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LUNG CANCER IMMUNOTHERAPY: STATUS QUO, PROBLEMS, AND PROSPECTS

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Introduction. Lung cancer is the leading cause of cancer mortality in men and women. Due to its high prevalence and significant recurrence rate after standard therapy, the search for new methods of lung cancer treating is an urgent task. A promising treatment strategy is immunotherapy that elicit immune response against tumor cells.

Objective. Evaluation of the clinical efficacy and prospects for the safe use of immunotherapy in malignant neoplasms of the pleural cavity.

Discussion. The introduction of immunotherapeutic approaches, including adoptive cell therapy with tumor-infiltrating lymphocytes (TIL) or CAR-T cells, the development of neoantigen vaccines, oncolytic viruses, in combination with chemotherapy and blockade of immune checkpoints (ICP) have shown optimistic results in preclinical studies and are currently at different stages of clinical trials for safety and efficacy.

Conclusions. Immunotherapy of lung cancer is a promising area of adjuvant therapy. For clinical introduction, immunotherapeutic approaches should be further investigated to increase their effectiveness and minimizing side effects by combining different therapies, improving bioengineered and cellular drugs, and reducing the cost of treatment.

Keywords: lung cancer; adoptive immunotherapy; chimeric T-cell antigen receptor; tumor-infiltrating lymphocytes; immune checkpoint inhibitors; oncolytic viruses

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ИММУНОТЕРАПИЯ РАКА ЛЕГКОГО: STATUS QUO, ПРОБЛЕМЫ И ПЕРСПЕКТИВЫ

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Введение. Рак легкого является основной причиной онкологической смертности и у мужчин, и у женщин. Ввиду высокой распространенности и значительной частоты рецидивов после стандартной терапии поиск новых методов лечения рака легкого является актуальной задачей. Одним из обнадеживающих направлений стала иммунотерапия, целью которой является активация цитотоксического иммунитета против опухолевых клеток.

Цель. Оценка клинической эффективности и перспектив безопасного использования иммунотерапии при злокачественных новообразованиях плевральной полости.

Обсуждение. Внедрение иммунотерапевтических подходов, включающих адоптивную клеточную терапию опухоль-инфильтрирующими лимфоцитами (TIL) или CAR-T- клетками, разработку онковакцин, онколитических вирусов, в комбинации с химиотерапией и блокированием иммунных контрольных точек (ИКТ) показало положительные результаты на стадии доклинических исследований и находится на разных этапах клинических испытаний безопасности и эффективности.

Выводы. Иммунотерапия рака легкого является перспективным направлением адъювантной терапии. Клиническая трансляция иммунотерапевтических подходов нуждается в повышении их эффективности и минимизации побочных эффектов путем комбинации различных методов терапии, совершенствования биоинженерных и клеточных препаратов, а также снижения стоимости лечения.

Ключевые слова: рак легкого; адоптивная иммунотерапия; химерный антигенный рецептор антигена Т-клеток; опухоль-инфильтрирующие лимфоциты; ингибиторы иммунных контрольных точек; онколитические вирусы

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INTRODUCTION

Lung cancer remains the leading cause of cancer deaths worldwide (18.4% of total cancer deaths), resulting in significant socioeconomic losses. According to estimates by GLOBOCAN and the International Agency for Research on Cancer (as of 2018), 2.09 million new cases and 1.76 million deaths from lung cancer were registered, which exceeded the data of 2012 [1]. Due to the long-term asymptomatic course and nonspecific initial symptoms, along with an insufficiently developed strategy of active cancer screening, almost half of patients are diagnosed with this nosology at the metastatic stage of the disease, when radical surgical treatment is almost impossible [2]. According to Kelsey et al., one third of patients diagnosed with the disease and treated in the early stages develop relapse and resistance to chemotherapy [3]. In this regard, the search for new therapeutic methods for lung cancer remains to be an urgent clinical task.

Immunotherapy as a whole represents a broad scientific direction in oncopathology treatment. This direction involves activation of antitumor immunity through the use of antibodies, cytokines, immune cells, chimeric T-cell receptors, inhibitors of immune control points, etc. Immunotherapy has shown its efficacy and safety in the treatment of oncohematological diseases and melanoma [4, 5]. In relation to other solid tumors, clinical studies have shown inconsistent results; however, the prospects of this approach are beyond doubt [6].

The aim of immunotherapy for lung cancer is to enhance the targeted cytotoxicity of immune cells mainly due to specific binding to tumor-associated antigens [7]. This aim is hard to achieve due to the ability of tumor cells to avoid the effects of the immune system by secreting immunosuppressive cytokines, loss of expression of antigens of the main histocompatibility complex, and expression of molecules inhibiting T-cell activation, i.e., cytotoxic T-lymphocyte glycoprotein 4 (CTLA-4), programmed cell death protein 1-PD-1, programmed death ligand 1 (PD-L1) [8]. Due to the immunosuppressive tumor microenvironment, early attempts at immunotherapy for non-small cell lung cancer (NSCLC) proved ineffective [9]; however, the development of molecular biology and immunogenetics over the past ten years contributed to the development of new approaches to overcoming immunosuppression and increasing the focus of the antitumor response, which revived interest in this topic. At present, according to ClinicalTrials.gov, more than 923 studies are being conducted in lung cancer immunotherapy, with this number growing steadily. The types of immunotherapeutic treatment are highly diverse, including, e.g., antitumor vaccines based on sensitized dendritic cells and tumor neoantigens, oncolytic viral therapy, therapy with immune checkpoint inhibitors (ICI), therapy with tumor-infiltrating lymphocytes, CAR-T, CAR-NK therapy, etc. [10].

In this article, we evaluate the clinical efficacy and prospects for the safe use of immunotherapy in malignant neoplasms of the pleural cavity.

DISCUSSION

Therapy with tumor-infiltrating lymphocytes (TIL) in lung cancer

Therapy using tumor-infiltrating lymphocytes (TIL) is a type of adoptive cell therapy that involves TIL extraction from the tumor stroma, their subsequent reproduction and activation outside the body (*ex vivo*), and reinfusion back into the patient's body [11]. TILs isolated from the tumor microenvironment can be targeted against various tumor-specific neoantigens, which renders them more effective against heterogeneous lung cancer cells. Due to stimulation by tumor antigens in vivo, TILs possess a significant number of effector memory T-cells expressing chemokine receptors (CCR5 and CXCR3) on their surface, which contributes to more efficient and targeted delivery to the tumor site [12]. Due to the negative selection of the T-cell receptor in the early stages of immune development and the use of autologous cells in patients without gene modifications, TIL therapy exhibits low toxicity [13].

The immune microenvironment in lung cancer is a complex system that includes T-lymphocytes, B-lymphocytes, natural killers, macrophages, dendritic cells, etc. The type, density, and location of immune cells in the tumor microenvironment play a key role in the processes of carcinogenesis, cancer progression, and treatment efficacy [14]. A study of the immune microenvironment in NSCLC revealed that long-term treatment outcomes, such as overall survival, depend on the nature of infiltrating lymphocytes, rather than on their number. Thus, an abundance of $CD8^+$ T-cells expressing cytolytic enzymes, $CD4^+$ T-cells lacking expression of inhibitory receptors, and an increased level of tumor infiltrating B-cells are associated with improved survival rates [15]. Tumor B-cells secrete tumor-specific antibodies that stimulate T-cell responses and support the structure and function of tertiary lymphoid structures. However, B-cells with a variety of effects can become immunosuppressants, producing IL-10 and promoting tumor growth. New immunotherapy strategies should simultaneously activate antitumor B-cells and suppress Breg phenotypes [16]. TILs can also be predictive biomarkers of response to therapy with ICI. A relationship was found between the $CD8^+/CD4^+$ ratio in tumor tissue and the response to treatment with ICI in patients with NSCLC, which can be used for prognostic purposes [17].

Currently, several clinical studies are being conducted to assess the safety and efficacy of administration of both unchanged and genetically engineered TIL to patients with progressive NSCLC (Table 1). The effectiveness of adoptive cell therapy is further enhanced by the use of non-myeloablative lymphodepletion (Cyclophosphamide + Fludara bine) before infusion of TIL, subsequent administration of interleukin-2, as well as due to combination with therapy with ICI. In one of the completed phases I clinical trials (NCT03215810), the safety and efficacy of autologous TIL therapy was proven in 20 patients with progressive NSCLC after ineffective nivolumab monotherapy with an overall response rate of 70% [18]. The results of the remaining studies have yet to be analyzed (Table 1).

It should be noted that therapy with tumor-infiltrating lymphocytes has limitations associated with the complexity and high cost of obtaining a sufficient amount of TIL from tumor tissue for therapy. At the same time, TIL therapy should currently be considered only as adjuvant therapy, i.e., after surgical removal of the tumor, to combat distant metastases. Simplification and cost reduction of TIL production technology is, therefore, extremely important for widespread clinical implementation.

In general, despite the accumulated data on the potential efficacy of TIL therapy in NSCLC, widespread adoption of this technology requires both overcoming technological problems of standardization, simplification and cheapening of TIL production technology. In addition, further clinical trials of TIL in various combinations and at various stages of lung cancer are required to clarify the indications for immunotherapy and identify groups of patients for whom a certain immunotherapy will be most effective.

CAR-T cell therapy for lung cancer

Chimeric T-cell antigen receptor cells (CAR-T) are patient T-cells that, due to genetically modified chimeric antigen receptors, are capable of recognizing antigens on tumor cells and trigger a signaling cascade of activation of effector functions of T-cells. CAR-T cells, divided into five generations according to intracellular signaling structural domains, have an extracellular domain for antigens, a transmembrane domain, and an intracellular domain for signal transmission into the cell [19]. One of the advantages of CAR-T therapy is its specificity, independence from the expression of proteins of the major histocompatibility complex (MHC), which is often suppressed in tumor cells, as well as the ability to provide a stable and long-lasting antitumor response due to the continued proliferation of injected cells in the patient's body [20].

The use of CAR-T-cell therapy in oncohematological diseases has demonstrated impressive results, leading to the approval of the FDA (USA Food and Drug Administration) of this treatment method [21]. The current research is focused on extending the indications for the CAR-T-cell therapy to combat solid tumors.

A meta-analysis that included 22 studies involving 262 patients showed that the overall response rate to CAR-T cell therapy in various solid tumors was 9%. Moreover, various strategies (lymphodepletion before T-cell infusion, transfection method, CAR-T cell persistence, total cell dose, and IL-2 administration) did not significantly affect the effectiveness of treatment [22]. Modest results of CAR-T therapy in relation to solid tumors are often associated with a lack of tumor-specific antigens, a low level of infiltration of CAR-T cells into tumor tissue, and a pronounced

Table 1. Clinical studies of the adaptive cell therapy with autologous tumor-infiltrating lymphocytes in non-small cell lung cancer

№	Diagnosis	Treatment	Phase	*n*	Result	Side effects	Clinical trial ID
1	NSCLC	TIL (LN-145) + IL-2 + non-myeloablative lymphodepletion (Cyclophosphamide + Fludarabine) + Nivolumab	I	20	70% — overall response rate; 10% — complete response; 60% — partial response	Associated with lymphodepletion and with the introduction of IL-2	NCT03215810
2	NSCLC; metastatic melanoma; squamous cell carcinoma of the head and neck	TIL (LN-145) + IL-2 + non-myeloablative lymphodepletion (Cyclophosphamide + Fludarabine) + Pembrolizumab/ Ipilimumab/Nivolumab	II	178	The research is ongoing	No data available	NCT03645928
3	NSCLC	TIL (LN-145) + IL-2 + non-myeloablative lymphodepletion (Cyclophosphamide + Fludarabine)	II	95	The research is ongoing	No data available	NCT04614103
4	stages III and IV NSCLC; metastatic melanoma	Genetically modified TIL (IOV-4001) + IL-2 + non-myeloablative lymphodepletion (Cyclophosphamide + Fludarabine)	I/II	Set	The research is ongoing	No data available	NCT05361174
5	NSCLC; cervical cancer; melanoma	TIL (LM103) + IL-2 + non-myeloablative lymphodepletion (Cyclophosphamide + Fludarabine)	I	15	The research is ongoing	No data available	NCT05366478
6	NSCLC	L-TIL (Liquid Tumor Infiltrating Lymphocytes) + Tislelizumab + Docetaxel	II	33	The research is ongoing	No data available	NCT05878028
7	NSCLC; melanoma; colorectal cancer	Epigenetically reprogrammed TIL (LYL845)	I	108	The research is ongoing	No data available	NCT05573035
8	NSCLC; colorectal cancer; melanoma and others	TIL + IL-2 + non-myeloablative lymphodepletion (Cyclophosphamide + Fludarabine)	I	18	The research is ongoing	No data available	NCT05902520
9	NSCLC	TIL + IL-2 + non-myeloablative lymphodepletion (Cyclophosphamide + Fludarabine) + Aldesleukin	II	85	The research is ongoing	No data available	NCT02133196
10	NSCLC; breast cancer; colorectal cancer; melanoma	TIL (TBio-4101) + IL-2 + non-myeloablative lymphodepletion (Cyclophosphamide + Fludarabine) + Pembrolizumab	I	60	The research is ongoing	No data available	NCT05576077

Table prepared by the authors according to the ClinicalTrials.gov data

immunosuppressive tumor microenvironment [23]. In addition, this method of immunotherapy leads to serious side effects, including cytokine storm and neurotoxicity [24]. In order to resolve the problem of low recruitment of T-cells into the tumor site, CAR-T cells were injected into the tumor, which showed encouraging results in an experimental mouse model [25]. Methods of molecular modifications in T-cells can also be used to enhance targeted delivery [26]. In order to overcome the immunosuppressive microenvironment, attempts have been made to combine CAR-T cell therapy with ICI therapy [27]. Toxicity and optimal therapeutic dosage remain to be determined.

The first step in successful adoptive T-cell therapy is to select the optimal tumor-associated antigen (TAA) for CAR-T cells. Most of the antigens used in CAR-T therapy for lung cancer (EGFR, MSLN, MUC1, PSCA, CEA, D-L1, CD80/CD86, ROR1, and HER2) are also expressed in normal human tissues, which can lead to non-targeted toxic effects [28]. Recently, a new target for lung cancer has been found in the form of LunX (lung-specific protein X), an antigen belonging to the family of clone proteins of the palate, lungs, and nasal epithelium. [29]. Unlike other antigens, LunX is often highly expressed in NSCLC cells, although not being expressed in normal lung tissues [30]. Preclinical studies evaluating the effectiveness of LunX-CAR-T therapy on a xenograft model of lung cancer have shown promising results. It has been experimentally proven that LunX-CAR-T cells inhibit the growth of LunX-positive tumor cells and prolong the survival of mice [31]. In parallel, CAR-T cells targeting c-Met, a transmembrane receptor with tyrosine kinase activity expressed mainly in epithelial cells, are being developed [32]. Preliminary studies have shown that c-Met-directed CAR-T cells demonstrate pronounced antitumor activity both *in vitro* and *in vivo* against NSCLC, offering promising treatment routes [33].

Currently, phase I and II clinical trials of CAR-T therapy for NSCLC are underway, targeting various targets (epidermal growth factor, mesothelin, PD-L1, mucin-1) in combination with or without immunotherapy, with varying efficacy and toxicity [34–36]. In particular, the response to EGFR-CAR-T-cell therapy for EGFR + NSCLC was noted in two patients out of 11 (18%) [34]. In another phase I clinical trial study with intrapleural administration of mesothelin-targeted CAR-T in combination with pembrolizumab therapy for lung cancer and pleural mesothelioma, a good response was observed in only two patients out of 27 (7%) [35]. MUC1-CAR-T-cell therapy in 20 patients with NSCLC led only to stabilization of the disease without visible signs of improvement in 11 patients, while the remaining patients showed disease progression [36]. A number of studies have been discontinued due to the high toxicity of CAR-T-cell drugs.

Note should be made that despite intensive research, immunotherapy with CAR-T cells has not yet shown any significant clinical effect in the fight against lung cancer. In addition, in its current form, such an immunotherapy is burdened with a rather high toxicity. The research into CAR-T cell therapy for solid tumors in general and lung cancer in particular is in its nascent stage, requiring additional efforts in assessing the possibility of its clinical application.

Inhibitors of immune control points in lung cancer

Immunotherapy using checkpoint inhibitors (ICI) of the immune system is one of the most significant breakthroughs in the treatment of oncological diseases. Indeed, a number of multicenter studies have shown its efficacy in increasing the median survival rate in numerous malignancies, including lung cancer. This technology is associated with the inhibition of immunosuppressive proteins CTLA-4 and PD-1/PD-L1, which, in turn, activates cellular antitumor immunity [37]. The interaction of PD-1, located on the surface of thymocytes and other elements of the immune system, with its PD-L1 ligand on tumor cells suppresses the activity of T-cells, reducing their ability to recognize and destroy tumors. Lung cancer often uses this mechanism to avoid the immune response. CTLA-4 is another inhibitory receptor on T-cells, the blockade of which contributes to an increase in the number of activated T-cells and memory T-cells, enhancing the immune system attack on the tumor [38]. The following immune control molecules are being evaluated as potential targets for cancer immunotherapy: molecule 3 containing T-cell immunoglobulin and mucin domain (TIM-3), transmembrane glycoprotein type I (B7-H3), immunoglobulin suppressing activation of T-cells in the V domain (VISTA), lymphocyte activation gene-3 (LAG-3), T-cell immunoglobulin, and ITIM domain (TIGIT) [39].

At the moment, over 300 clinical trials aimed at studying the effectiveness of the ICI in lung cancer therapy have been successfully completed. On their basis, the European Medicines Agency and the USA Food and Drug Administration approved one CTLA-4 inhibitor drug (ipilimumab), five PD-1 inhibitor drugs (nivolumab, pembrolizumab, cemiplimab, sintilimab, camrelizumab), and two PD-L1 inhibitors (durvalumab, atezolizumab) for the treatment of NSCLC. Some other drugs undergo different stages of approval. In the nearest future, new drugs in each of the ICI groups are likely to appear [40].

Randomized clinical trials in patients with PD-L1-positive tumors with an expression of at least 50% showed single-component immunotherapy with ICI to be superior to adjuvant chemotherapy in terms of both toxicity and overall survival [41, 42]. The KEYNOTE-024 trial (phase III, 305 patients) revealed that pembrolizumab, as a first-line therapy in patients with metastatic NSCLC with PD-L1 expression>50%, significantly improved overall survival rates with a lower level of side effects compared to platinum-containing chemotherapy [43]. In addition, KEYNOTE-042 trial (1,274 patients, phase III) [44] and IMpower110 trial (phase III, 572 patients with metastatic NSCLC who had not previously received chemotherapy and whose PD-L1 expression was at least ≥1%) confirmed that ICI therapy provides a significant improvement in the survival of patients with various degrees of PD-L1 expression. However, a particularly pronounced effect was noted in individuals with higher expression levels [45]. This indicates the expediency of selecting immunotherapy as the primary treatment method in patients with locally advanced unresectable or metastatic NSCLC with PD-L1 expression of more than 1%.

When developing advanced treatment methods for lung cancer, special attention is paid to the potential of combining immunotherapy and chemotherapy. According to the results of the 5-year clinical trial KEYNOTE-189 phase III (NCT02578680) in 616 randomized patients with untreated metastatic NSCLC without EGFR/ALK changes on combined immunotherapy and chemotherapy (n = 410 pembrolizumab plus pemetrexed plus platinum), the 5-year overall survival rate was 19.4%. At the same time, the use of only mono-chemotherapy (n = 206 placebo plus pemetrexed plus platinum), the 5-year overall survival rate was 11.3%. Among 57 patients who completed 35 cycles of taking pembrolizumab, the objective response rate was 86.0% [46]. A meta-analysis of 66 studies showed that neoadjuvant immunotherapy for resectable non-small cell lung cancer is safe and effective. In comparison with chemotherapy alone, chemoimmunotherapy improved therapeutic response and survival rates to a greater extent [47]. These data continue to confirm that the combination of ICI therapy with chemotherapy improves the survival of patients with NSCLC, regardless of PD-L1 expression. A phase III CheckMate 9LA large trial demonstrated positive results in overall survival with nivolumab plus ipilimumab compared with chemotherapy in patients with NSCLC, regardless of PD-L1 expression. This prompted the use of a dual immunotherapy approach without chemotherapy [48]. Combination of immunotherapy with other therapeutical approaches to achieve the best effect and reduce side effects deserves further study.

The most common side effects of ICI therapy related to immunity are skin and endocrine disorders, such as rash, itching, and thyroid dysfunction [49]. There is an increasing amount of literature data on cardiovascular toxicity, in particular myocarditis, which requires a more comprehensive assessment of the baseline parameters of the cardiovascular system and optimization of risk factors [50]. Fatal cases are rare, ranging from 0.36% with single-agent immunotherapy to 1.23% with combined immunotherapy [51].

It should be noted that despite significant clinical improvements, most patients ultimately do not respond to ICI therapy due to the development of primary or secondary resistance [52]. A retrospective study of 1201 patients with NSCLC treated with PD-1 inhibitors showed that 78% of 243 cases developed secondary resistance after the initial response [53]. In 74% of patients with NSCLC with an effective initial response to immunotherapy, disease progression was observed within five years. The mechanism of resistance to immunotherapy is rather complex, being most likely associated with changes in the interaction between cells and surrounding cell populations within the tumor microenvironment (TME) [54]. Research into cellular interactions within TME and creation of reliable methods for evaluating immune cells and their effect on the tumor may shed light on the mechanism of overcoming resistance and increasing the effectiveness of ICI therapy. Nevertheless, checkpoint inhibitors have already significantly changed treatment approaches to lung cancer in a positive way. Along with advancement of theories and technologies, more effective treatment options can be expected.

Oncolytic phytotherapy for lung cancer and some other tumors of the pleural cavity

Oncolytic virotherapy (OVT) is another type of immunotherapy for malignant neoplasms that has the potential to overcome the immunosuppressive microenvironment and improve clinical outcomes. Oncolytic viruses (OV) are focused on selective damage and reproduction in tumor cells. This process destroys tumor cells, activating simultaneously the systemic immune response against cancer [55]. Cell death, accompanied by the release of molecules such as DAMPs and PAMPs, as well as cytokines, stimulates the activation and recruitment of antitumor immune cells, including $CD4^+$ and $CD8^+$ T-lymphocytes [56]. The current research focuses on various viruses, including adenoviruses, herpesviruses, measles viruses, Coxsackie viruses, polioviruses, reoviruses, Newcastle disease virus, etc. Malignant tumor cells may be susceptible to infection and replication of the virus as a result of their defective virus perception mechanisms. Some viruses do not require the presence of specific receptors [57]. Individual viruses are purposefully modified to make them oncospecific, e.g., by introducing a defect in the thymidine kinase sequence, in which replication is possible only in tumor cells with a high content of this enzyme [58].

Currently, the only oncolytic virus, which is a genetically modified form of the herpes simplex virus type 1, has been approved by the USA FDA for the treatment of malignant melanoma [59]. A systematic review and meta-analyses evaluating the efficacy and safety of OVT in solid tumors showed that the objective response rate was significantly higher in patients receiving monotherapy with oncolytic adenovirus H101 or combination with chemotherapy, compared to patients receiving chemotherapy alone [60]. According to the ClinicalTrials.gov data more than 20 studies are currently being conducted (Table 2), mainly the first or second phase of clinical trials, with an assessment of the efficacy and safety of oncolytic virotherapy for lung cancer and some other malignant tumors of the pleural cavity, in particular pleural mesothelioma. The effectiveness of intra-tumor administration of ADV/HSV-tk oncolytic virus was shown in 28 patients with metastatic non-small cell lung cancer in combination with stereotactic radiation therapy and further ICI immunotherapy (valciclovir and pembrolizumab) (NCT03004183). Disease stabilization was observed in 10 patients (37.5%), disease progression was observed in 10 patients (37.5%), 6 patients (21.4%) had a partial response, and 2 patients (7.1%) achieved a complete response. The results of another study (NCT02053220) showed that intravenous administration of ColoAd1 adenovirus for resectable NSCLC led to stimulation of the local antitumor immune response in the form of infiltration by $CD8^+$ T-cells [61]. At present, clinical trials of oncolytic virotherapy for lung cancer remain to be launched, requiring data predicting its potential therapeutic efficacy.

The clinical efficacy of OVT as a monotherapy remains limited, attracting research attention to exploring various combined treatment tactics. With respect to the combination of OVT with standard methods of lung cancer

treatment, one meta-analysis involving 1494 patients (the combination therapy group — 820 patients; the traditional treatment group — 674 patients) showed that the OVT in combination significantly improves the objective response in patients compared to standard therapy [62]. OVT is a particularly attractive option as adjuvant therapy to increase overall survival, due to the possibility of targeting residual tumor foci and modulating the suppressed immune system after surgery [63]. There is also evidence that combined radiation therapy and oncolytic virotherapy can enhance their individual antitumor effects, selectively destroying lung tumor cells [64].

Depending on the location and availability of the tumor, the virus can be injected directly into the tumor (single or repeated injections) or systemically (intravenous or intraarterial injection). Intra-tumor administration may be limited by the extracellular matrix, which serves as a barrier preventing the penetration and spread of the virus. Another difficulty in delivering the virus is the activation of antiviral immunity when administered systemically. Introduced viruses are detected by the host's immune system and inactivated by neutralizing antibodies, which reduces their replication and effectiveness. Attempts were made to circumvent this problem by encapsulation of oncolytic adenovirus into extracellular vesicles, which significantly increased *in vitro* infection rates and enhanced the effect of suppressing tumor growth in experimental models of human lung cancer [65]. Such approaches can be integrated into clinical practice to improve the effectiveness of systemic drug delivery, overcoming the immune response.

The modern possibilities of designing recombinant viruses are of great interest. The large viral genome VV allows the introduction of up to 50 kb of foreign genes, as a result of which the effect of OVT can be enhanced by the tumor-selective expression of therapeutic biological drugs, including antibodies, cytokines, chemokines, and ligands. Cytokine genes are among the most commonly used immunomodulatory genes due to the capacity of cytokines to recruit and regulate T-cell homeostasis [66]. Viruses encoding IL-2, IL-12, IL-15, TNF, or other cytokines have been designed to stimulate an increase in the lymphoid cell population after local administration. Studies have demonstrated successful and safe delivery of IL-2 into the tumor microenvironment, reducing tumor load and increasing the number of $CD8^+$ lymphocytes [67]. It was confirmed that IL-15 performs important functions in the activation and survival of T-lymphocytes, natural killer (NK), and NK-T-lymphocytes, with the combination of IL-15 and IL-15Ra enhancing their biological activity [58].

Recombinant virus design techniques may be the key to developing new approaches to treating lung cancer and improving immunotherapy. Due to their good safety profile and a variety of antitumor mechanisms, such approaches are appropriate for combination therapy. Viral infections and tumor lysis processes transforms cold tumors into hot tumors, increasing the infiltration and involving immune cells in the TME. OVT in combination with ICI demonstrate a powerful synergistic effect. The development of strategies for combination therapies requires care, since ICI can affect the ability of OV replication. In order to achieve optimal results, it is necessary to harmonize both treatment methods, avoiding potential risks associated with OV gene activation [68].

In general, oncolytic virus therapy shows broad clinical prospects for future effective treatment strategies of lung cancer. The versatility and relative safety of agents suggest that they are a powerful tool for optimizing combined immunotherapy. Continued clinical research in these directions is required.

CONCLUSION

Lung cancer is characterized by a pronounced immunosuppressive tumor microenvironment. This impedes both the antitumor immune response and the antitumor effectiveness of currently existing methods of adoptive cellular immunotherapy. At the same time, the combined effect of selective ICI, enhanced/targeted TIL, CAR-T and TCR-T, and recombinant oncolytic viruses on the tumor and its microenvironment can overcome the antitumor immune response and become decisive in suppressing tumor growth and improving clinical outcomes.

Each of the discussed methods individually have a number of advantages and disadvantages. This is why a combined and personalized approach to lung cancer immunotherapy seems to be justified. The development of technologies for recombinant oncolytic viruses that cause production of activating cytokines and chemokines by microenvironment cells, along with inhibition of the CTLA-4 and PD-1/PD-L1 signaling axes, as well as the creation of genetically-engineered cytotoxic cells, will undoubtedly raise adoptive immunotherapy to a new level capable of reverting the course of metastatic lung cancer.

Table 2. Clinical studies of oncolytic virotherapy for pleural cavity malignant neoplasms

№	Diagnosis	Treatment	Phase	Selection	Result	Side effects	Clinical trial ID	Event location
1	2	3	4	5	6	7	8	9
1	Solid tumors (lung cancer, head and neck cancer, melanoma, etc.)	Intra-tumor injection of recombinant adenovirus LIF N	1	28	Status unknown	No data available	NCT05180851	Shanghai, China
2	Metastatic NSCLC	Stereotactic radiation therapy in combination with intracellular administration of EBV/HSV-tk oncolytic virus, ICI therapy (valciclovir and pembrolizumab)	2	28	Complete response of 2 patients (7.1%); partial response of 6 patients (21.4%); stabilization of the disease of 10 patients (37.5%); disease progression of 10 patients (37.5%). The overall survival rate is 12.9%.	There are no cases of toxicity to the administration and no serious side effects from the treatment	NCT03004183	Houston, Texas, USA
3	Malignant pleural mesothelioma	Intrapleural administration of a vaccine strain of measles virus encoding a thyroid carrier of sodium iodide	1	15	The results have not been published	No data available	NCT01503177	Rochester, Minnesota, USA
4	NSCLC	Quaratusugene ozeplasmid (Remorse) in combination with pembrolizumab in patients with previously treated NSCLC	1 и 2	180	Recruitment is underway	No data available	NCT05062980	Houston, Tampa, St. Louis, USA
5	Disseminated small cell lung cancer	Intra-tumor injection of an oncolytic virus (RT-01)	1	20	Recruitment is underway	No data available	NCT05205421	Bengbu, China
6	Recurrent progressive solid tumors	Recombinant herpes simplex oncolytic virus type 1 (R130)	1	24	Recruitment is underway	No data available	NCT05886075	Anqing, Anhui, China
7	Progressive solid tumors	Recombinant herpes simplex oncolytic virus type 1 (R130)	1	20	Recruitment is underway	No data available	NCT05860374	Shanghai, Jiangsu, China
8	Progressive solid tumors	Recombinant herpes simplex oncolytic virus type 1 (R130)	1	20	Recruitment is underway	No data available	NCT05961111	Linyi, Shandong, China
9	Resistant to inhibitors of the NCLR immune checkpoint	Oncolytic adenovirus TILT-123 in combination with pembrolizumab	1	22	Recruitment is underway	No data available	NCT06125197	The location is not specified
10	Progressive malignant pleural mesothelioma	Oncolytic adenovirus H101 in combination with an inhibitor PD-1	1	15	Recruitment is underway	No data available	NCT06031636	Tianjin, Tianjin, China
11	Solid tumors	Intra-tumor injection of MEM-288 and nivolumab	1	61	Recruitment is underway	No data available	NCT05076760	Tampa, USA
12	Resectable NSCLC, resectable bladder cancer, resectable colon cancer, etc.	Intra-tumor injection or intravenous infusion of group B oncolytic adenovirus (ColoAd1)	1	17	High local infiltration of $CD8^+$ cells in 80% of the tested tumor samples, indicating a potential immune response.	There are no cases of toxicity to the administration and serious side effects from the treatment	NCT02053220	Madrid, Spain
13	Non-small cell lung cancer	VSV-IFN-β-NIS + Pembrolizumab + ipilimumab + nivolumab	1 и 2	70	Recruitment is underway	No data available	NCT03647163	Rochester, Minnesota, USA

Table 2 (continued)

№	Diagnosis	Treatment	Phase	Selection	Result	Side effects	Clinical trial ID	Event location
1	2	3	4	5	6	7	8	9
14	HER2 positive tumors	Intra-tumor injection of CAdVEC adenovirus	1	45	Recruitment is underway	No data available	NCT03740256	Houston, Texas, USA
15	Progressive NCLR	Intra-tumor injection of adenovirus (CVA21) in combination with pembrolizumab	1	11	Is unknown	No data available	NCT02824965	Heidelberg, Victoria, Australia
16	Progressive solid tumors	Intravenous injection of herpes virus T3011	1 и 2	74	Recruitment is underway	No data available	NCT05598268	Beijing, China
17	Metastatic solid tumors	Intra-tumor or intravenous injection of TBio-6517 (Oncolytic smallpox vaccine virus) in combination with pembrolizumab	1 и 2	27	Stopped	No data available	NCT04301011	USA
18	Metastatic solid tumors	Intra-tumor injection BT-001 (TG6030), alone and in combination with pembrolizumab	1 и 2	48	Recruitment is underway	No data available	NCT04725331	Brussels, Belgium
19	Metastatic solid tumors	Intra-tumor injection of recombinant GM-CSF vaccine; RAC VAC GM-CSF (JX-594)	1	23	Recruitment is underway	No data available	NCT00625456	USA
20	Malignant pleural mesothelioma	Intrapleural HSV1716, an oncolytic virus, is a type I mutant herpes simplex virus (HSV) deleted in the RL1 gene, which encodes the ICP34.5 protein	1 и 2	12	Completed	No data available	NCT01721018	Glasgow, United Kingdom
21	Common solid tumors with neuroendocrine features	Intra-tumor injection of picornavirus Seneca Valley Virus (SVV001)	1	60	Recruitment is underway	No data available	NCT00314925	USA

Table prepared by the authors according to the ClinicalTrials.gov data

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