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Analysis of Pulmonary Complications in Pediatric Acute Lymphocytic Leukemia Patients following Three Years of Chemotherapy Treatment: A Cross-Sectional Study

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Abstract

Background: This study aimed to investigate the pulmonary side effects of chemotherapy drugs in children with Acute Lymphocytic Leukemia (ALL) three years after treatment. The results could be of great help in managing lung complications in pediatric oncology patients.

Materials and Methods: This cross-sectional descriptive study included 50 patients (22 males and 28 females) with ALL. Data were collected from patients' files, including age, sex, duration of illness, last dose of chemotherapy, and medications such as PEG.Asparginas, Cyclophosphamid, thioguanine, Dexamethason, cytarabin, cytosin.arabinosid, vincristine, mercaptopurine, and methotrexate. Pulmonary function tests (Forced Vital Capacity (FVC), FEV1 (Forced Expiratory Volume in the first second)) were assessed by spirometry.

Results: Out of 50 patients, 47 (94%) did not have pulmonary disorders, while 3 (6%) had pulmonary dysfunction. Forty-seven patients (94%) did not have respiratory symptoms. FVC results showed that 45 patients were normal, and 5 were abnormal. Similarly, 45 patients had normal FEV1, and 5 had abnormal results. Spirometry results were normal in 45 patients and abnormal in 5. A significant relationship was found between the use of these drugs in different doses and spirometry results, recurrence rate, and pulmonary complications ($P < 0.05$). No significant relationship was observed between pulmonary dysfunction and other drugs ($P > 0.05$). No correlation was found between pulmonary complications due to chemotherapy with duration of chemotherapy, patient age, and patient gender ($P > 0.05$).

Conclusion: Pulmonary dysfunction and respiratory syndrome were observed in 6% of patients receiving chemotherapy. A significant relationship was found between the frequency of pulmonary and respiratory complications with some chemotherapy drugs in children with ALL. Further research is needed to optimize treatment strategies and minimize lung complications in pediatric oncology patients.

Keywords: Acute lymphoblastic leukemia, Chemotherapy, Pulmonary complications

Introduction

Acute lymphocytic leukemia (ALL) was the most prevalent form of childhood cancer, accounting for a significant proportion of cancer diagnoses in children. The majority of ALL cases were diagnosed in children between the ages of 2 and 6 years, with approximately 93% of cases occurring during childhood (1,2). Chemotherapy had emerged as a crucial approach to cancer treatment, employing antineoplastic drugs to eliminate cancer cells and halt the progression of the disease (3-5).While chemotherapy drugs had proven effective in managing ALL, they also possessed harmful effects on the body's normal cells (6-10). Consequently, long-term survival was often accompanied by adverse effects resulting from various treatment methods, including chemotherapy and radiotherapy, many of which could be prevented (11-16). One of the potential side effects associated with chemotherapy drugs was the development of lung problems. These pulmonary

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complications manifested in various forms, ranging from respiratory symptoms to severe and life-threatening conditions (17-20). Given the severity and potential fatality of these pulmonary reactions, it was crucial to promptly and accurately differentiate pulmonary disease caused by chemotherapy drugs from other causes of pulmonary infectious diseases (21, 22). Failure to do so resulted in delayed diagnosis and suboptimal treatment, further exacerbating the patient's condition. Regular monitoring of pulmonary complications and timely intervention were essential in preventing and managing these complications, ultimately reducing associated costs and complications (23). Despite the recognized importance of monitoring pulmonary complications in pediatric ALL patients, existing literature on this topic presented limited and contradictory information. Furthermore, no comprehensive study had been conducted in our country to investigate the pulmonary side effects of chemotherapy drugs in children with ALL. This knowledge gap hindered our understanding of the long-term pulmonary health outcomes of children undergoing chemotherapy for ALL and impeded the development of targeted interventions to mitigate these side effects (24, 25). Therefore, the primary objective of this study was to investigate the pulmonary side effects of chemotherapy drugs in children with ALL three years after treatment.

Materials and Methods

This cross-sectional descriptive study selected 50 pediatric cancer patients who had undergone chemotherapy treatment for ALL at least three years prior. The study obtained ethical approval from Shahid Sadoughi University of Medical Sciences (Ethical code: IR.SSU.MEDICINE.REC.1399.214). A sample size of 50 patients was selected based on a previous study that reported a prevalence of pulmonary complications in pediatric ALL patients following chemotherapy of 20% (24). With a 95% confidence level and a margin of error of 10%, a minimum sample size of 42 patients was required. To ensure adequate power, 50 patients were selected for the study.A structured questionnaire was used to collect demographic and clinical data from the patients, including the duration of the disease, the last round of chemotherapy, type of drug, age, sex, recurrence rate, and metastasis. The spirometry test was performed to assess the pulmonary function of the patients, and the results, including FVC (Forced Vital Capacity) and FEV1 (Forced Expiratory Volume in the first second), were recorded. The normal values of FVC and FEV1 were determined based on the patient's age, sex, height, and ethnicity, as recommended by the American Thoracic Society. Descriptive statistics were used to summarize the demographic and clinical data, including the mean and standard deviation for continuous variables and frequency and percentage for categorical variables. The Kolmogorov-Smirnov test was used to assess the normality of the distribution of continuous variables. The Chi-square test was used to assess the association between categorical variables, and the independent t-test and Mann-Whitney U test were used for comparing continuous variables between two groups. One-way ANOVA and Kruskal-Wallis tests were used for comparing continuous variables between more than two groups. Multiple linear regression analysis was performed to assess the relationship between FVC and FEV1 with the duration of the disease, the last round of chemotherapy, type of drug, age, sex, recurrence rate, and metastasis. All statistical tests were two-sided, and a p-

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value of less than 0.05 was considered statistically significant. Data analysis was performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA).

Results

The present study included fifty patients, with demographic information presented in Table I. The recurrence rate was 4%. Seventy-four percent of patients underwent chemotherapy for less than 3 years. Table II summarizes the prevalence of pulmonary disorders, respiratory symptoms, FVC, FEV1, FVC/FEV1, and spirometry results. Of the fifty patients, 47 had no pulmonary symptoms, while 3 (6%) had symptoms. Forty-seven patients had no respiratory symptoms (94%). Forty-five patients had normal FVC, FEV1, and FVC/FEV1, while five patients had abnormal results. Spirometry results were normal in 45 patients.

Table III shows the frequency of spirometry results according to the type of drug. A significant relationship was found between drug consumption in different doses and spirometry results ($P<0.05$), except for Dexamethasone and vincristine.

Table IV summarizes the frequency of spirometry results in terms of gender, age of disease onset, current age of the patient, and duration of chemotherapy. No significant difference in spirometry results was found between male and female patients ($P>0.05$). No correlation was observed between the age of disease onset and pulmonary dysfunction caused by chemotherapy drugs ($P>0.05$). Similarly, no correlation was found between spirometric results and the age of disease onset ($P>0.05$), current age of the patient ($P>0.05$), or duration of chemotherapy ($P>0.05$).

Table I: Demographic information and pulmonary complications of chemotherapy drugs in children with acute lymphocytic leukemia after three years of treatment

Variable	Frequency (%)
Sex	
Male	22 (44)
Female	28 (56)
Recurrence rate	
Yes	2 (4)
No	48 (96)
The last time of chemotherapy (Year)	
<3	14 (28)
≥3	36 (72)
Metastasis	
Yes	0 (0)
No	50 (100)
Pulmonary dysfunction	
Yes	3 (6)
No	47 (94)

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Table II: Frequency of pulmonary disorders, respiratory symptoms, spirometry, FVC, FEV1, FVC/FEV1, and metastasis

Variable	Frequency (%)
Pulmonary disfunction	3 (6)
Respiratory symptoms	
Absent	47 (94)
Present (Grade 1-4)	3 (6)
FVC	
>80	45
≤80	5
FEV1	
>85	45
≤85	5
FVC/FEV1	
>100	45
≤100	5
Spirometry	
Normal	45
Abnormal (Grade 1-2)	5

Table III: Frequency of spirometry results according to chemotherapy drugs

Chemotherapy Drug	Normal	Abnormal (Grade 1-2)	P-value
PEG.Asparginas.2500ium2	17 (89.5)	2 (10.5)	0.0187
Cyclophosphamid.1000mgm2	23 (95.8)	1 (4.2)	0.0187
thioguanine	42 (91.3)	4 (8.7)	0.039
Dexamethason.6mgm2	44 (94.4)	3 (6.6)	0.78
cytarabin.75mgm2	43 (91.5)	4 (8.5)	0.013
cytosin.arabinosid.35m2	44 (93.6)	3 (6.4)	0.000
vincristin.1.5mgm2	29 (94.2)	1 (3.3)	0.79
mercaptopurine.50mgm2	40 (90.9)	4 (9.1)	0.000

Table IV: Frequency of spirometry results according to gender, age of disease, current age of patient, and duration of chemotherapy

Variable	Normal	Abnormal (Grade 1-2)	P-value
Gender			
Male	20 (90.9)	2 (9.1)	0.918
Female	25 (93.0)	2 (7.0)	0.918
Age of Disease			
<5	12 (92.9)	1 (7.1)	0.221
5-6	20 (91.3)	2 (8.7)	0.221
>6	13 (100)	0 (0)	0.221
Current Age of Patient			
<10	15 (92.9)	1 (7.1)	0.569
11-15	21 (87.5)	3 (12.5)	0.569
>15	10 (85.7)	2 (14.3)	0.569
Duration of Chemotherapy			
<3	35 (94.6)	1 (2.7)	0.173
>3	10 (76.9)	3 (23.1)	0.173

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Discussion

In the present study, a significant relationship was observed between the use of Cyclophosphamide and Cytosine Arabinoside and pulmonary dysfunction, but no significant relationship was found between pulmonary dysfunction and the use of other drugs. Among the 50 patients, 47 did not have pulmonary disorders, while 3 patients (6%) had pulmonary disorders. Hemberg et al. conducted a study on breast cancer patients and found that FEV1 and FVC decreased after chemotherapy in both treatment groups, indicating a significant relationship between lung complications and chemotherapy drugs (24). Macêdo et al. investigated children with leukemia and found no significant difference in spirometric values between patients and healthy controls (25). However, Muldre et al. reported a higher prevalence of pulmonary disorders in patients who received pulmonary radiotherapy in combination with bleomycin and surgery (26). These findings suggest that the type of treatment protocol can influence pulmonary complications in patients. Lyudmila et al. investigated changes in pulmonary function after chemotherapy and found that pulmonary function tests are useful for early detection of lung damage, particularly in patients receiving first-line treatment (27). Borje et al. observed pulmonary complications in 22% of patients with Acute Lymphocytic Leukemia, with a significant relationship between lung damage and the dose of chemotherapy drugs (12). Vasilios Mihailidis et al. reported significant changes in FEV1 and FVC after chemotherapy, indicating that intermittent chemotherapy can lead to significant changes in lung function (28). Our study showed that 47 patients did not have respiratory symptoms, but 3 patients had respiratory complications, and a significant relationship was found between drug use in different doses and pulmonary complications, while no significant relationship was observed between pulmonary dysfunction and other drugs. Chaoui et al. reported that respiratory symptoms are common during chemotherapy in patients with leukemia (29). Azoulay et al. found that 25% of patients experienced mild respiratory complications during chemotherapy (30). These findings suggest that some degree of respiratory complications may occur in patients undergoing chemotherapy. Our study showed no relationship between spirometry results and the duration of chemotherapy, but other studies have reported an association between long-term chemotherapy use and pulmonary complications. The relationship between pulmonary complications and the age of patients was not significant in our study, although some studies have reported younger age as a risk factor for decreased lung function. The frequency of pulmonary side effects of chemotherapy drugs in children with ALL was not significantly different between genders, but some studies have found a higher prevalence in males. The physical examination of the pulmonary system was normal in all patients treated with the studied drugs, and the prevalence of clinical respiratory symptoms was very low. Our study found a significant relationship between drug use in different doses and the relapse rate, with a higher relapse rate observed in patients receiving bortezomib + reinduction therapy (31). These findings suggest that the treatment protocol can influence the recurrence rate. Overall, our study highlights the importance of considering the type of treatment protocol, drug doses, and individual patient factors when assessing

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pulmonary complications in children undergoing chemotherapy for cancer.

Conclusion

Based on the findings of this study, pulmonary dysfunction was observed in 6% of patients after chemotherapy. Additionally, a significant relationship was found between the frequency of pulmonary and respiratory complications and certain chemotherapy drugs in children with ALL. These results suggest that early detection and management of these side effects in patients may be possible by adjusting treatment regimens, such as stopping treatment, reducing drug dosage, or switching to alternative medications. However, it is important to note that the duration of chemotherapy, age, and gender of the patient may influence the frequency of these complications.

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Authors' contribution

Abdolhamid Jafari Nodoshan: Conceptualization, Methodology, Data Collection, Formal Analysis, Writing - Original Draft, Supervision.

Hadi Zare-Zardini: Conceptualization, Methodology, Data Collection, Formal Analysis, Writing - Review & Editing, Supervision.

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Azam Hashemi: Data Collection, Formal Analysis, Writing - Review & Editing.

Alireza Jenabzadeh: Conceptualization, Methodology, Writing - Review & Editing.

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Conflict of interest

The authors declare that they have no conflict of interest regarding the publication of this article

Ethical cosiderations

This study was conducted in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Ethical approval for the study was obtained from Shahid Sadoughi University of Medical Sciences (Ethical code: IR.SSU.MEDICINE.REC.1399.214).

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