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Morphological Features and Morphometric Parameters of the Lungs after Correction with an Immunomodulator Under the Conditions of Experimental Chemotherapy

Shomurodova Mukhayo Rakhmonovna
Bukhara State Medical Institute

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ABSTRACT

Immunotherapy is an innovative method of cancer treatment. It is based on interference in the interaction of the patient's immune system and a malignant tumor. Immunotherapy goes well with classical methods of treatment [Ivanisova D.N., 2022]. The results of the analysis of literature data on the use of immunomodulators in the complex treatment of cancer patients with lung cancer during chemotherapy are presented.

Relevance. Lung cancer is one of the most common causes of death in cancer patients. Among the morphological forms, non-small cell lung cancer (NSCLC) of epithelial origin is most common, represented mainly by adenocarcinoma and squamous cell carcinoma. Neuroendocrine tumors, in particular, small cell lung cancer (SCLC), are much less common. Most cases of lung cancer are diagnosed at advanced stages. Until the 2000s, the decision on the tactics of therapeutic measures was based on the differential diagnosis only between small cell and non-small cell lung cancer. Therefore, all diagnostic measures were aimed at obtaining a small sample of tumor tissue for subsequent simple histological examination, which, together with non-invasive techniques, made it possible to stage the tumor according to the TNM classification. The idea that NSCLC does not have histological variability (NOS), along with the predominant diagnosis already at advanced stages, determined the development of anticancer drugs until the 2000s, during this period, platinum derivatives were included in the basis of drug palliative therapy for stage IV NSCLC [Schiller JH, Harrington D, Belani CP, Langer C, Sandler A, Krook J, et al., 2020]. The need to separate the histological subtypes of NSCLC appeared after the development of new chemotherapy drugs (pemetrexed) and monoclonal antibodies (bevacizumab), which, depending on the morphological type of the tumor, could both improve the results of treatment and initiate pronounced toxic reactions [Scagliotti GV, Parikh P, von Pawel J et al., 2017]. Histochemical and immunohistochemical methods are widely used for the differential diagnosis of adenocarcinoma and squamous cell lung cancer based on the material

obtained by biopsy. In 2011, the International Association for the Study of Lung Cancer, the American Thoracic Society, and the European Respiratory Society (IASLC/ATS/ERS) developed minimum clinical guidelines for the immunohistochemical analysis of NSCLC. Tumors previously classified as undifferentiated should now be classified as squamous cell carcinoma or adenocarcinoma. These changes currently determine the requirements for diagnostic approaches, tools and their further development [Usachev V.S., Ragulin Yu.A., Silantyeva N.K., 2016]. In the last decade, the need for methods of adequate tissue sampling has increased, since modern drugs for the treatment of NSCLC require careful morphological and genomic diagnostics in order to individualize treatment. It is known that cancer is a heterogeneous group of malignant tumors from epithelial tissues characterized by a tendency to infiltrative growth and metastasis, abnormal vascular growth, replicative immortality of cells, their resistance to cytotoxic agents, impaired growth suppressors and immune surveillance, and a stable proliferative signal. The latter is especially prevalent in NSCLC subtypes. A persistent signal for proliferative activity is usually due to genetic mutations in certain oncogenes that code for the operation of tyrosine kinases. Three main genomic events directly lead to the activation of tyrosine kinases in NSCLC: overexpression or amplification (increase in the number of copies of a particular gene), mutations (point or insertion / deletion), and permutations in paired genes (due to the preservation or activation of the kinase domain in oncogenes) [Hanahan D, Weinberg RA., 2021].

Immunotherapy is an innovative method of cancer treatment. It is based on interference in the interaction of the patient's immune system and a malignant tumor. Immunotherapy goes well with classical methods of treatment [Ivanisova D.N., 2022].

Immunotherapy for lung cancer is gaining more and more popularity. One of its promising directions is the development of therapeutic anti-PD 1 and anti-PD-L1 monoclonal antibodies, leading to the reactivation of a specific antitumor immune response. Evaluation of the expression level of PDL1 molecules is considered as a potential biomarker for predicting the effectiveness and duration of treatment for malignant neoplasms, as well as a predictor of response to anti-PD1/PDL1 immunotherapy [14].

The speed and quality of diagnosis, its temporary tumor staging in lung cancer are determined by the effectiveness of diagnostic measures, including the minimum required set of procedures before starting treatment. The ideal situation is when procedures are performed simultaneously that provide biological material for diagnosis, allow for molecular testing, and establish the extent of the tumor for full staging [Giroux Leprieur E, Dumenil C, Julie C, Giraud V, Dumoulin J, Labrune S, et al ., 2017].

Immunotherapy is a fundamentally new method of treating malignant tumors, which has already proven its effectiveness in various solid tumors. Immune checkpoint inhibitors are approved for use in kidney cancer, bladder cancer, melanoma, colon cancer (in the presence of microsatellite instability), hepatocellular cancer, non-small cell lung cancer, etc. Therefore, it was extremely interesting to study the effectiveness of this type of therapy in SCLC - extremely a malignant tumor for which no effective inhibitor has been found in the era of targeted therapy. Over the past 20 years, no new drugs have been registered for the treatment of SCLC. SCLC has always been considered as a tumor with a high immunogenic potential due to its characteristic paraneoplastic syndromes, in particular the Lambert-Eaton syndrome, which manifests itself with increasing myasthenia gravis as a result of an immune response against antigens expressed by both SCLC and nervous tissue. For this reason, SCLC patients with paraneoplastic syndromes

have a better prognosis due to the activation of the immune system against the tumor. The prognosis of patients with SCLC is also affected by the composition of the population of tumor-infiltrating lymphocytes. Thus, it is known that there are significantly more effector CD4+T-lymphocytes in patients with localized SCLC compared with widespread, including those producing interleukin-17, which in turn recruits effector T-lymphocytes, activates dendritic cells and has a direct antiproliferative effect and the ability to induce apoptosis. It is also known that in patients with SCLC with a long relapse-free period, the ratio of effector to regulatory T-lymphocytes is higher than in patients with disease progression. That is, this ratio can affect the dissemination of SCLC. In addition, it is known that the expression of PD-L1 indicates the activation of the T-cell immune response and is associated with a better prognosis in patients with SCLC [Young M.R., 2016]. SCLC is a tumor with one of the highest levels of somatic mutations, including mutations in the DNA repair system [Gazdar A.F., Bunn P.A., Minna J.D., 2017]. The more somatic mutations in the tumor, the more neoantigens associated with the tumor, which ultimately can trigger an adaptive immune response [Sabari J.K., Lok B.H., Laird J.H., Poirier J.T., Rudin C.M., 2017] and increase the effectiveness of immunotherapy [Efremova M., Finotello F., Rieder D., Trajanoski Z, 2017]. It has also been shown for various tumors that mutational load predicts the effectiveness of immunotherapy [Goodman A.M., Kato S., Bazhenova L., Patel S.P., Frampton G.M., Miller V., et al., 2017]. Despite the high level of mutation load, SCLC is characterized by a clear immunosuppressive phenotype. SCLC, including cell lines, is characterized by a low level of expression of antigens of the 1st class of the major histocompatibility complex - HL-A, B, C and β2-microglobulins. And antigens of the 2nd class of the major histocompatibility complex in the tumor (SCLC) and tumor-infiltrating lymphocytes are not detected at all [He Y., Rozeboom L., Rivard C.J., Ellison K., Dziadziuszko R., Yu H., et al., 2017]. Loss of histocompatibility antigens allows SCLC cells to evade the immune response and contributes to resistance to immune checkpoint inhibitors. Despite the high level of mutation load, SCLC is characterized by a low content of tumor-infiltrating lymphocytes and the CD8/CD3 ratio is clearly low [Schalper K.A., Carvajal-Hausdorf D.E., McLaughlin J.F., Altan M., Chiang A.C., Velcheti V. et al., 2016]. Thus, the immune characteristics of SCLC did not allow us to reliably state that immunotherapy would be highly effective, and only clinical studies could give a convincing answer [A.E. Kuzminov et al., 2019].

"The goal of cancer immunotherapy is to get the patient's immune system to work in such a way that it can counteract the growth of a malignant tumor on its own." With regard to chemotherapy, in most cases, its combination with immunotherapeutic drugs is most effective. For example, vaccination with dendritic cells may occur between cycles of chemotherapy, or chemotherapy may precede CAR T cell therapy. Certain chemotherapy regimens can enhance the immune response against tumors, which allows patients to achieve cancer remission faster [Zhilyuk D.V., 2022]. Chemoradiation therapy can be used in a number of nosologies not for the purpose of actively influencing the tumor, but as a conditioning regimen to create favorable conditions for the activity of administered specific autologous CTLs, with which immunotherapy should be started in these cases [6].

At the moment, it is time to think about changing the paradigm of the treatment of certain types of cancer from chemotherapeutic to immunotherapeutic as relatively low toxicity, which allows for a personalized approach to the patient, has a broad base for development, provides a good quality of life for patients and has shown its effectiveness in a number of studies. This requires the formation of treatment protocols based precisely on the principles of immunotherapy

and excluding chemoradiotherapy where it has not demonstrated its effectiveness. Undoubtedly, the implementation of immunotherapeutic programs requires a clinical base with modern laboratories and specialists in the field of cell cultivation, immunology, molecular genetics and can only be implemented in specialized centers with high scientific potential [I.S. Dolgopolov, G.Z. Chkadua, 2018].

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