THE INFLAMMATORY STATUS AND LYMPH NODE METASTASES IN NON-SMALL CELL LUNG CANCER

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Abstract

Introduction. The development of inflammation is characterized by changes in blood hematology parameters and indices. Various inflammatory parameters are used to assess the inflammatory status (IS) during cancer treatment. Recent studies have revealed a relationship between tumor progression and the presence of chronic inflammation. Consequently, there have been many attempts to predict the risk of tumor recurrence and distant metastases, as well as patient’s survival assessing the various inflammatory markers. The relationship between IS parameters and lymph node metastasis remains poorly understood in non-small cell lung cancer (NSCLC).

Material and Methods. The prospective study included 35 patients with NSCLC (T1–4N0–2M0). Seventeen patients received 2–3 cycles of neoadjuvant chemotherapy (NAC). A leukocyte formula was determined in the peripheral blood and inflammatory indices, such as neutrophils to lymphocytes ratio (NLR), platelets to lymphocytes ratio (PLR), lymphocytes to monocytes ratio (LMR) and systemic immuno-inflammatory index (SII) were calculated. In addition, the concentrations of fibrinogen, C-reactive protein (CRP) and cortisol were evaluated.

Results. NAC alone did not significantly change the parameters of patients’ IS. Lymph node metastases were associated with changes in parameters indicating the enhanced IS. In the group of patients who did not receive NAC, lymph node metastasis was associated with fibrinogen blood levels (cut-off value 5.35 g/L), PLR index value (cut-off value 7.18) and cortisol blood concentration (cut-off value 414 nmol/mL). The confidence level was χ²=10.118; p=0.018. In the group of patients who received NAC, lymph node metastasis was associated with the leukocyte count (cut-off value 7.1×10⁹/L), PLR index value (cut-off value is 7.18) and CRP blood concentration (cut-off value is 8.5 mg/L). The confidence level was χ²=8.193; p=0.042.

Conclusion. Risk of lymph node metastasis in NSCLC is associated with IS. Parameters of IS can be used to predict the risk of lymph node metastases.

Key words: non-small cell lung cancer, inflammatory status, neoadjuvant chemotherapy, lymph node metastasis.
СВЯЗЬ ПАРАМЕТРОВ ВОСПАЛИТЕЛЬНОГО СТАТУСА С РАЗВИТИЕМ ЛИМФОГЕННЫХ МЕТАСТАЗОВ У БОЛЬНЫХ НЕМЕЛКОКЛЕТОЧНЫМ РАКОМ ЛЁГКОГО

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Аннотация

Введение. Развитие воспаления находит отражение в изменении ряда гематологических показателей и индексов, объединенных понятием воспалительный статус (ВС). Исследования последних десятилетий выявили связь прогрессии опухолей с наличием хронического воспаления. Предпринимаются попытки прогнозировать риск возникновения рецидивов и отдаленных метастазов опухоли, а также выживаемости пациентов на основе различных воспалительных индексов. Наименее изученной остается ассоциация ВС с лимфогенным метастазированием немелкоклеточного рака лёгких (НМРЛ). Материал и методы. Исследование проведено на 35 больных, прооперированных по поводу НМРЛ T1–4N0–2M0 стадии, 17 больным было проведено 2–3 курса неоадъювантной химиотерапии (НАХТ). В периферической крови определяли лейкоцитарную формулу и рассчитывали «воспалительные» индексы: отношение количества нейтрофилов к количеству лимфоцитов (NLR), количество тромбоцитов к количеству лимфоцитов (PLR), количество лимфоцитов к количеству моноцитов (LMR) и системный иммуно-воспалительный индекс (SII) как отношение произведения числа нейтрофилов и тромбоцитов к числу лимфоцитов. Кроме этого, оценивали концентрацию фибриногена, С-реактивного белка (СРБ) и кортизола. Результаты. Неоадъювантная химиотерапия существенно не изменяет параметры ВС у пациентов. Наличие лимфогенных метастазов ассоциировано с изменением параметров, свидетельствующих об усилении ВС. У больных, не получавших НАХТ, значимыми для лимфогенного метастазирования были изменения уровня фибриногена (пороговый уровень – 5,35 г/л), величины индекса PLR (пороговый уровень – 7,18) и кортизола (пороговый уровень – 414 нмоль/мл). Степень достоверности χ²=10,118; р=0,018. В группе пациентов, получавших НАХТ, лимфогенное метастазирование было ассоциировано с количеством лейкоцитов (пороговый уровень – 7,1×10⁹/л), величиной индекса PLR и концентрацией СРБ (пороговый уровень – 8,5 мг/л). Степень достоверности данной модели: χ²=8,193; р=0,042. Заключение. Риск лимфогенного метастазирования при НМРЛ ассоциирован с ВС, его параметры, с учетом НАХТ, могут быть использованы для прогноза риска развития лимфогенных метастазов.

Ключевые слова: немелкоклеточный рак легких, воспалительный статус, неоадъювантная химиотерапия, лимфогенное метастазирование.

Introduction

Chronic inflammation contributes to the onset and progression of the tumor (recurrence, metastasis). It has been shown that the chronic inflammation often precedes the development of some malignant tumors [1]. The focus of chronic persistent inflammation may be the site of the pre-niche formation [2], then the pre-metastatic niche [3] and, subsequently, metastasis. Additionally, it is known that surgical removal of a primary tumor is a stressor, on the one hand, and the cause of local inflammation and a source of pro-inflammatory factors on the other hand. Thereby, the risk of metastases and recapses in the early postoperative period is increased. The use of anti-inflammatory drugs during this period prevents their occurrence [4].

The term «inflammatory status» (IS) is rarely used. Inflammatory status is the state of the macroorganism characterized by elevated biochemical, cytokine, and cellular parameters traditionally associated with the development of inflammation and determined in peripheral blood. The counts of neutrophils, lymphocytes, monocytes and platelets, as well as their ratios – inflammatory indices (NLR [5, 6], PLR [7, 8], SII [9–11], LMR [12, 13] and others) are used as the parameters of IS.

It has been shown that the values of these inflammatory indices are associated with the patient’s survival in various types of cancer. Recently, there have been many attempts to predict the risk of recurrence and distant metastases, as well as patient’s survival after assessing the various inflammatory indices. The systemic immuno-inflammatory index (SII) is the most informative among these indices [10, 11]. However, it should be noted that the relationship between IS parameters and lymph node metastasis remains poorly understood.
Although inflammatory indices as well as the count of different forms of blood leukocytes characterize systemic IS, it is well known that all these parameters are sensitive to changes in the concentration of glucocorticoids and other hormones that reflect the general adaptation syndrome. In this regard, the level of IS indices simultaneously reflects the activation of the hypothalamic-pituitary-adrenal axis [14, 15]. The patient’s IS parameters are influenced by the primary tumor, neoadjuvant chemotherapy (NAC), as well as the development of recurrence and metastases, which are inducers of the pro-inflammatory cytokine synthesis and other pro-inflammatory factors, on the one hand, and stressors, on the other hand.

The purpose of our study was to examine the relationship between the IS parameters and lymph node metastasis in NSCLC before and after NAC.

Material and Methods

The prospective study included 35 patients, male – 27 (77 %), female – 8 (23 %) with T1–4N0–2M0 NSCLC treated at Cancer Research Institute, Tomsk National Research Medical Center (tabl. 1). The study was approved by the Local Committee for Medical Ethics of our Institute, and informed consent was obtained from all patients prior to analysis. Seventeen (49 %) of the 35 patients received 2–3 courses of neoadjuvant chemotherapy (paclitaxel 175 mg/m², IV day 1 + carboplatin AUC 6, IV day 1 with a 3-week interval). Dexamethasone was given to patients to reduce adverse reactions to paclitaxel + carboplatin. Patients were followed up for 5 years after treatment initiation.

The histological diagnosis of lung cancer was made according to «Histological classification of lung tumors» (WHO, Geneva, 2003). Squamous cell carcinoma was diagnosed in 20 (57 %) cases and lung adenocarcinoma was diagnosed in 14 (40 %) cases. Squamous cell carcinoma was more frequently observed in men (20 cases, 74 %). Adenocarcinoma was revealed in 7 women and mucoepidermoid carcinoma in 1 woman. Synchronous lymph node metastases were detected in 13 patients (37 %).

Venous ethylenediaminetetraacetic acid (EDTA) blood samples were taken 12 days before surgery, but not earlier than 23 weeks after the last course of NAC and glucocorticoids in the scheme «paclitaxel + carboplatin». Indicators of the general blood test and the leukocyte formula, as well as the concentration of the

| Клинико-патологические показатели пациентов с немелкоклеточным раком легкого | The clinicopathological parameters of the patients with the non-small cell lung cancer |
|-----------------------------|------------------------------------------------------------------|
| Клинико-патологические показатели/ | Clinicopathological parameters                               |
| Возраст (лет)/Age (year)    | 62 ± 6.87                                                        |
| Пол/Sex                     | Мужской/Male 27 (77 %)                                           |
| Женский/Female              | 8 (23 %)                                                        |
| Тип НМРЛ/NSCLC variant      | Плоскоклеточный рак/Squamous cell carcinoma 20 (57 %)           |
| Аденокарцинома/Adenocarcinoma| 14 (40 %)                                                      |
| Мукоэпидерmoidный рак/Mucoepidermoid carcinoma | 1 (3 %)        |
| Лимфатический статус/Lymph node status | Нет/No 22 (63 %)   |
| Неoadъювантная химотерапия/Neoadjuvant chemotherapy | Да/Yes 18 (51 %)   |
| Операция/Surgery            | Лобэктомия/Lobectomy 26 (74 %)                                 |
| Пневмоэктомия/Pulmonectomy  | 9 (26 %)                                                       |
| Размер опухоли/Tumor size    | Т1 2 (5.7 %)                                                    |
| Т2 11 (31.4 %)               |                                                                |
| Т3 19 (54.3 %)               |                                                                |
| Т4 3 (8.6 %)                 |                                                                |
| Стадия/Stage                | I 2 (5.7 %)                                                     |
| IIа 9 (25.7 %)               |                                                                |
| IIb 2 (5.7 %)                |                                                                |
| IIIа 19 (54.3 %)             |                                                                |
| IIIб 3 (8.6 %)               |                                                                |
The acute phase of inflammation protein – fibrinogen, were determined by standard hematological methods. The concentration of another «inflammatory» C-reactive protein (CRP) and cortisol was determined by enzyme immunoassay in accordance with the protocols of manufacturers («HEMA» and «VECTOR-BEST», Russia). The «inflammatory» indices, such as NLR – neutrophil-to-lymphocyte ratio, PLR – platelet-to-lymphocyte ratio, LMR – lymphocyte-to-monocyte ratio and systemic immune-inflammation index SII – (neutrophil count × platelet count / lymphocyte count) were calculated.

All statistical analyses were performed in the GraphPad Prism version 8.3.0 (GraphPad Software, USA). The assessment of the normal distribution of the results was performed using the Shapiro–Wilk test. The significance was assessed using the nonparametric Mann–Whitney test (for independent samples). The data were presented as the median (Me) and the upper and lower quartiles (Q1–Q3). The logistic regression models were developed for predicting lymph node metastases. The threshold level of indicators was determined using ROC analysis for development of the logistic regression models. Two-sided p-values of <0.05 were considered statistically significant, p-values of ≤0.1 were considered as trends.

**Results**

The IS parameters were analyzed in patients with NSCLC before surgical treatment. The clinicopathological parameters of the patients with NSCLC are presented in Tabl. 1. A tentative comparison of patients’ parameters with regard to the age, gender, and NSCLC type showed no statistical differences. This made it possible to exclude the influence of these parameters on the study results.

**Effects of neoadjuvant chemotherapy on the IS parameters**

Neoadjuvant chemotherapy did not cause significant changes in the IS parameters in patients with NSCLC regardless of the presence or absence of lymph node metastases (fig. 1).
Association of IS parameters with lymph node metastasis in patients without NAC

The relationship between the IS parameters and lymph node metastasis was analyzed in patients, who did not receive NAC before surgical treatment. Lymph node metastases in NSCLC patients were shown to be associated with decreased lymphocyte count (p=0.09) and LMR index (p=0.09) compared to patients without lymph node metastases (fig. 2). Besides, the neutrophil (p=0.1) and monocyte (p=0.1) counts and the NLR index (p=0.1) were tended to increase (fig. 2). The platelet count and PLR index, as well as the SII index and ESR (fig. 2) were not associated with the presence of lymph node metastases.

Thus, lymph node metastasis was associated with a strong trend towards enhanced IS, in which the lymphocyte count and the LMR index were decreased and the neutrophil count and the NLR index were increased. However, similar changes (drift in the lymphocyte and neutrophil ratio in favor of neutrophils) were also typical for the glucocorticoid effects.

Association of the IS parameters with lymph node metastasis in patients with NAC

After NAC, a strong trend towards decrease in the lymphocyte count (p=0.06) and increase in the platelet count (p=0.07) and SII index (p=0.08) was observed. The PLR index was significantly higher (p=0.02) in NSCLC patients with lymph node metastases compared to patients without lymph node metastases (fig. 3). Thus, IS parameters were higher in patients with lymph node metastases compared to patients without metastases regardless of NAC administration.

Prediction of lymph node metastasis in patients with NSCLC depending on the NAC administration

Differences in the IS parameters associated with lymph node metastases allowed us to use a multifactor analysis to predict NSCLC progression. The method of logistic regression revealed a complex of relationships between the studied parameters, which was associated with a high risk of lymph node metastases in patients with NSCLC. The logistic regression model also included parameters which did not differ in groups with the presence and absence of lymph node metastases after the Mann-Whitney test (tabl. 2). The cut-off value of indicators was determined using ROC analysis for development of the logistic regression model.

Fig. 2. The IS parameters depending on the presence of lymph node metastases in NSCLC patients, who did not receive NAC.
Table 2/Table 2

The CRP, cortisol and fibrinogen concentrations in NSCLC patients depending on the lymph node metastases and NAC administration

| Parameters/ Параметры | NАХТ-/NAC- | N+ | NАХТ+/NAC+ | N+ |
|-----------------------|------------|----|------------|----|
| CRP, mg/l/ СРБ, мг/л | 5.6 (2.8–7.8) | 8.8 (4.5–9.1) | 6.3 (4.2–8.3) | 11.4 (4.7–18.0) |
| Cortisol, nmol/L/ Кортизол, nmol/L | 403 (312–488) | 350 (307–364) | 387 (321–454) | 377 (231–524) |
| Fibrinogen, g/L/ Фибриноген, г/л | 5.4 (4.7–6.8) | 5.4 (4.7–6.6) | 6.9 (5.7–7.0) | 6.5 (5.6–7.6) |

The CRP, cortisol and fibrinogen blood levels and leukocyte counts were included in the logistic regression model for patients without NAC. Regression model confidence level was $\chi^2=10.118$; $p=0.018$. The sensitivity of this model was 87.5 %, the specificity was 100 %. The parameters of ROC curve analysis are demonstrated in Tabl. 3 and Fig. 4.

The leukocyte blood count (cut-off value: $7.1 \times 10^9$/L), PLR index value (cut-off value: 7.18) and CRP blood concentration (cut-off value: 8.5 mg/L) before surgical treatment were included in the logistic regression model for patients with NAC administration. Regression model confidence level was $\chi^2=8.193$; $p=0.042$. The sensitivity of this model was 100 %, the specificity was 100 %.

Table 3/Table 3

Area under curve (AUC), cut-off values, sensitivity and specificity for IS parameters in NSCLC patients

| Parameters/ Параметры | AUC | Стандартная ошибка/ Std Error | Р значение/ P value | Пороговые значения/ Cut-off value | Чувствительность – Специфичность/ Sensitivity – Specificity |
|-----------------------|-----|-------------------------------|--------------------|----------------------------------|-----------------------------------------------|
| Leukocytes/ Лейкоциты | 0.731 | 0.095 | 0.028 | 7.1 | 91.67 % – 59.09 % |
| PLR | 0.818 | 0.074 | 0.003 | 7.18 | 83.33 % – 68.18 % |
| Fibrinogen/ Фибриноген | 0.604 | 0.108 | 0.359 | 5.35 | 81.82 % – 47.06 % |
| Cortisol/ Кортизол | 0.708 | 0.172 | 0.307 | 414 | 100.00 % – 50.00 % |
| CRP | 0.583 | 0.156 | 0.640 | 8.5 | 66.67 % – 87.50 % |

Models. The fibrinogen blood level (cut-off value: $5.35$ g/L), PLR index value (cut-off value: 7.18) and cortisol blood concentration (cut-off value: $414$ nmol/mL) before surgical treatment were included in the logistic regression model for patients without NAC. Regression model confidence level was $\chi^2=10.118$; $p=0.018$. The sensitivity of this model was 87.5 %, the specificity – 100 %. The parameters of ROC curve analysis are demonstrated in Tabl. 3 and Fig. 4.

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Discussion

The levels of different leukocyte forms and inflammatory indices, such as CRP, fibrinogen and ESR are a combination of parameters characterizing the IS. In recent years, an increasing number of studies have shown a relationship between inflammatory indices and cancer progression [5, 6, 9–13]. Based on these data, some inflammatory indices are recommended as the prognostic factors of carcinoma progression [16, 17]. The IS parameters reflect not only the influence of various factors that can cause inflammation, but also a variety of stressful effects. Our data indicate that changes in the studied IS parameters in NSCLC are associated with lymph node metastases and NAC. Moreover, each of these factors simultaneously has a potential proinflammatory and a stressor effect that changes the concentration of adaptive hormones, including cortisol.

The results of our study suggest that lymph node metastasis is associated with a more pronounced level of IS. This is confirmed by changes in the studied parameters, indicating the enhanced IS in patients who did not receive NAC. Apparently, the stress plays a significant role in the mechanism of changes in proinflammatory markers. This may explain why the cortisol concentration, along with other parameters, was included in the regression model for predicting lymph node metastases in NSCLC patients who did not receive NAC; and the total leukocyte count was included in the prediction model in patients who received NAC. Changes in the leukocyte count in this case is due to an increase in the neutrophil count [16, 18].

The influence of NAC on the IS parameters is am- bivalent. On the one hand, preoperative chemotherapy
Conclusion

The IS parameters are integral values associated with lymph node metastasis and NAC in patients with NSCLC. The presence of synchronous lymph node metastases in NSCLC can be predicted using mathematical models based on the appropriate IS parameters before surgical treatment. To predict the presence of lymph node metastases in patients treated and not treated with NAC, different prognostic models have been developed. Further studies are needed to clarify the contribution of inflammation itself and stress changes into the IS parameters.
СВЕДЕНИЯ ОБ АВТОРАХ

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ВКЛАД АВТОРОВ

Письменный Дмитрий Сергеевич: проведение экспериментальной части исследования, статистическая обработка, анализ полученных результатов, составление черновика рукописи.

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Завьялова Марина Викторовна: редактирование статьи, обсуждение результатов исследования.

Родионов Евгений Олегович: набор клинического материала, анализ научной работы.

Таширева Любовь Александровна: редактирование статьи, обсуждение результатов исследования.

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Финансирование
Исследование выполнено при поддержке гранта Президента РФ НШ-2701.2020.7.

Конфликт интересов
Авторы объявляют, что у них нет конфликта интересов.

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Dmitry S. Pismenny: data analysis and interpretation, statistical data analysis, drafting of the manuscript.
Olga E. Savelieva: study concept and design, implementation of the studies, data analysis and interpretation, statistical data analysis, drafting of the manuscript.
Marina V. Zavyalova: editing of the manuscript, discussion of the study results.
Evgeny O. Rodionov: clinical data collection, data analysis.
Liubov A. Tashireva: editing of the manuscript, discussion of the study results.
Sergey A. Tuzikov: data analysis, critical review with valuable intellectual content.
Olga V. Pankova: data analysis critical review with valuable intellectual content.
Vladimir M. Perelmuter: supervision, data analysis, critical review with valuable intellectual content.

Funding
The study was supported by The Council for grants of President of Russian Federation (grant НШ-2701.2020.7).

Conflict of interest
The authors declare that they have no conflict of interest.