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Immunotherapy in Lung Cancer

Liying Chen

University of South China, Hengyang, Hunan, 421001

ABSTRACT
Lung cancer, one of the most prevalent malignant tumors globally, presents numerous challenges in its treatment. In recent years, immunotherapy has emerged as an important tool in the treatment of lung cancer, particularly non-small cell lung cancer (NSCLC), and significant progress has been made. Immune checkpoint inhibitors (ICIs) has come to be the cornerstone of lung cancer treatment by restoring T-cell activity. Additionally, immunotherapies for instance adoptive cell therapy, tumor vaccines, and cytokine therapy reveal considerable prospect. Although immunotherapy has significantly improved survival rates for some patients, problems remain, such as a low response rate, drug resistance and immune-related side effects. Future research will focus on optimizing treatment regimens, overcoming resistance, and enhancing individualized therapies, aiming to make immunotherapy a more precise and safer treatment option for lung cancer.

KEYWORDS
Lung Cancer; Immune Therapies; Immune Checkpoint Inhibitors; Adoptive Cell Therapies; Cancer Vaccines; Cytokine Therapies.

1 Introduction

Lung cancer represents a critical global health challenge, with one of the highest rates of morbidity and mortality of any malignant tumour. It accounts for 11.6% of all cancers, including non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC).Non-small cell lung cancer has a five-year survival rate of less than 15% and accounts for about 85% of all lung cancers. [1]. SCLC represents about 15%[2] of lung cancer cases. The treatment of lung cancer typically involves surgery, chemotherapy, and radiotherapy, however, the 5-year survival rate for patients with advanced lung cancer is under 5%. [3]. Thus, research into new novel treatment modalities is crucial.

In the last few years, immunotherapy has emerged as a promising option for the treatment of cancer because it offers excellent efficacy and a unique mechanism of action. Tumor immunotherapy seeks to restore and maintain the tumor-immunity cycle[4-5], which has demonstrated substantial anti-tumor activity and improved survival in a subset of patients. Immunotherapy, especially for advanced lung cancer, has gradually replaced traditional chemotherapy as the first-line treatment due to its enhanced survival benefits and better tolerability[6].

2 Main Types of Lung Cancer Treatment

Currently,the main immunotherapy strategies applied to lung cancer include:

2.1 Immune Checkpoint Inhibitors (ICIs)

Immune checkpoints (ICs) are mechanisms by which the immune system regulates its response, primarily consisting of inhibitory receptors and their ligands.ICIs can restore antitumor immunity by blocking the interaction between ICs and their ligands on immune or tumor cells[7], thus promoting anti-tumor effects. This strategy has become one of the mainstay treatments for the treatment of lung cancer, being well-tolerated, selective, and effective with minimal adverse effects.

The pathways commonly studied are cytotoxic T lymphocyte-associated antigen-4 (CTLA-4), programmed death receptor-1 (PD-1) and programmed death ligand-1 (PD-L1). These signalling pathways have had significant effects in the treatment of several types of cancer, particularly melanoma, lung cancer and kidney cancer[8-9].

PD-1/PD-L1 Inhibitors: PD-1 is an inhibitory receptor found on T-cells, and its binding to PD-L1 (expressed on tumor cells) suppresses T-cell activation. Blocking this interaction restores T-cell function, enhancing anti-tumor immunity. Drugs such as nivolumab, pembrolizumab, atezolizumab, and sintilimab are widely used. Ran Fanglan et al. [10] showed that ORR in advanced NSCLC patients after EGFR TKI resistance can exceed 50%, suggesting that the use of PD-1/PD-L1 immune checkpoint inhibitors in second-line chemotherapy may improve clinical response rates and survival, improve serum cancer marker expression levels, and enhance patient survival.

CTLA-4 Inhibitors: CTLA-4, expressed on T-cells and regulatory T-cells (Tregs), inhibits T-cell activation by binding to

Correspondence: C929681188@163.com

CD80/CD86 molecules[11]. Blockade of this interaction enhances T-cell activity and promotes anti-tumour immune responses. Ipilimumab, an FDA-approved CTLA-4 monoclonal antibody, has shown effectiveness in treating melanoma and other cancers[12]. Tumours such as melanoma and colorectal cancer have been approved for this class of drugs, and has achieved remarkable results in clinical practice[13-15] . Currently, several novel CTLA-4 inhibitors are in clinical trials to explore their application in other cancers, such as renal cell carcinoma and triple-negative breast cancer, showing promising clinical prospects.

PD-1 inhibitors usually have fewer side effects than CTLA-4 inhibitors and are therefore more widespread use in clinical practice. However, they can also be used in combination to further improve anti-tumor effects by double blocking immune checkpoints, such as nivolumab combined with ipilimumab, which has shown improved activity in melanoma, NSCLC and other cancers[16] .

2.2 Adoptive Cell Therapy (ACT)

ACT uses the immune cells of the patient, either expanded or genetically engineered, to target and destroy tumor cells. ACT is categorized into specific and non-specific therapies, with specific therapies showing more promising results. Tumor-infiltrating lymphocyte (TIL) therapy, T-cell receptor (TCR)-T cells, and chimeric antigen receptor (CAR)-T cells are prominent examples[17]. ACT has been an important direction of tumor immunotherapy in recent years, especially in hematologic system malignant tumors and some solid tumors have shown good efficacy. It mainly includes:

Tumor Infiltrating Lymphocyte Therapy (TIL): Tumor infiltrating lymphocytes are a class of specific killer lymphocytes, mainly T-lymphocytes, present in the tumor mesenchyme and tumor parenchyma, primarily due to tumour-specific natural killer (NK) cells, dendritic cells (DC), macrophages and suppressor cells of myeloid origin, etc.[18] . It is indicated for tumors with a high degree of mutational load (TMB), such as melanoma. In a single arm, phase I clinical trial[19] ,in 11 out of 16 patients, tumor regression was observed on the first CT scan one month after treatment with TILsACT, with a median best change in total lesion diameter of -35.5%, and 2 of these patients achieved complete remission. And most of the adverse events that occurred after treatment were resolved within 1 month of TILs treatment. This study shows that it is now possible to collect and expand TILs from patients with non-small cell lung cancer (NSCLC) whose tumour has already progressed to a certain extent.

Chimeric antigen receptor T-cell therapy (CAR-T): is a kind of T-cell therapy using genetically engineered modified overt T-cell therapy, which has the characteristics of high specificity, strong tumorigenic cell death, and long-lasting efficacy. Currently, it has produced excellent results in haematological malignancies, but its use in solid tumours such as lung cancer remains a challenge, such as the inhibitory effect of the tumor microenvironment and antigenic inhibition. Currently, integrating treatments such as immune checkpoint inhibitors and lysoviruses with CAR-T cell combination therapy, as well as by optimisation and modification of CAR T-cell structure, has become a new direction to improve CAR-T cell immunotherapy[20]. Studies have shown[21] that retinoic acid-associated orphan nuclear receptor 1CAR-T cells can effectively induce apoptosis in a 3D lung cancer tumor model in static culture. In a Phase I clinical study of MSLN-CAR-T for advanced malignancies (NCT01583686) [22] , a total of 15 patients were enrolled. These included patients with lung, pancreatic, malignant mesothelioma, cervical and ovarian cancer, and the incidence of serious adverse events was 40% (6/15), with one case maintaining stable disease for 3.5 months. Several clinical studies of MSLN-CAR-T for lung cancer (NCT02414269, NCT-02580747) are ongoing.

2.3 Tumor Vaccines

Tumor vaccines are an immunotherapy strategy that identifies and destroys cancer cells using the body's own immune system. It targets a tumour-specific antigen (TSA) or tumour-associated antigen (TAA), activates cytotoxic T lymphocytes, T helper cells and other immune cells through the action of the head-histone compatibility complex and Improves human immune system's ability to specifically recognise antigens, ability to effectively target solid tumors or hematologic tumors[23] .Despite the fact that tumor vaccines are highly specific, safe, and can establish long-term immune memory, there are still some challenges and limitations. For example, lung cancer is highly heterogeneous, and lung cancer cells can evade immune attacks through modification changes in the cells themselves and alterations in the immune microenvironment, attenuating the therapeutic effects of lung cancer vaccines[24] . In recent years, with the continuous progress of precision medicine and sequencing technology, the field of tumor vaccine therapy has made remarkable development. It mainly includes:

Dendritic cell (DC) vaccines: are important immune cells that activate anti-tumor T cells and keep the effector response going, which are able to fuse with tumor cells, efficiently uptake, process and present antigens, attenuate immune tolerance, and remodel the tumor immune microenvironment. In recent years, DC-based vaccines have been tested in more than 200 clinical trials, and early studies have shown that these vaccines have a favorable safety profile and strong immunogenicity, and mediate significant clinical responses in certain tumors[25-26] . Skachkova et al.[27] showed that DC

vaccines reduce the risk of recurrence in postoperative period in NSCLC patients. The study[28] showed that DC fusion vaccine significantly prevented the growth of weakly immunogenic mouse Lewis lung cancer cells (LLC), with a 50% reduction in the size of some masses and a reduction in lung metastasis, which suggests that DC fusion cells to induce the apoptosis of tumour cells.

Peptide vaccines are cancer vaccines that are based on peptides of tumour antigens that prevent or treat the disease by inducing the body's own immune system to recognise and target tumour cells. A 2022 study on the characteristics of registered global clinical trials of therapeutic vaccines for NSCLC[29] noted that current research on therapeutic tumor vaccines is predominantly on peptide vaccines (41.88%), with a predominantly Stage III or IV patient population (26.5%), and a majority of single-arm trials (52.14%) with predominantly small sample sizes (50 or fewer people in a trial compared to 56.41%). In 2021, a clinical trial (NCT03645148) [30] treated patients with advanced pancreatic cancer with an individualized peptide vaccine, iNeo-Vac-P01. In seven patients, the median overall survival was 24.1 months and the median progression-free survival was 3.1 months, and 71.4% of patients showed an increase in specific T-cell responses.

mRNA vaccine: It involves leveraging mRNA encoding tumor antigens to be translated into proteins within the body, thereby triggering an immune response. in 2017, scholars began to invoke the concept of an individualized vaccine with the first clinical trial of an individualized mRNA vaccine, which found that the trial patients all produced a high immune response. In a phase Ib study[31](NCT01915524), BI1361849's safety and efficacy,an mRNA vaccine complexed with cationic fisetin, in combination with graded local radiotherapy was evaluated in 26 cases of non-small cell lung cancer in stage IV. When the immune response was examined,the results showed in 80% of patients, an increased antigen-specific immune response,with 52% of them showing elevated levels of antigen-specific antibodies, while 46% showed elevated functional T-cells, and a minority of patients (2%) were involved in multiple antigen-specific immune responses. It is shown that mRNA vaccines can provide more effective tumor therapy for cancer patients by targeting tumor mutations.

2.4 Cytokine Therapy

Cytokine therapy is a therapeutic strategy that uses cytokines released by immune cells to modulate and enhance the immune system of the body, a group of small protein molecules that modulate immune cell activity and stimulate anti-cancer immune responses, and play a major role in the immune response against cancer. By means of exogenous supplementation or genetic engineering to modify cytokines, immune cells such as T lymphocytes, NK cells and macrophages can be activated, thereby enhancing the body's anti-tumor, anti-infection or immune regulatory capabilities , and to improve their recognition and killing power of tumor cells, thus improving the effect of cancer treatment. Mainly include:

Interleukins (ILs): a class of cytokines secreted by leukocytes and other immune cells that enable short-range communication between immune cells by paracrine and autocrine means, and are capable of controlling leukocyte proliferation, differentiation, effector function, and survival. [32] More than 40 interleukins (IL-1 to IL-40) have been identified, many of which have important roles in immunotherapy and disease treatment. The results of a study some time ago[33] showed that the area under the curve (AUC) of IL-6 alone in predicting the prognostic adverse effects in lung cancer patients was 0.877. The reason for this analysis was that IL-6 is one of the classical inflammatory factors of the interleukin family, and the higher level suggests stronger inflammatory response and the possibility of recurrence even after treatment, so the predictive efficacy of the combined assay with NSE and TNF-α was Therefore, combined with NSE and TNF-α, the predictive efficacy of the test is better.

Interferons (IFNs): are a class of cytokines secreted by cells, originally named for their ability to fight viral infections. They are primarily produced by immune cells in response to infection by viruses, bacteria, parasites, and other pathogens. [34] In a study[35] showed that IFN-gamma levels were lower in lung cancer patients than in healthy people, and IFN-γ serum levels were lower in poorly prognostic lung cancer patients than in well prognostic lung cancer patients, suggesting that IFN-γ plays an important role in causing lung cancer.

Tumor Necrosis Factors (TNFs): a family of cytokines with multiple biological activities in the human body, produced mainly by means of activated macrophages, T cells, NK cells and other immune cells, there are about 30 kinds of them, among which the most researched and clinically applied ones are TNF-α and TNF-β[36] . One study[37] showed that the AUC of serum TNF-α was 0.872, 95% CI 0, 792-0, 953 and specificity was 94.1%. In the diagnosis of lung cancer, TNF-α has a greater AUC and potentially higher clinical value than NSE and CYFRA21-1.

3 Challenges and Future Directions

Immunotherapy has been widely used in a variety of malignant tumors represented by lung cancer. This emerging cancer immunotherapy approach is more targeted than traditional chemotherapeutic agents, and can effectively enhance the body's immune response to inhibit tumor progression. However, immunotherapy still faces many challenges,

such as non-response in some patients, acquired resistance, immune-related adverse events (irAEs), and limitations of immune cell therapy for solid tumors. Therefore, future research focuses on optimizing immunotherapy strategies to improve response rates, overcome drug resistance, and reduce side effects, leading to individualized and precise treatment.

First, low response rate is one of the main challenges, with only 20-30% of lung cancer patients benefiting in the long term. Tumor antigen deficiency, immunosuppressive microenvironment (TME) and T-cell failure are key factors[38-40] . To address this issue, researchers are exploring novel biomarkers (e. g., TMB, MSI, intestinal flora) as well as combination therapies (ICIs + chemotherapy/CTLA-4 inhibitors) to improve treatment efficacy. Second, drug resistance limits the long-term efficacy of immunotherapy. Some patients are initially effective, but tumor cells may escape immune attack through PD-L1 re-regulation, JAK/STAT pathway mutations, or antigen loss. To overcome resistance, investigators[41] are developing novel immune checkpoint inhibitors (LAG-3, TIGIT, TIM-3) and exploring cellular therapies such as CAR-T and TIL. In addition, immune-related adverse events (irAEs) may affect organs like the lungs, liver and kidneys, and can be life-threatening in severe cases. Solutions include early monitoring, glucocorticoid therapy, and development of locally acting ICIs with lower side effects.

In summary, immunotherapy has significantly improved the survival of lung cancer patients, but continues to face challenges such as low responding rates, drug resistance, immune-related side effects and difficulties in treating solid cancer cells. Future research directions mainly include the development of novel immune checkpoint inhibitors (LAG-3, TIGIT, etc.), optimization of personalized immunotherapy (gene sequencing, AI prediction, intestinal flora regulation), advancement of cancer vaccines (mRNA vaccine, DC vaccine), and the exploration of more effective combination therapies (ICIs + radiotherapy, chemotherapy, targeted therapy, etc.). Through these innovations, immunotherapy is expected to become a more precise, effective, and safer anti-cancer strategy, bringing longer survival benefits to patients with lung cancer and other malignant tumors.

4 Conclusion

Immunotherapy has become a key player in lung cancer treatment, with significant improvements in patient survival, particularly through immune checkpoint inhibitors. However, challenges such as drug resistance and immune-related side effects remain. Future advancements, including novel immune targets and combination therapies, hold the potential to further improve immunotherapy ' s precision, efficacy, and safety, ultimately benefiting lung cancer patients.

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