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Exhaled phospholipids as a prognostic factor of pulmonary complications in children with acute lymphoblastic leukemia

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Introduction. Pulmonary complications are common in children with acute lymphoblastic leukemia (ALL). The assessment of phospholipids (PL) in the exhaled breath condensate can provide more information about pathological processes in the lungs in children with ALL.
Purpose — to assess the level of PL in the exhaled breath condensate (EBC) in children with ALL and its prognostic value.
Materials and methods. 40 children with ALL aged 6–17 years were examined. 1st group included newly diagnosed children with ALL (n=18). 2nd group involved ALL survivors, who had completed the total course of chemotherapy (n=22). The control (C) group consisted of 15 healthy children. The levels of PL in the EBC were investigated by spectrophotometric thin-layer chromatography using an SPh 46 spectrophotometer.
Results. The frequency of pulmonary complication was 82.5% during chemotherapy protocols and 18.4% in ALL survivals. The statistically significant increase in the level of phospholipids in 1st (150.75 (137.62; 158.45) mmol/l) and 2nd (130.12 (120.59; 138.34) mmol/l) ALL groups compared with the group C (54.80 (48.30; 60.80) mmol/l) has been detected (p_{1-C}=0.0000; p_{2-C}=0.0000). Children of the 1st group had significantly higher levels of PL in the EBC than children of the 2nd group (p_{1-2}=0.002911). PL level in EBC collected during induction phase of chemotherapy >132.15 mmol/l can be prognostic for the development of acute pulmonary complications (Sensitivity 93.75%; Specificity 100%). PL level in EBC collected after a complete course of chemotherapy >133.28 mmol/l can be predictive for persistent pulmonary complications (Sensitivity 100.00%; Specificity 83.33%).
Conclusions. PL level in EBC can be prognostic for the development of pulmonary complications, both during chemotherapy and in long-term remission after completed chemotherapy course.
The research was carried out in accordance with the principles of the Helsinki Declaration. The study protocol was approved by the Local Ethics Committee of the participating institution. The informed consent of the patient was obtained for conducting the studies.
No conflict of interests was declared by the authors.
Keywords: pulmonary complications, leukemia, children, blood-air barrier, phospholipids, surfactant, exhaled breath condensate, pneumonia.

Фосфоліпіди в конденсаті повітря, що видихається, як прогностичний фактор легеневих ускладнень у дітей з гострою лімфобластною лейкемією

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Вступ. Легеневі ускладнення є характерними в дітей з гострою лімфобластною лейкемією (ГЛЛ). Визначення рівня фосфоліпідів (ФЛ) у конденсаті повітря, що видихається, (КВП) може надати більше інформації про патологічні процеси в легенях дітей з ГЛЛ.
Мета — оцінити рівень ФЛ у КВП у дітей з ГЛЛ та його прогностичне значення.
Матеріали та методи. Обстежено 40 дітей з ГЛЛ віком 6–17 років. До 1-ї групи увійшли діти зі щойно діагностованою ГЛЛ (n=18). До 2-ї групи — реконвалесценти ГЛЛ, які пройшли повний курс хіміотерапії (n=22). Контрольну групу (С) становили 15 здорових дітей. Рівні ФЛ у КВП досліджено методом спектрофотометричної тонкошарової хроматографії на спектрофотометрі «SPh 46».
Результати. Частота легеневих ускладнень становила 82,5% на тлі хіміотерапевтичних протоколів і 18.4% у дітей після закінчення хіміотерапії. Виявлено статистично вірогідне підвищення рівня ФЛ у 1-й (150,75 (137,62; 158,45) ммоль/л) та 2-й (130,12 (120,59; 138,34) ммоль/л) групах порівняно з групою С (54,80 (48,30; 60,80) ммоль/л) (p_{1-C}=0,0000; p_{2-C}=0,0000). Діти 1-ї групи мали вірогідно вищі рівні ФЛ у КВП, ніж діти 2-ї групи (p_{1-2}=0,002911). Рівень ФЛ у КВП, отриманий під час протоколу 1, >132,15 ммоль/л, може бути прогностичним для розвитку гострих легеневих ускладнень (чутливість — 93,75%; специфічність — 100%). Рівень ФЛ у КВП, отриманий після повного курсу хіміотерапії, >133,28 ммоль/л, може бути прогностичним для стійких легеневих ускладнень (чутливість — 100,00%; специфічність — 83,33%).
Висновки. Рівень ФЛ у КВП може бути прогностичним для розвитку легеневих ускладнень, як під час хіміотерапії, так і в тривалій ремісії після завершеного курсу хіміотерапії.
Дослідження виконано відповідно до принципів Гельсінської декларації. Протокол дослідження ухвалено Локальним етичним комітетом зазначеної в роботі установи. На проведення досліджень отримано інформовану згоду батьків, дітей.
Автори заявляють про відсутність конфлікту інтересів.
Ключові слова: легеневі ускладнення, лейкемія, діти, аерогематичний бар'єр, фосфоліпіди, сурфактант, конденсат повітря, що видихається, пневмонія.

Introduction

Acute lymphoblastic leukemia (ALL) is the most common cancer in children [8,23]. In recent years, there has been an improvement in the quality of diagnosis and treatment of this disease [3,4]. Nowadays more and more attention is paid to the study of complications of acute leukemia [3,5,11]. Pulmonary complications are common and are associated both with the course of the underlying disease and with the side effects of the treatment [24]. The main reasons for these complications are immunosuppression and cytopenia [16,17],

the direct cytotoxic effect of drugs on lung tissue [22,26,27]; bone marrow transplantation [9], blast infiltration of the lungs on the background of hyperleukocytosis [13]. Lung infections can influence the prognosis of acute leukemia in the acute period [12]. There are several studies that noted that the severity of pneumonia and the spread of pneumonic infiltrates during the induction phase of chemotherapy is an important prognostic criterion for early mortality during the treatment of leukemia [10,19]. In catamnesis, complications during chemotherapy exceed the mortality rate from relapse of leukemia [11], due to pauses in protocol treatment. In addition, it should be noted that some pulmonary complications still persist in the long-term period among pediatric cancer survivors [1,15,20]. A multi-institutional retrospective cohort Childhood Cancer Survivor Study reported that pediatric cancer survivors by the age of 45 years were more likely to have a chronic cough, oxygen need, lung fibrosis, and recurrent pneumonia compared to sibling controls [7]. Despite the growing attention to the study of pulmonary complications in children with acute leukemia, the problem is still insufficiently studied and systematized.

Phospholipids (PL) are the main component of pulmonary surfactants, as well as the structural element of alveolocytes. These lipid components of lung surfactant provide the functionality and stability of the alveolar epithelium to ensure complete gas exchange [2,14]. So, the determination of the level of PL in the exhaled breath condensate will allow us to assess the state of this component of the blood-air barrier. Previous studies held in our institution confirmed the diagnostic and prognostic value of PL level in exhaled breath condensate (EBC) in children with pneumonia [21], wheezing, and bronchial asthma [18]. The review made by B. Tlatelpa—Romero, V. Cázares—Ordoñez et al. (2022) summarized the potential role of various pulmonary surfactant PL in the pathology of fibrosing lung diseases, including idiopathic pulmonary fibrosis and pulmonary fibrosis due to adult respiratory distress syndrome [25].

However, there is a lack of studies on the status of the blood-air barrier in the lungs in leukemic children. The assessment of PL level in EBC can be useful for a more detailed understanding of pathological processes in the lungs and their connection with pulmonary complications in children with ALL.

Purpose of the study — to assess the level of PL in the EBC in children with ALL and its prognostic value.

Materials and methods of the study

During our study 40 children (26 boys and 14 girls) with ALL aged 6–17 years were examined. All these patients were treated in the hematological department of the Kharkiv Municipal Clinical Children's Hospital No 16. The control group (C) consisted of 15 healthy children, who visited Kharkiv City Outpatient Hospital No 16 for routine health control or vaccination. None of the children in the control group had any chronic diseases of the respiratory tract or acute respiratory diseases at the moment of examination. All examined the patients were Caucasians.

The criteria for inclusion in the study were verified diagnosis of ALL, age 6–17 years, signed consent from parents, and/or patients. *The criteria for exclusion* in the study were refusal of the parents or/and patients to sign the consent, age less than 6 years or problems in following instructions during EBC collection, relapsed or secondary ALL, diagnosed chronic pulmonary diseases before the debut of ALL; any hereditary diseases that lead to changes in the structure and functioning of the respiratory system, including cystic fibrosis; proven hereditary immune deficiency.

40 examined children with ALL consisted of 2 groups. The Group 1 included newly diagnosed children with ALL (n=18). The Group 2 involved ALL survivors, who had completed the total course of chemotherapy and had a remission for at least two years (n=22). Presence of pulmonary complications in patients with newly diagnosed ALL (the Group 1) was reordered by clinical observation from the manifestation of the main disease till the complete completion of the chemotherapy course. Information about the diagnosis and pulmonary complication of ALL survivors (the Group 2) have been received retrospectively by studying their case histories.

The diagnosis and treatment of children were carried out by the protocol «Acute Lymphoblastic Leukaemia Intensive Chemotherapy Berlin Frankfurt Munich 2009» (ALL IC BFM 2009) [31]. The diagnosis of ALL was verified if the blast count in bone marrow was 25% or more. Peripheral blood and bone marrow smears were evaluated according to French-American-British (FAB) criteria, immunophenotyping, and chromosomal analyses were performed. The therapy was carried out according to the ALL IC BFM 2009 protocol which consists of induction (Protocol I), consolidation (protocol M for the standard risk group, HR —

Table 1

General characteristics of studied patients with acute lymphoblastic leukemia

Parameter	Total (n=40)	Group 1 (n=18)	Group 2 (n=22)
Age, Me (Uq; Lq) years	9 (7; 14)	7 (6; 15)	9,5 (7; 13)
Gender (male/female), n	26/14	11/7	15/7
Immunophenotype, n B-lineage T-lineage	 36 4	 15 3	 21 1
FAB classification, n L1 L2	 31 9	 11 7	 20 2
Risk group, n Standard High	 29 11	 12 6	 17 5

Note: FAB classification — French-American-British classification.

for the high-risk group) re-induction (Protocol 2) periods, and maintenance treatment.

In addition to standard protocol methods of diagnostics, an assessment of the PL level in EBC was conducted. In children with newly diagnosed ALL (the Group 1) EBC was collected during induction remission (Protocol 1) in a period without signs of pulmonary complications and critical neutropenia between the 7th and 14th day of chemotherapy. In ALL survivors (the Group 2) the level of PL in EBC was assessed during their planned visit to the hematological department for observations after a complete course of chemotherapy. The levels of PL in the EBC were investigated by spectrophotometric thin-layer chromatography using an SPh 46 spectrophotometer. The EBC was taken using the developed EBC collection device, modified at the Department of Pediatrics No. 2 of Kharkiv National Medical University (patent No. 108795). The technique is a non-invasive and non-traumatic method in which it is possible to obtain up to 0.4–1.0 ml of condensate in 12–18 minutes following biochemical analysis. Children less than 6 years were an exclusion criterion due to differences in the method of collecting EBC in different ages and possible problems in following instructions correctly in younger children to avoid diagnostic mistakes and possible differences in the PL levels for these reasons.

For statistical analyses of data, STATISTICA 8 (Tulsa, OK) and MedCalc 17.2 has been used. Shapiro—Vilka test has been used for verification of the distribution according to the Gauss law. Taking into account the fact that the samples had a non-normal distribution, the median (Me), and interquartile range (Lq — lower, quartile; Uq — upper quartile) were determined for the statistical analysis. To compare two independent samples, a non-parametric Mann—Whitney (MW) U-test has been used. The difference in the parameters has been considered significant at $p<0.05$. Receiver operating characteristic (ROC) curves were drawn for variables by MedCalc 17.2 to determine the optimal «cut-off» values to predict an endpoint, that defines the highest sensitivity with a minimal number of false positive results. Area Under Curve (AUC) is the area bounded by the ROC curve and the percentage axis of false positive classifications, reflects the statistical characteristics of classifier accuracy. An ideal classifier will have an AUC of 1.0, indicating perfect discrimination, whereas a random classifier will have an AUC of 0.5, indicating no discrimination. Sensitivity (Se) is the proportion of true positive cases that were correctly identified by the predictive method. Specificity (Sp) is the proportion of true negative cases of the predictive method. 95% CI is a confidence interval. Positive likelihood ratio (+LR) is ratio between true positive test result and the probability false test result. Negative likelihood ratio (-LR) is a ratio between the probability of a true negative test result and the probability of a false negative test result.

Each study participant and his/her parents were informed about the nature of the study. Informed consent for participation in the study from the parents of all patients and patients aged 14–18 was obtained. The study was approved by the Ethics and Bioethics Committee of Kharkiv National Medical University and was conducted according to Helsinki Declaration (1975).

Results of the study and discussion

General characteristics of patients with ALL are highlighted in Table 1. There was a significant prevalence of boys than girls ($p=0.0385$). Bone marrow examination detected that B cell lineage ALL was prevalent ($p=0.0002$). Most children had the standard risk group ($p=0.0067$). Among children of the

Table 2

Pulmonary complications in children with acute lymphoblastic leukemia

Complication	During chemotherapy (n=40)		After complete course of chemotherapy (n=38)	
	n	%	n	%
Acute bronchitis	23	57.5	–	–
Recurrent episodes of acute bronchitis	3	7.5	2	5.3
Wheezing	9	22.5	–	–
Bronchial asthma	–	–	3	7.9
Pneumonia	18	45.0	–	–
Interstitial pneumonia	1	2.5	–	–
Pleurisy	1	2.5	–	–
Pneumothorax	3	7.5	–	–
Lung fibrosis	–	–	2	5.3
Respiratory failure	6	15.0	–	–
Total	33	82.5	7	18.4

Group 1 two (11.11%) children die due to the progression of the main disease.

We recorded all pulmonary that occur in different periods of ALL in children of both groups. The frequency of detected pulmonary complications is presented in table 2. We could record pulmonary complications after complete course of chemotherapy only in 38 children, because 2 children of the Group 1 died due to progression of ALL.

Our study revealed, that most children had pulmonary complications. Some children had more than one variant of complications during different stages of the disease. Acute lung complications during ALL IC BFM protocols were frequent. The fact that complications mainly manifested in the acute phase of chemotherapy protocol treatment corresponds to literature data [6,12]. In our study acute pulmonary complications were recorded in 33 (82.5%) children. The most frequent complications were acute bronchitis (23 (57.5%) cases), pneumonia (18 (45.0%) cases), and wheezing (9 (22.5%) cases). Pneumonias tended to rapid progression of lung infiltration. They were complicated by pleurisy in 1 case (5.6% of pneumonias), by pneumothorax in 3 cases (16.7% of pneumonias), and by respiratory failure in 6 cases (33.3% of pneumonias).

Also, there was 1 (2.5%) case of interstitial pneumonia, that was probably induced by chemotherapy toxicity. This complication developed during HR-protocol, and methotrexate (MTX) and cytosine arabinoside (ARA-C) are reported to have pulmonary toxicity [22,27].

The frequency of pulmonary complication was in 7 (18.4%) cases after a completed course of chemotherapy. These complications included 2 (5.3%) cases of lung fibrosis, 3 (7.9%) cases of bronchial asthma, and 2 (5.3%) cases with recurrent episodes of acute bronchitis. Among children that formed bronchial asthma, none had any wheezing episodes before the debut of ALL. Therefore, this allows us to suppose that this pathological state is connected with ALL courses and its treatment. Cases of fibrosis are probably related to chemotherapy toxicity [26]. According to previous studies, the prevalence of distant pulmonary complications of varying severity in survivors of pediatric cancer ranges from 45.5% to 84.1%, among which only 8% are clinically detected [1,14]. Differences in this frequency can be explained by differences in patient samples.

According to our results, the statistically significant increase in the level of PL in the Group 1 (150.75 (137.62; 158.45) mmol/l) and the Group 2 (130.12 (120.59; 138.34) mmol/l) compared with the Group C (54.80 (48.30; 60.80) mmol/l) has been detected ($p_{1\text{-}C}$=0.0000; $p_{2\text{-}C}$=0.0000).

It was found that children with ALL on the background of active chemotherapy (the Group 1) have significantly higher levels of PL in the EBC than children who had completed chemotherapy (the Group 2): $p_{1\text{-}2}$=0.002911. So, the highest PL levels in the EBC are expectedly registered in a group of children with ALL receiving chemotherapy (the Group 1). This fact confirms the hypothesis of a negative effect of the course and chemotherapy treatment of ALL on the blood-air barrier of the lungs. Damage of surfactant and epithelial components of the blood-air barrier, detected by assessment of our studied marker, becomes a background for the formation of pulmonary complications.

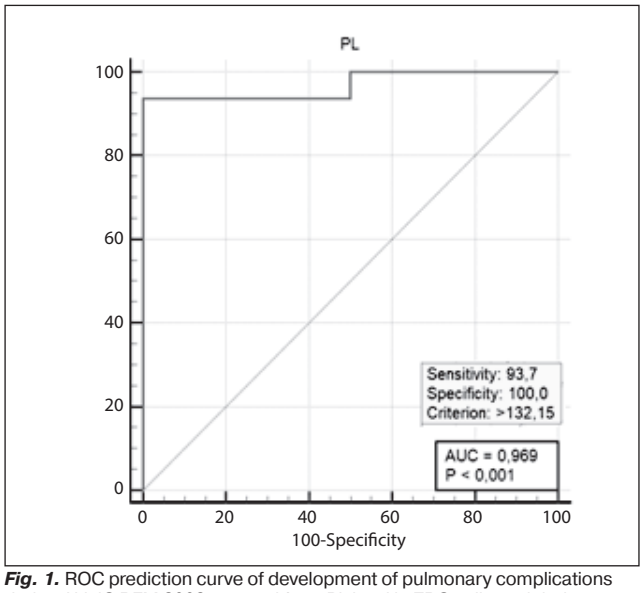

Fig. 1. ROC prediction curve of development of pulmonary complications during ALL IC BFM 2009 protocol from PL level in EBC collected during induction phase of chemotherapy (Protocol 1)

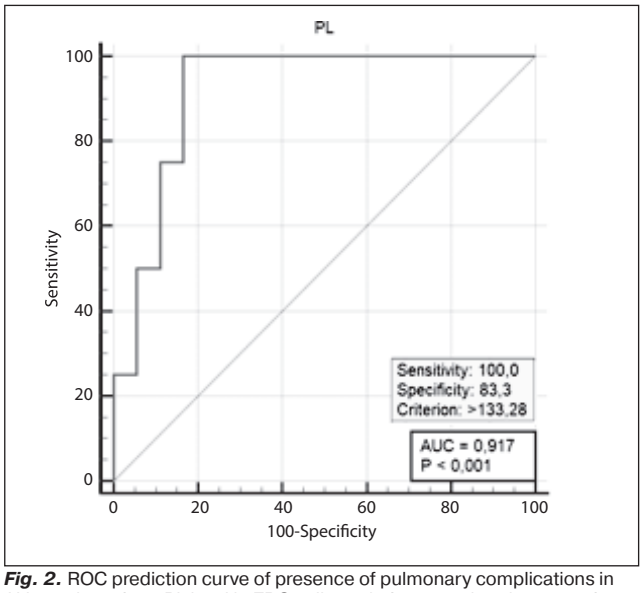

Fig. 2. ROC prediction curve of presence of pulmonary complications in ALL survivors from PL level in EBC collected after completed course of chemotherapy

In accordance with our data, despite the decrease in PL in children after the end of chemotherapy protocols, this parameter in ALL survivors does not reach the normal level of children of the control group. These changes confirm the preservation of the destruction of surfactant and cell membranes of the bronchopulmonary system, even after the cure of the underlying disease and completed course of aggressive protocol treatment.

As it was mentioned before, acute complications during chemotherapy protocols were common. It has been found that the levels of PL in EBC were significantly higher in cases with the presence of acute pulmonary complications among children of the Group 1 in the period of chemotherapy protocols (p=0.035091). The conducted ROC analysis (Fig. 1) determined that the PL level in EBC collected during the induction phase of chemotherapy higher than 132.15 mmol/l can be prognostic for the development of acute pulmonary complications during ALL IC BFM 2009 protocols (AUC 0.969; Se 93.75% (95% CI 69.8–99.8); Sp 100% (95% CI 15.8–100.0); +LR 0.00; -LR 0.063).

Despite achieved remission and total completion of protocol chemotherapy treatment some children still had respiratory complaints. Among children in remission of the Group 2 children with persistent pulmonary complications had significantly higher levels of PL (p=0.010657). According to ROC analysis (Fig. 2), PL level in EBC collected after a complete course of chemotherapy higher than 133.28 mmol/l can be predictive for persistent pulmonary complications (AUC 0.917; Se 100.00% (95% CI 39.8–100.0); Sp 83.33% (95% CI 58.6–96.4); +LR 6.00; -LR 0.00).

Detected statistically significantly higher PL levels in children with lung complications and ROC-analysis results confirm the relation of PL levels in EBC and formation of lung complications.

In contrast to previous studies, we firstly assess the level of PL in children with ALL and its relation to pulmonary complications in different periods of pediatric ALL. The combination of high levels of PL and high incidence of pulmonary complication in ALL children allows us to suggest the possibility of a relation between the damage of the surfactant and epithelial layer of the blood-air barrier and the formation of the inflammation process in the lungs.

Our study has several limitations. We could not detect whether recorded pulmonary complications are connected with the course of the main disease or toxic effects of cytostatic therapy, because these factors influence at the same time and most of them are not specific. Another limitation is connected with a small sample of patients, due to the fact that oncological diseases are comparatively rare pathologies in general pediatrics population. Therefore, further studies with larger samples, including multi-central research can be useful for a more in-depth study of the problem.

Conclusions

According to the study children with ALL can be classified as a risk group for the development of pulmonary pathology, both during the period of

ALL IC BFM 2009 protocol treatment and in long term remission after completion of chemotherapy. As a result, this group of children requires more careful management by pediatrician and hematologist. The study of PL in EBC is non-invasive and informative method for an objective assessment of the severity of damage of blood-air barier, and therefore can be included in the algorithm for examining patients with acute leukemia. Moreover, the PL level in EBC collected during the induction phase of chemotherapy higher than 132.15 mmol/l can be prognostic for development of acute pulmonary complications during ALL IC BFM 2009 protocols with Se 93.75% and Sp 100%, PL level in EBC collected after complete course of chemotherapy higher than 133.28 mmol/l can be predictive for persisted pulmonary complications with Se 100.00% and Sp 83.33%.

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