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ORIGINAL ARTICLE

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Clinical and pathogenetic justification for the use of therapeutic plasma exchange in the complex of preoperative preparation of patients with non-small cell lung cancer complicated by the inflammatory process

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ABSTRACT

Purpose of the study. Determination of pathogenetic substantiation and indication criteria for the inclusion of extracorporeal detoxification methods in preoperative preparation of patients with non-small cell lung cancer (NSCLC) complicated by inflammation.

Patients and methods. This study included the data on 222 patients with newly diagnosed stage I–IV NSCLC referred for elective surgical treatment to the Department of Thoracic Oncology, National Medical Centre for Oncology, in 2017–2019. Endogenous intoxication was evaluated in all patients depending on the leukogram results: leukocytic intoxication index (LII), body resistance index (BRI), reactive neutrophil response (RNR), and neutrophil-lymphocyte ratio (NLR). Indicators of the inflammatory response, i.e. interleukin 6 and procalcitonin, were also studied.

Results. 36.5 % of NSCLC patients developed inflammation. That over 70 % of the NSCLC patients showed pronounced clinical and laboratory signs of endogenous intoxication and inhibited protective systems of homeostasis. Initial sub- or decompensated endotoxicosis together with reduced overall reactivity of the body poses a high risk of systemic inflammatory response to antitumor surgical treatment. This justifies the inclusion of extracorporeal detoxification into preoperative preparation of this category of patients as an active preoperative therapy.

Conclusions. Simultaneous elevation of LII, RNR and NLR characterizing the presence of endotoxicosis in sub- and decompensation of endogenous intoxication by own physiological detoxification systems requires an active preoperative preparation with extracorporeal detoxification.

Keywords: lung cancer, inflammatory complications, endogenous intoxication, body reactivity, extracorporeal detoxification, therapeutic plasma exchange

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Compliance with ethical standards: the ethical principles presented by the World Medical Association Declaration of Helsinki, 1964, ed. 2013 were observed in the study. The study was approved by the ethics committee of the National Medical Research Centre for Oncology (extract from the protocol of the meeting No. 19 dated 22/11/2021). Informed consent was received from all participants of the study

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ОРИГИНАЛЬНАЯ СТАТЬЯ

Клинико-патогенетическое обоснование к применению в комплексе предоперационной подготовки больных немелкоклеточным раком легкого, осложненным воспалительным процессом, терапевтического плазмообмена

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РЕЗЮМЕ

Цель исследования. Определить патогенетическую обоснованность и критерии показаний к включению в комплекс предоперационной подготовки больных немелкоклеточным раком легкого (НМРЛ), осложненным воспалительным процессом, методов экстракорпоральной детоксикации.
Пациенты и методы. В исследование включены данные историй болезни 222 больных первично выявленным НМРЛ I–IV стадий, поступивших на плановое хирургическое лечение в отделение торакальной онкологии ФГБУ «НМИЦ онкологии» Минздрава России в период 2017–2019 гг. Всем больным проводили оценку показателей эндогенной интоксикации – лейкоцитарного индекса интоксикации (ЛИИ), индекса резистентности организма (ИРО), реактивного ответа нейтрофилов (РОН), нейтрофильно-лимфоцитарного соотношения (НЛС). Также изучали показатели воспалительного ответа – интерлейкин-6 и прокальцитонин.
Результаты. Выявлено, что развитие воспалительных осложнений у больных НМРЛ наблюдается в 36,5 % случаев. Более чем у 70 % больных впервые диагностированным НМРЛ течение онкологического заболевания сопровождается выраженными клинико-лабораторными признаками эндогенной интоксикации с угнетением защитных систем гомеостаза. Наличие исходного эндотоксикоза в суб- или декомпенсированной форме на фоне снижения общей реактивности организма представляет высокий риск развития генерализованного воспалительного ответа на проведение противоопухолевого хирургического лечения. Это актуализирует включение в комплекс предоперационной подготовки данной категории больных экстракорпоральной детоксикации в качестве активной предоперационной терапии.
Заключение. Одновременное повышение показателей ЛИИ, РОН и НЛС, характеризующих наличие эндотоксикоза в условиях суб- и декомпенсации эндогенной интоксикации собственными физиологическими системами детоксикации, определяют необходимость проведения активной предоперационной подготовки с включением компонента экстракорпоральной детоксикации.

Ключевые слова: рак легкого, воспалительные осложнения, эндогенная интоксикация, реактивность организма, экстракорпоральная детоксикация, терапевтический плазмообмен

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Соблюдение этических стандартов: в работе соблюдались этические принципы, предъявляемые Хельсинкской декларацией Всемирной медицинской ассоциации (World Medical Association Declaration of Helsinki, 1964, ред. 2013). Исследование одобрено этическим комитетом ФГБУ «НМИЦ онкологии» Минздрава России (выписка из протокола заседания № 19 от 22.11.2021 г.). Информированное согласие получено от всех участников

Финансирование: работа проведена при поддержке ФГБУ «НМИЦ онкологии» Минздрава России

Конфликт интересов: все авторы заявляют об отсутствии явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи

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INTRODUCTION

To date, lung cancer (LC) occupies a leading position among all malignant neoplasms, representing a significant socio-economic problem in Russia and the world overall. In the Russian Federation, the increase in morbidity and mortality from LC is especially noticeable among the male population in the age group over 60 years, while 85 % of detected cases are represented by non-small cell lung cancer (NSCLC) [1]. Unfortunately, in more than 70 % of patients, a malignant neoplasm of the lung is diagnosed at the stage of a locally widespread process, or there is a metastatic lesion, including the pleura, the opposite lung, and the chest wall [2].

According to current data, the surgical method in combination with antitumor therapy significantly affects the prognosis of the disease, improving the survival of patients with NSCLC at virtually all stages compared with maintenance therapy [3]. At the same time, the nature of the course of the disease depends not only on the effectiveness of the method used, but also on the occurrence of severe complications that may cause the refusal of specialized care or restriction of full-fledged antitumor treatment.

It is fair to note that all cancer patients are susceptible to various infectious complications, which is 4–8 times more common than in the general population. This is due to a defect in the immune system, provoked by both tumor development and increased catabolic processes against the background of impaired physiological detoxification and excretion processes, as well as secondary changes in organs and tissues due to antitumor therapy [4]. In predicting complications, including septic ones, it is necessary to consider not only the primary infection of the tumor, but also the aggressive tactics of extended operations, including total removal of the organ affected by the tumor and suspected metastatic spots [5]. According to some data, the incidence of inflammatory pulmonary complications in patients with progressive NSCLC ranges from 12 to 40 %, and the mortality rate reaches 26.5–33 % [6]. These indicators are due to several reasons. Thus, endobronchial tumor growth leads to the formation of a secondary inflammatory focus in the lung tissue and in most patients, LC presents as pneumonitis, pleurisy, pleural empyema or lung abscess with pneumonia [7]. In addition, the late stages of LC are characterized by the disintegration of the tumor with the formation of necrosis and an inflammatory zone in the tissue of the affected lung. The necrotic focus becomes a source of intoxication, which is caused by the prolonged intake of cellular breakdown products into the blood [8].

The factors determining the prognosis of the functional state of patients with LC after radical surgical treatment, which involves total organ removal or extended lung resection with regional lymphadenectomy, should also include the features of ensuring gas exchange during surgery. The cessation of air circulation in the lung during surgery provokes a massive release of inflammatory cascade mediators into the bloodstream, and inadequate gas exchange with a decrease in oxygen partial pressure and a decrease in cardiac output cause the development of hypercapnia and tissue hypoxemia [9]. In addition, rotational surgical manipulations on a lung "turned off" from gas exchange contribute to aggravating the situation caused by the powerful release of tumor cell decay products into the general bloodstream, initiating the launch of a systemic inflammatory reaction, the development of acute lung damage in the early postoperative period [7].

In the conditions of the initial inflammatory process, surgical stress, accompanied by functional disorders of the sympathetic nervous system, paradoxical endocrine responses, as well as immunological and hematological changes, it promotes the activation of leukocytes, fibroblasts, endothelial cells, and platelets, followed by massive release of biologically active substances. A cascade of pathological changes and disruption of the normal functioning of the microcirculatory bed in patients with LC leads to the development and rapid progression of acute lung injury, as a result one in three patients dies [10].

Everything listed above determines the relevance of the concept of endotoxicosis correction and of prevention of acute respiratory distress syndrome in patients with NSCLC complicated by the inflammatory process that is already happening in the preoperative period. At the same time, the inclusion of extracorporeal detoxification in the complex of preoperative preparation, which ensures the removal of excessive concentrations of pathognomonic endogenous toxic substances, can probably contribute to improving the results of the inpatient period of care for this category of patients.

The purpose of the study was to determine the pathogenetic validity and criteria of indications for inclusion of therapeutic plasma exchange in the complex of preoperative preparation of patients with NSCLC complicated by the inflammatory process.

MATERIALS AND METHODS

The study included data obtained from the medical histories of 222 patients with primary NSCLC of stages I–IV who were admitted for elective surgical treatment at the Department of Thoracic Oncology of the National Medical Research Center of Oncology, in the period 2017–2019.

The median age in the study group was 61 years, the average age was 63.9 ± 1.7 years, the range was 37–78 years, with 77 % men and 23 % women. The age categories according to the criteria of the World Health Organization were represented by people: under 45 years – 2.3 % (*n* = 5), 45–59 years – 30.6 % (*n* = 68), 60–74 years – 61.7 % (*n* = 137), over 75 years – 5.4 % (*n* = 12). According to preliminary data of clinical examination and histological analysis of the surgical material, the staging of the tumor process was carried out (TNM classification 8-edition, 2017) [11]: $T_1N_0M_0$ in 6.3 % (*n* = 14), $T_{2a}N_0M_0$ in 26.6 % (*n* = 59), $T_{2b}N_0M_0$ in 8.1 % (*n* = 18), $T_3N_1M_0$ in 14.9 % (*n* = 33), $T_{3-4}N_{1-2}M0$ in 36.5 % (*n* = 81), $T_{3-4}N_3M_0$ in 6.7 % (*n* = 15), $T_{3-4}N_{2-3}M_1$ in 0.9 % (*n* = 2) patients. Morphological parameters of the tumor: the largest number was squamous cell carcinoma of varying degrees of differentiation, which was detected in 80.1 % of patients. According to the clinical and anatomical classification of RL, the following were presented: central cancer – 27.45 % (*n* = 61), peripheral cancer – 64.9 % (*n* = 144), peripheral cancer with centralization – 7.65 % of cases (*n* = 17). Surgical treatment included: lobectomy and bilobectomy – 67.9 % (*n* = 55), pneumonectomy – 8.7 % (*n* = 7), pleuropneumonectomy – 4.9 % (*n* = 4), combined pneumonectomy – 17.3 % (*n* = 14), pneumonectomy with tracheal bifurcation resection – in 1.2 % (*n* = 1) to the patient. Clinically significant concomitant diseases were identified: ischemic heart disease – 63.5 %, arrhythmias – 27.5 %, hypertension – 51.7 %, postinfarction cardiosclerosis – 22.9 %, chronic nonspecific lung diseases – 25.2 %, type 2 diabetes mellitus – 18.9 %, deep vein thrombophlebitis of the lower extremities – 28.4 %, gastric ulcer or 12 duodenum – 35.1 % of patients.

The control group consisted of 24 relatively healthy men and women without cancer, comparable in age and gender to the study group.

To diagnose the presence and nature of the course of endogenous intoxication (EI) accompanying the development of the oncological process, all patients upon admission were assessed according to leukogram data for indicators of endogenous intoxication – leukocyte intoxication index (LII), body resistance index (BRI), neutrophil reactive response (NRR), neutrophil-lymphocyte ratio (NLR). The indicators of the inflammatory response – interleukin-6 (IL-6) and procalcitonin (PCT) – were also studied. Criteria for inclusion of patients: primary diagnosed NSCLC in persons over 18 years of age. The exclusion criterion was under the age of 18, small cell lung cancer.

This study was approved by the Ethical Committee of the institution, It was also carried out the prior consent of patients to the processing of their personal clinical and laboratory data for scientific purposes (Protocol No. 19 of 11/22/2021).

The main material for this study was the blood (erythrocytes, plasma) of patients. Blood sampling was carried out in sterile vacuum tubes with preservative in the morning from the ulnar vein when patients were admitted to the hospital before any medical measures were carried out. A general clinical blood test was performed using the colorimetric method. The concentration of PCT was studied by the Brahms PCTQ test (Brahms Diagnostica, Germany), IL-6 in blood serum was determined by enzyme immunoassay (Vector-Best reagents, Novosibirsk).

Statistical verification of compliance with the normal distribution was carried out according to the Shapiro-Wilk and Kolmogorov-Smirnov W-criterion, the results are presented in the form of $M \pm m$ (M is the sample mean, m is the error of the mean, the median (*Me*), which in all groups practically did not differ from *M*, and the interquartile range in the form of a calculation of the lower and upper quartiles: (Q25 and Q75).

STUDY RESULTS

A retrospective analysis of the data from 222 medical histories showed that in 81 patients (36.5 %), the manifestation of cancer manifested clinical signs of the inflammatory process and was diagnosed as

paracancerous pneumonia in 11, pneumonitis in 62, pleuritis and pleural empyema in 8 cases. These patients formed the basis for further research.

An analysis of the data of 81 patients in whom the course of NSCLC was complicated by inflammatory complications indicated that 58 patients (71.6 %) were initially diagnosed with central LC, 6 patients (7.4 %) had a peripheral form and 17 patients (21.0 %) had peripheral cancer with centralization of the process. In the group with complications, 92.9 % (*n* = 75) of men and 7.1 % (*n* = 6) of women. According to age indicators, the group of patients in the age category 60–74 years prevailed 59.3 % (*n* = 48), then 45–59 years – 33.3 % (*n* = 27), at the age of 45 years and over 75 there were 3 patients (3.7 %). The complicated course was more often observed in patients with stage 3a – in 64.4 % (*n* = 52), then 2b – 21.1 % (*n* = 17), 3b – in 11.1 % (*n* = 9), stage 2a and stage 4 in 2 patients.

In 69 of 81 (85.2 %) patients, clinical signs of EI were noted, which had manifestations in the form of complaints of weakness and increased fatigue, fever with varying degrees of myalgia, sleep disorders and decreased psychoemotional activity, or a combination of these clinical signs of EI. When analyzing the white blood cell panel, it was revealed that upon admission, 63 out of 81 (77.7 %) patients had laboratory signs of EI due to tumor autolysis, and in some cases with the addition of bacterial infection – 22 (27.2 %) (Table 1).

It was noted that in 13 (16.0 %) patients with NSCLC with the development of mild EI, stability of the general reactivity of the body with a compensated state of homeostasis was observed. In 19 (23.5 %) patients, signs of mild EI were accompanied by inhibition of general reactivity, but the stability of homeostasis was ensured by detoxification systems of the body, the level of NRR was within physiological norms. In 10 (12.3 %) patients, a mild degree of EI was recorded with signs of inadequate compensation due to inhibition of the general reactivity of the body and instability of homeostasis – in addition to an increase in LII, an increase in the level of NRR and NLR was observed. In 21 (25.9 %) patients, an average degree of severity of EI was revealed with a marked decrease in BRI, a manifestation of subcompensation or decompensation of physiological detoxification systems, which was manifested by a significant increase in relative to normal values of neutrophil reactive response indicators.

Laboratory signs of initial systemic inflammation were revealed in 8 out of 81 (9.9 %) patients with initially diagnosed pleurisy and pleural empyema, according to IL-6 and PCT indicators. The serum concentration of PCT was 0.422 ± 0.15 ng/ml, exceeding the values of healthy people by 3.7 times ($p < 0.001$). The IL-6 values were 67.3 ± 4.1 pg/ml, which exceeded the normal values by 14.3 times ($p < 0.001$).

The probability that a full-fledged and radical surgical treatment in these patients in conditions of failure of homeostasis and protective systems of the body can provoke a further decrease in compensatory reactions with the subsequent development of systemic and organ dysfunctions. An analysis of the nature of the course of the early postoperative period in these patients showed that 28 out of 81 (34.6 %) patients were diagnosed with complications in the first three days after surgery – acute respiratory distress syndrome, pneumonia, sepsis, multiple organ failure. In all these patients, in the preoperative period, according to leukogram data, the presence of mild and moderate EI was recorded in combination with a decrease in overall reactivity and the state of sub- and decompensation of EI by physiological detoxification systems of homeostasis, an increase in NLR indicators, which amounted to 93.3 % of the total number of patients with initially identified disorders according to leukogram data (28 out of 30 patients). The hospital mortality rate in this cohort of patients was 28.6 % with a total mortality rate of 5 %.

The severity of postoperative complications and high mortality have determined the relevance of the development and implementation of the concept of reducing the risk of early post-surgical complications at the stage of the preoperative period.

DISCUSSION

In general, the data accumulated to date indicate that in the conditions of actively developing surgical technologies, personalization of targeted and radiotherapy, the long-term results of treatment of patients with NSCLC remain disappointing [12]. It is obvious that a locally widespread tumor process with an inflammatory component is the cause of a number of pathological transformations that can lead to severe systemic complications in patients with LC. The data obtained in the study indicate ini-

tially pronounced changes in the functional state of patients with NSCLC. Thus, in the preoperative period, 71.55 % of patients registered the tension of non-specific protective systems of the body with simultaneous detection of limited reserve capabilities of the immune system.

To obtain a complete picture of the initial state of protective, including physiological detoxification systems, we conducted a retrospective analysis of the medical histories of patients with NSCLC with the determination of the level of integral intoxication indices LII, NRR, BRI, NLR. The leukocyte intoxication index (LII is a characteristic indicator of tissue degradation processes and various levels of EI. In fact, the formula represents the absolute ratio of the number of neutrophilic leukocytes to lymphocytes, monocytes, eosinophils:

LII = (4 MC + 3 MMC + 2 RSN + SN) × (PC + 1) / (Lf + M) × (E + 1), where MC are myelocytes, MMC – metamyelocytes, RSN – rod-shaped neutrophils, SN –

Table 1. LII, NRR, BRI, NLR values in patients with NSCLC prior to the surgical intervention (*M ± m*)

Endogenous intoxication level	White blood cell panel indicators (U)			
	LII (with normal range 1–1.6 ± 0.2)	BRI (with normal range 50–100)	NRR (with normal range 10.6 ± 2.1)	NLR (with normal range 1–2.1 ± 0.1)
EI absence, stability of the general body reactivity (*n* = 18)	1.101 ± 0.307 1.004 (0.4; 2.112) *p* = 0.000000	89.82 ± 2.36 91.22 (82.24; 98.6) *p* = 0.014440	11.674 ± 1.31 11.4 (4.295; 18.95) *p* = 0.001268	1.262 ± 0.412 2.724 (1.1; 1.427) *p* = 0.011258
Mild EI. stability of the general body reactivity, physiologic EI compensation (*n* = 13)	1.603 ± 0.114 1.559 (1.1; 3.012) *p* = 0.01024	74.62 ± 3.32 76.42 (72.44; 81.5) *p* = 0.010140	13.684 ± 1.11 14.4 (12.999; 15.96) *p* = 0.001277	1.844 ± 0.611 1.661 (1.541; 1.997) *p* = 0.011001
Mild EI, decrease in the general body reactivity, physiologic EI compensation (*n* = 19)	3.603 ± 0.417* 3.154 (2.4; 5.232) *p* = 0.000000	49.55 ± 3.46 46.25 (44.43; 58.1) *p* = 0.021040	13.085 ± 1.62 12.4 (10.991; 16.75) *p* = 0.001441	2.242 ± 0.312 2.724 (1.7; 3.227) *p* = 0.011258
Mild EI, decrease in the general body reactivity, physiologic EI subcompensation. (*n* = 10)	3.422 ± 0.312* 3.214 (2.9; 5.889) *p* = 0.010102	41.09 ± 2.34* 42.34 (32.29; 48.4) *p* = 0.010630	19.24 ± 1.27 19.1 (18.399; 24.92) *p* = 0.001252	7.173 ± 0.227* 6.664 (6.2; 8.138) *p* = 0.011056
Moderate EI, decrease in the general body reactivity, physiologic EI compensation. (*n* =11)	3.206 ± 0.217* 2.812 (2.2; 5.435) *p* = 0.020101	36.22 ± 3.41* 35.33 (31.11; 46.1) *p* = 0.010442	36.22 ± 3.21* 35.22 (29.30; 47.11) *p* = 0.01102	9.402 ± 0.217* 9.661 (8.6; 10.286) *p* = 0.010256
The average degree of EI, a decrease in the overall reactivity of the body, the physiological inadequacy of EI compensation (*n* = 10)	3.992 ± 0.202* 3.913 (3.2; 6.204) *p* = 0.012135	21.88 ± 3.11* 20.24 (16.37; 24.2) *p* = 0.010625	28.11 ± 2.83* 26.93 (22.12; 36.4) *p* = 0.010331	13.453 ± 0.212* 13.254 (12.2; 15.931) *p* = 0.012401

Note: * – $p < 0.05$ compared to the indicators in healthy people. LII – Leucocytinc indicator of intoxicatin, NRR – neutrophil reactive response, BRI – body resistance index, NLR – neutrophil-lymphocytic ratio

segmented neutrophils, PC – plasma cells, Lf – lymphocytes, M – monocytes, E – eosinophils.

LII is one of the most common intoxication indices, the indicators of which are: norm – 0.62–1.6 U, mild degree of intoxication – 2.7–3.7 U; average degree 3.6–4.8 U; severe degree – 5.8–8.5; above 8.6 U – extremely severe degree of EI. An increase in LII indicators to 4–9 U indicates the presence of bacterial toxins, the interval from 2 to 3 U is an indicator of intoxication by autolysis products. In addition to LII, the body resistance index (BRI) is considered as an objective indicator of EI, which is calculated as the ratio of the number of leukocytes to the product of the patient's age by the LII coefficient.:

BRI = L (thousand/l) / patient's age × LII.

BRI indicators vary from 50 to 100 U. At the same time, low BRI numbers indicate the development of an acute septic process.

The neutrophil NRR is also an EI index and is equal to the product of the sum of myelocytes, young (a coefficient of 1 is added if the total is less than one) multiplied by the percentage of rod-shaped and segmented neutrophils divided by the product of the sum of the percentage of basophils, lymphocytes, and monocytes by the number of eosinophils.

NRR = ((MC + MMC +1) × RSN × SN) / ((Lf + B + M) × E), where MC are myelocytes, MMC – metamyelocytes, RSN – rod-shaped neutrophils, SN – segmented neutrophils, E – eosinophils, Lf – lymphocytes, M – monocytes, B – basophils. The normal values of NRR are 10.6 ± 2.2 rel. U. NRR level 15–25 rel. U. compensation of EI is indicated, 26 –40 rel. U – subcompensation, more than 40 rel. U – decompensation of the inflammatory process [13].

There is no doubt about the objectivism of evaluating EI indicators with the possibility of predicting the complicated course of the early postoperative period using integral intoxication indices calculated from a leukogram. Undoubtedly, this is an urgent and effective way that allows in a short time, according to a general blood test, to assess the initial state of the patient's homeostasis with the determination of EI and to develop tactics for necessary and timely treatment. In addition, according to modern data, the integral indicators of the neutrophil reactive response have a pronounced informative character. This criterion characterizes the effects of toxins on the change in the ratio index of cells with varying degrees of nuclear differentiation (rod-shaped and segmented neutrophils). Numerous studies have determined the role of the neutrophil-lymphocyte ratio as a marker of prognosis and severity of chronic diseases such as cirrhosis of the liver, cholecystitis, pancreatitis, chronic obstructive pulmonary disease, as well as in determining the risk of cardiovascular complications in cardiac surgery. The Russian and foreign literature reflects aspects of the dynamics of NLR indicators in oncology, which shows the prognostic significance of this indicator [14]. The role of activated neutrophils in the reactivity of the body determines the restructuring of metabolic processes, migration and adhesion, the formation of regulatory and secretory functions. A number of authors believe that an increase in NLR is one of the signs of activation of systemic inflammatory processes in patients with multiple organ dysfunction syndrome, in which, due to increased secretion of inflammatory mediators and cytokines, the role of neutrophils is important. Numerous clinical studies indicate a certain sensitivity of NLR for stratification of the systemic inflammatory response of the body in infection and bacteremia, which has an important prognostic value [15].

In addition, it is generally recognized that the course of the disease largely depends on the reactivity of the body, which is largely determined by the immune system. IL-6 and PCT levels are true and chronologically valuable biomarkers of the development of an inflammatory response. These indicators demonstrate a pronounced stimulation of immune reactions in the structure of the inflammatory response of the patient's body, which makes it possible to choose a rational and timely therapy tactic. The prognostic significance of the markers is determined by the fact that the increase in indicators indicates the development of an unfavorable course of the disease [16].

The coexistence of tumor and inflammatory processes in patients with NSCLC is associated with a significant increase in the number of postoperative complications, including inflammatory genesis, which, accordingly, worsens the prognosis and treatment outcomes of the hospital period of this category of patients. In the studied group of patients, the incidence of purulent-septic complications was 36.5 % of cases. We studied the nature of early postoperative complications in patients with NSCLC.

Of the 222 patients, 141 (63.2 %) had an uncomplicated course, and 81 (36.5 %) patients had a complicated course. Early postoperative complications were diagnosed in 28 (34.5 %) patients. At the same time, 34.6 % of these patients in the early postoperative period (the first 3 days after surgery) revealed the development of life-threatening complications: acute respiratory distress syndrome, pneumonia and others. It was revealed that the course of cancer in 81 patients with a complicated course of the malignant process was accompanied by the development of endogenous intoxication, determined by an increased level of LII and NLR. At the same time, only in 28 patients with a complicated course of the early postoperative period, a significant increase in the indicators of the neutrophil reactive response was recorded, characterizing the inadequacy of compensation for EI by physiological detoxification systems of homeostasis, in some cases in combination with a decrease in the reactivity of the body. In patients with severe postoperative complications, the values of inflammatory markers turned out to be indicative: the PCT content exceeded the normal limits by 3.7 times, and IL-6 by 14.3 times, which indicated systemic inflammation.

Taking into account the presence of endotoxicosis and systemic inflammatory response in the studied patients, the complex of standard preoperative preparation should be supplemented with extracorporeal detoxification. The choice of the therapeutic plasma exchange (TPE) method is justified by its maximum detoxification potential, which allows removing all types of toxic substances from the bloodstream, including those associated with proteins. During the TPE procedure, inflammatory mediators actively adhere from the systemic bloodstream to the filter membrane, which reduces the risk of generalized systemic inflammation and, as a result, acute damage to the lung parenchyma [17].

The study made it possible to establish that the manifestation of cancer in patients with stage I–IV LC is characterized by the presence of endogenous intoxication of varying degrees of compensation. In this regard, it is justified to conduct detoxification therapies in the preoperative period in patients with the manifestation of EI in combination with inhibition of the general reactivity of the body and instability of homeostasis. It is most likely that full-fledged and radical surgical treatment in these conditions can provoke a further decrease in the compensatory potential of homeostasis with the subsequent development of systemic disorders, which justifies the need for active preoperative preparation of patients with NSCLC aimed at preventing severe inflammatory complications.

An example of the development of life–threatening complications in this category of patients is the clinical case of treatment of a patient with acute damage to a single lung after radical surgery – pneumonectomy, described by us in 2020 [18]. The presented clinical example demonstrates the severe course of the postoperative period in a patient 67 years after radical surgical treatment for cancer of the lower lobe of the left lung $cT_3N_0M_0$ art. II, with disintegration and abscessing paracancerous pneumonia, a condition after 3 courses of polychemotherapy. The scope of the operation included an extended combined pneumonectomy on the left, resection of the left atrium, resection of the pericardium, partial pleurectomy, plastic pericardium with polypropylene mesh. The severity of the patient's condition was due to the development of generalized inflammation with acute damage to a single lung on the 1st day of the postoperative period. Respiratory function was compensated by artificial lung ventilation (LV) (Hamilton G5 device). Ventilation parameters: respiratory rate – 16 v min.; airway pressure – 10 cm of water; positive pressure at the end of exhalation (Positive pressure at the end of exhalation – PEEP) – 5 cm of water; fraction of oxygen in the inhaled air (Fraction of Inspired Oxygen – FiO_2) – 80 %; respiratory volume – 330 ml; minute volume of respiration – 5.5 l/min. Against this background, SpO_2 is 90 %. Indicators of acid-base state: partial pressure of carbon dioxide in arterial blood (pCO_2) 36.5 mmHg; partial pressure of oxygen in arterial blood (pO_2) 114 mmHg; pH 7.43; base deficit (BE) 0.2; bicarbonate ($HCO_{3.}$) 32.4 mmol/L. According to blood tests: leukocytosis 32 × 10^9/l; neutrophilosis 80 %; leukocyte activity of endotoxin – 0.67 (Response – 0.92); PCT – 46 ng/ml; IL-6–1860 pg/ml. X-ray examination data: inflammatory infiltration in the lower lateral sections of the only lung. The probability of death on the MPM II scale (Mortality prediction model) was 75.3 %, which required a complex of high-tech intensive treatment with the inclusion of an extracorporeal detoxification program. In this case, the outcome of the hospital treatment period was favorable, the patient was discharged

from the hospital. Saving the life of this patient became possible with full-fledged treatment, timely inclusion in the treatment complex of extracorporeal detoxification. At the same time, it is possible that active preoperative preparation aimed at relieving the severity of EI and optimizing the functional state of the body's own physiological detoxification systems in the preoperative period could prevent the development of such a formidable complication in the postoperative period. However, this dictates the need for confirmation and, therefore, further research.

CONCLUSIONS

It was revealed that the development of inflammatory complications in patients with NSCLC is observed in 36.5 % of cases. In conditions of a combination of a tumor disease and an inflammatory component, a decrease in the compensatory capabilities of the patient's body can be expected with a high degree of probability and, as a result, the development of inflammatory complications of varying severity in the early postoperative period. The data obtained demonstrate that in more than 70 % of patients with newly diagnosed NSCLC, the course of cancer is accompanied by pronounced clinical and laboratory signs of EI with inhibition of protective homeostasis systems.

The presence of initial endotoxicosis in a sub- or decompensated form against the background of a decrease in the general reactivity of the body poses a high risk of developing a generalized inflammatory response to antitumor surgical treatment. This actualizes the inclusion of extracorporeal detoxification as an active preoperative therapy in the complex of preoperative preparation of this category of patients.

The simultaneous increase in the indicators of LII, NRR and NLR, characterizing the presence of endotoxicosis in conditions of sub- and decompensation of EI by their own physiological detoxification systems, determine the need for active preoperative preparation with the inclusion of a component of extracorporeal detoxification, i. e. therapeutic plasma exchange.

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Kharagezov D. A. – carried out the development of the research design;
Popova N. N. – provided with clinical support of the study.