher than those in other malignancy groups. Also, after chemotherapy, the LDH level decreased significantly. The findings of

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that study were in line with our results. Similar to our findings, the ALL patients studied by Simore et al. (27) had a significant decrease in their mean LDH level after 4-6 weeks of chemotherapy. Based on the present study, echocardiography before and after chemotherapy was not significantly different. In this regard, there has been just a little research. In line with our results, Bahoush et al. (28) investigated the toxic effects of chemotherapy on children's heart and found no significant difference in the mean baseline echocardiographic parameters after chemotherapy, such as E-wave and A-wave ratio (E/A), although they stated that an increased dose of anthracycline can be a factor reducing the systolic function of the heart (decrease in EF). In contrast to our findings, Horacek et al. (29) showed that anthracycline chemotherapy was associated with changes in myocardial electrical activity, QRS voltage reduction, and left ventricular dysfunction in ALL patients. The different sample sizes and study designs may have caused this discrepancy. Keihanian et al. (11) examined 46 patients with breast cancer who took chemotherapy containing anthracycline. After the third cycle of chemotherapy, EF was equal to or greater than 50% in 89.2% of the patients. However, 12 months after the start of chemotherapy, this frequency decreased to 84.7%. The findings of that study were contradictory to our results. Generally, the differences among the results discussed above are probably due to the duration of follow-ups, the dose of drugs, and the type of cancer. The study by Lin et al. aimed to investigate the effect of echocardiography after anthracycline therapy in 120 AML patients, (before treatment, 97% of patients had an LVEF greater than 50%). According to theire findings, echocardiographic results were normal in 99% of AML patients who underwent anthracycline chemotherapy (30). The findings of this study were consistent with our results.

Conclusion

It was concluded that chemotherapy had no significant effect on the mean levels of uric acid and echocardiographic parameters, while serum LDH level decreased after chemotherapy. Early measurement of serum LDH can be useful in identifying responses to chemotherapy, so it is important to determine the prognostic value of this biological marker. The limitations of this study were its small sample size and retrospective nature. It is recommended that clinical trials with larger sample sizes be conducted in order to verify the results reported in the literature.

Ethical Considerations

The Ethics Committee of Ahvaz Jundishapur University of Medical Sciences approved this study (IR.AJUMS.HGOLESTAN.REC.1402.080).

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Authors' Contributions

A.A, R.M, and B.K. conceived and designed the evaluation, and drafted the manuscript. A.A, R.M, participated in designing the evaluation, performed parts of the statistical analysis, and assisted in drafting the manuscript. A.A, R.M, and R.S. reevaluated the clinical data, revised the manuscript, conducted the statistical analysis, and further revised the manuscript. A.A, R.M, and B.K. collected the clinical data, interpreted them, and revised the manuscript. S.B, and B.N re-

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analyzed the clinical and statistical data and revised the manuscript. All authors read and approved the final manuscript.

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Conflict of Interest
There is no conflict of interests to declare.

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