Review Article

Advances of cell therapy in lung cancer: a narrative review

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Background and Objective: Lung cancer is the second most prevalent malignancy and has the highest death rate. The main approaches for lung cancer treatment include surgery, chemotherapy, radiotherapy, targeted therapy, and immunotherapy. However, the treatments of the disease need to be further improved. An increasing number of scientific investigations indicated cell therapy to be a successful new treatment for lung cancer. Cell therapy can improve the host's immunity to disease and can compensate for the shortcomings in the therapeutic effects of traditional treatments, particularly in the case of cancer treatment. However, due to its recent development, its clinical efficacy still needs to be further examined. In order to provide an updated source on cell therapy for lung cancer, this paper summarizes the clinical use of chimeric antigen receptor T cells (CAR-Ts), stem cells, cytokine-induced killer cells (CIKs), and tumor-infiltrating lymphocytes (TILs) and discusses recent clinical advancements.

Methods: We performed a search of the PubMed database on March 28, 2023, and again on June 10, 2023. A review of retrieved literature related to cell therapy and treatments for lung cancer was completed.

Key Content and Findings: Cell therapy has been applied in clinical studies on the treatment of disorders of the hematologic system, digestive system, respiratory system, and other systems. CAR-T therapy has been successfully used in the treatment of B-cell malignancies, which suggests that cell therapy has broad prospects in the treatment of malignant tumors. CAR-T, stem cells, CIKs, and TILs exert antitumor activity and can recognize and could be used to treat lung cancer.

Conclusions: Cell therapy represents a novel solution in the treatment of lung cancer. Cell therapy, when combined with traditional therapies, can compensate for the shortcomings of these methods. Further research is needed to reduce the occurrence of adverse reactions and provide a more effective approach in treating lung cancer.

Keywords: Lung cancer; chimeric antigen receptor T cells (CAR-Ts); stem cells; cytokine-induced killer cells (CIKs); tumor-infiltrating lymphocytes (TILs)

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Introduction

According to the latest statistics from the American Cancer Society, there were 19.3 million new cases of cancer and nearly 10 million cancer-related deaths globally in 2020. Lung cancer, which accounts for around 11.4% of cancer diagnoses and 18.0% of fatalities, is the second most prevalent malignancy and has the highest death rate (1). In China, the age-standardized mortality rate of lung cancer increased from 1973 to 2015 (2), and the lung cancer incidence and mortality rate in China were 59.89/100,000 and 47.51/100,000 in 2016, respectively, according to data from the National Cancer Center (3), with patients having a poor prognosis.

At present, the main approaches for lung cancer treatment include surgery, chemotherapy, radiotherapy, targeted therapy, and immunotherapy. Surgery is the first choice for early lung cancer. The 5-year survival rate of patients with stage IA–IIB lung cancer after surgery can reach 53–92%. However, the risk of surgery is high, and surgery has certain requirements regarding the tumor-node-metastasis (TNM) classification of patients (4). Chemotherapy can effectively improve the cancer cure rate and slow the growth and metastasis of tumor. However, it has strong toxicity and numerous adverse effects and cannot completely eliminate cancer cells. Many patients of advanced age relapse due to drug resistance, and some others are not sensitive to chemotherapy (5). Radiotherapy is frequently used as an auxiliary treatment method to operation, but it can lead to serious adverse reactions such as decreased immunity and radiation pneumonitis (6). Targeted therapy is used in the treatment of gene mutation-related lung cancer, which can specifically kill tumor cells. However, it has certain drawbacks, such as drug resistance and a narrow range of applications. Immunotherapies, especially immune checkpoint inhibitors (ICIs) and adoptive cell therapy (ACT), have transformed the treatment landscape for a variety of solid malignancies. Yet, immunotherapy's unique toxicity needs to be examined further (7). From the year 2000 to 2014, the age-standardized 5-year net survival of lung cancer ranged from 10% to 20% in most countries, and thus treatments for this disease need to be further improved (8).

In 2018, the results of the first-in-human neural stem cell transplantation for the treatment of chronic spinal cord injury were published. After treatment, three of the four participants showed significant improvement in disease symptoms, with no complications (9). Cell therapy has been investigated in clinical studies as a treatment for disorders of the hematologic system, digestive system, respiratory system, and other systems. The majority of cell therapies are still in the early stages of development, but hematopoietic stem cell (HSC) transplantation is a proven method for treating hematological illnesses. Chimeric antigen receptor T cells (CAR-Ts) have been successfully used in the treatment of B-cell malignancies, resulting in a complete remission (CR) rate of up to 90% in patients with acute lymphoblastic leukemia, which suggests that cell therapy has good potential in the treatment of malignant tumors (10). As a novel therapeutic approach, cell therapy has been gradually applied to the treatment of lung cancer over recent years, and a degree of research progress has been made. In this paper, the theoretical basis, compelling evidence, research status, development potential, and current challenges of cell therapy for lung cancer are all thoroughly discussed. We present this article in accordance with the Narrative Review reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1015/rc).

Methods

We searched PubMed for references with the terms "lung cancer", "cell therapy", "CAR-T", "stem cells", "cytokine-induced killer (CIK)", and "tumor-infiltrating lymphocyte (TIL)" or their combination in the title or abstract. We also identified relevant articles from the reference lists of the selected articles. After inclusion and exclusion criteria were applied, with all authors implementing the same selection process, 81 papers were ultimately included. The search strategy is summarized in *Table 1*.

Cell therapy and lung cancer

Cell therapy is a type of ACT, which is a therapeutic method that involves isolating immune cells with antitumor activity from patients, expanding them *in vitro*, and then transplanting them back into patients to improve host immunity against diseases (*Figure 1*). A meta-analysis by Zhao *et al.* (11) showed that ACT could significantly improve the overall survival (OS) and progression-free survival (PFS) of patients with non-small cell lung cancer (NSCLC). Most cell therapies are still in the early experimental stage of development. Recent studies have demonstrated that these immunoregulatory cells are highly differentiated. If these cells are used in the clinical research

Table 1 Summary of the literature search strategy

Item	Specification
Date of search	March 28, 2023 and June 10, 2023
Databases and other sources searched	PubMed
Search terms used	Search terms: "lung cancer" OR "cell therapy" OR "lung cancer" AND "CAR-T" OR "lung cancer" AND "stem cells" OR "lung cancer" AND "CIK" OR "lung cancer" AND "TIL"
Time frame	1995–2023
Inclusion and exclusion criteria	Inclusion: all articles related to lung cancer and studies involving cell therapy
	Exclusion: articles not written in English
Selection process	L.L. conducted the literature search and analysis. All authors reviewed the final list of studies included in the review
Any additional considerations	Some papers were not obtained from PubMed but were rather referenced in papers from the original PubMed search

CAR-T, chimeric antigen receptor T cell; CIK, cytokine-induced killer cell; TIL, tumor-infiltrating lymphocyte.

of cell therapy, the deficiency in the treatment effect of traditional methods, especially in cancer therapy, can be remedied to a large extent (12). These cells, including T cells, stem cells, killer cells, dendritic cells (DCs), and TILs, among others, all exert immune function and can recognize and eliminate tumor-associated antigens (TAAs) (13).

CAR-Ts

CAR-Ts refers to the chimeric antigen receptor (CAR) expressed in T cells through genetic engineering technology, which can specifically recognize the antigen molecules of tumor cells so as to obtain T cells capable of specifically killing the antigen of tumor cells (*Figure 2*). The key structural element of CAR-Ts is the CAR, which is composed of a TAA binding domain (a single-chain fragment variable usually derived from the antigen-binding region of a monoclonal antibody), an extracellular hinge domain, a transmembrane domain, and an intracellular signaling domain (14). CAR-Ts specifically recognize tumor cell-surface antigens via major histocompatibility complex (MHC)-independent pathways to kill tumor cells, thereby avoiding the immune escape caused by the loss or downregulation of MHC. Moreover, CAR-Ts can increase costimulatory molecular signals, enhance the tumor destruction of T cells, and achieve an antitumor effect.

CAR-Ts were first applied in hematological diseases, exhibiting significant effectiveness against several hematological cancers (15). The safety and efficacy of CAR-T therapy in solid tumors are currently being examined in depth in a number of studies. Among these, the majority of feasibility clinical trials are related to CAR-T therapy for lung cancer. The optimal targets for CAR-T therapy are those that are specifically expressed or universally overexpressed in tumor cells and that are expressed at very low or limited levels in normal peripheral cells or tissues. Mesothelin (MSLN), mucin 1 (MUC1), glypican 3 (GPC3), prostate stem cell antigen (PSCA), epidermal growth factor receptor (EGFR), carcinoembryonic antigen (CEA), human epidermal growth factor receptor 2 (HER2), programmed death-ligand 1 (PD-L1), receptor tyrosine kinase-like orphan receptor 1 (ROR1), and other promising targets have been the focus of clinical trials of CAR-T for the treatment of NSCLC and small cell lung cancer (SCLC) (16). Zhang *et al.* (17) used EGFR subtype III-specific third-generation CAR-Ts in a mouse model of lung cancer metastasis. Their findings indicated that there was a considerable decrease in mouse mortality, decreased metastasis of lung cancer, and no overt signs of adverse reactions. Feng *et al.* (18) used CAR-Ts in the treatment of patients with advanced relapsed or refractory NSCLC expressing EGFR. Among 11 patients, two patients achieved partial response (PR), and five patients were stable for 2 to 8 months. In a phase I clinical trial conducted by Zhang *et al.* (19), EGFR-specific CAR-Ts generated by the piggyBac transposon system were used in patients with advanced relapsed or refractory NSCLC. The results showed that after

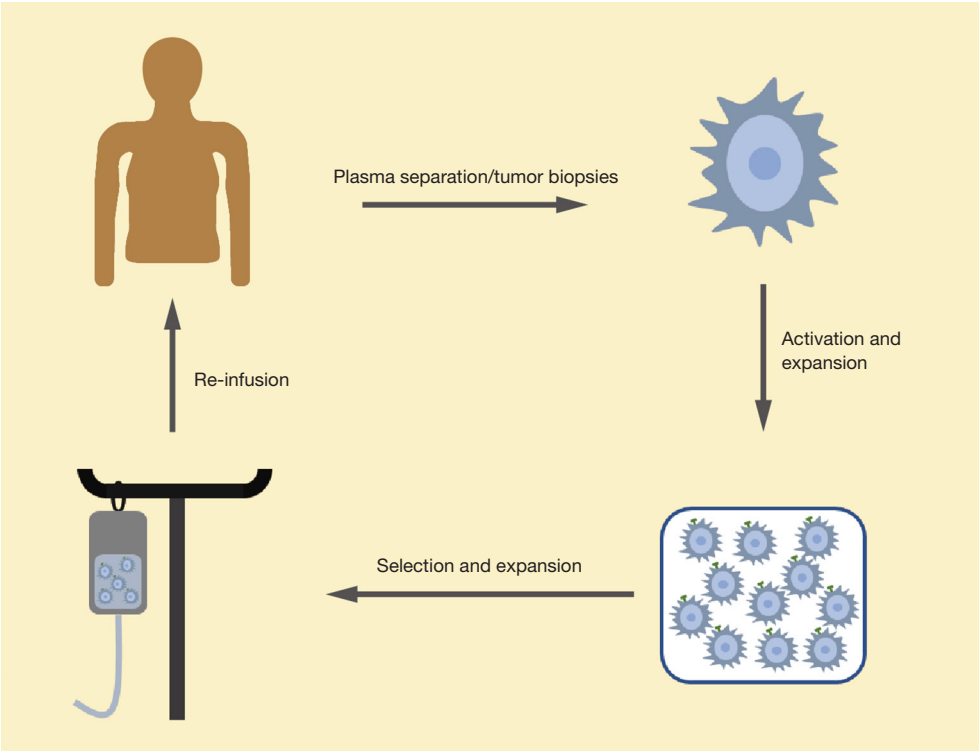

Figure 1 The principle of adoptive cell therapy involves isolating immune cells with antitumor activity from patients, expanding them *in vitro*, and reinfusing the cells into patients.

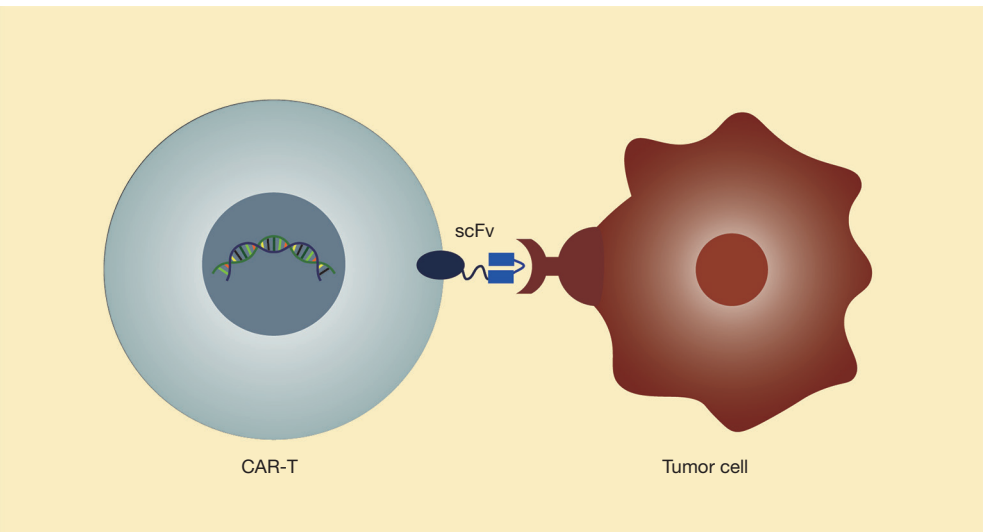

Figure 2 The tumor-associated antigen binding domain (single-chain fragment variable) on the surface of chimeric antigen receptor T cells specifically recognizes the surface antigen of tumor cells. CAR-T, chimeric antigen receptor T cell; scFv, single-chain fragment variable.

2 months of CAR-T cell infusion in nine patients, EGFR-CAR T cells were detected in the peripheral blood of eight patients, with one patient experiencing PR that lasted for more than 13 months, six patients with stable disease (SD), and two patients with progressive disease, which confirmed the safety and feasibility of CAR-T therapy for lung cancer. Common adverse effects after CAR-T infusion were mild skin toxicity, nausea, vomiting, dyspnea, and hypotension. MSLN is a tumor differentiation antigen that is underexpressed in normal mesothelial cells and overexpressed in a variety of solid cancers. including lung cancer, mesothelioma, and pancreatic cancer. In one study, MSLN-targeted CAR-T *in vitro* showed significant inhibitory effects on the proliferation and invasion of cancer cells (20).

T-cell receptor-engineered T cell (TCR-T) therapy is a more targeted cellular immunotherapy for cancer treatment. The modified T cells with new genes can express the T-cell receptor (TCR). The TCR-Ts can specifically recognize TAA and kill tumor cells. A recent study reported that TCR-T therapy could achieve anticancer activity in the treatment of NSCLC (21). PD-L1 is a significant immune checkpoint, is upregulated in multiple tumors, and can lead to the immune escape of tumor cells by binding to programmed cell death protein 1 (PD-1) on T cells. Agents targeting PD-1/PD-L1 signaling are flagship ICIs and constitute a breakthrough in the treatment of multiple types of advanced solid tumors. Studies have shown that PD-1 blockade could enhance the efficacy of CAR-T therapy in solid tumors (22,23) and represents an effective treatment strategy for NSCLC (24,25).

However, CAR-Ts have sufficient antitumor activity in solid tumors (26) because solid tumors rarely express specific tumor-associated antigens, resulting in off-target effects (27). CAR-Ts have limited persistence *in vivo* and the function is impaired (28). Prevention of CAR-T exhaustion may improve clinical outcomes for patients (29,30). A lack of highly immunosuppressive and metabolically challenging tumor microenvironments is an urgent problem that needs to be solved (31). In addition, CAR-T therapy induces a cascade of toxicity, including cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity (ICANS). Multiple organ damage and functional failure, along with other issues such as antitumor immune evasion response, physical barrier, and CAR-T depletion, can result from antigen-targeting and nontumor toxicity (16,32).

Stem cells

Stem cells are clonal cell populations derived from single cells that have the ability to indefinitely self-renew and differentiate into various cell types (33). Research into stem cells has revealed that the therapy of acute respiratory distress syndrome, myocardial infarction, and liver injury may all benefit from the use of stem cells (34). With their ability to invade cancer cells, release bioactive substances, and suppress the immune system, stem cells have substantial potential in treating cancer (35).

Mesenchymal stem cells (MSCs) are adult stem cells with the ability to differentiate into a variety of cell types and can be isolated from bone marrow, umbilical cord blood, peripheral blood, fallopian tube tissues, fetal liver tissue, and lung tissue. MSCs have the ability to specifically localize tumors and their metastases and have been employed to treat degenerative illnesses in preclinical and clinical trials (36). Among the types of MSCs, bone marrow MSCs can be used to deliver various anticancer drugs directly into tumors (*Figure 3*) (37). According to Loebinger *et al.*'s study (38), MSCs expressing tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) migrate to tumors, which can cause apoptosis and the death of lung cancer cells, hinder the formation of side population (SP) cells, reduce the growth and metastasis of primary tumor, and exert a synergistic effect with chemotherapy to induce apoptosis, which plays a role in preventing cancer recurrence. Sage *et al.* (39) are conducting phase I–II clinical trials of TRAIL-transduced MSCs in lung cancer treatment and remain in the experimental stage. TRAIL activates exogenous apoptotic pathways by binding to cell-surface death receptors and selectively induces apoptosis in cancer cells without affecting healthy cells. Additionally, MSCs' low immunogenicity, lack of MHC II, and expression of their costimulatory molecules (CD80, CD86, and CD40) may prevent allogeneic cells from inducing an immune response in patients, negating the necessity for human leukocyte antigen (HLA) matching and facilitating brief treatment with good safety (40). Chen *et al.* (41) prolonged the lifespan in a Lewis lung carcinoma model by using MSCs to express pigment epithelium-derived factor (PEDF). PEDF directly inhibited tumor effects via anti-angiogenesis, tumor differentiation, and apoptosis, indicating that MSCs can be used as an effective vector for tumor gene therapy. Yan *et al.* (42) applied human umbilical cord MSCs (HUC-MSCs) to express secretable soluble

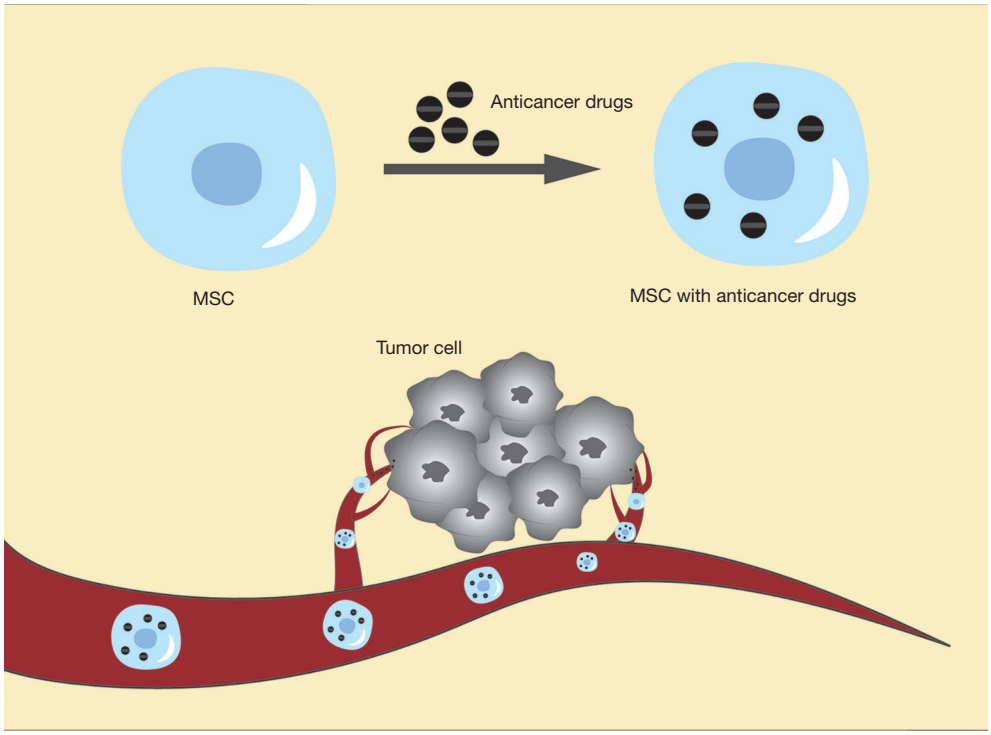

Figure 3 Mesenchymal stem cells carry anticancer drugs target to tumor cells and then release the drugs. MSC, mesenchymal stem cell.

TRAIL (sTRAIL). These cells migrated via the monocyte chemoattractant protein-1/CC chemokine receptor 2 (MCP-1/CCR2) axis to mouse lung cancer tissues that had been injected with A549 human lung cancer cells and exhibited antitumor effects *in vivo* without significant side effects. As the precursors of most stromal cells, MSCs can affect the disease progression of various tumors, including lung cancer (40,43), for which they may exert an inhibitory effect. Moreover, studies have shown that MSCs can effectively inhibit the proliferation and induce apoptosis of A549 cells (44,45).

MSCs are a critical factor in the growth, metastasis, and drug resistance of lung cancer cells and may be used as an effective method for the treatment of lung cancer. However, some studies have shown that MSCs can inhibit the apoptosis of lung cancer cells, promote tumor growth, and facilitate the occurrence and development of lung cancer (46). Liu *et al.* found that MSCs can spontaneously hybridize with NSCLC cells, which can enable these tumor cells to acquire abilities of epithelial-mesenchymal transition (EMT) and stem cell-like self-renewal. Indeed, the interaction between MSCs and lung cancer remains ambiguous, and further study in this direction is needed (43). In addition, the proliferation and differentiation potential of MSCs are greatly affected by environmental factors, and it has been shown the proliferation and differentiation abilities of MSCs gradually decrease after they are passaged *in vitro* (36).

CIKs

CIKs, a newly discovered antitumor effector cell, are a subtype of T lymphocytes. CIKs have the phenotype of natural killer (NK) T cells and express both CD3 and CD56 markers. In many studies, the $CD3^+CD56^+$ subsets show the highest levels of antitumor activity against a variety of tumor target cells with non-MHC-restricted cytotoxicity. Activated T cells induced by cytokines such as interferon-γ (IFN-γ) and interleukin-2 (IL-2) *in vitro* can directly kill tumor cells and generally enhance the immune function of patients with cancer (*Figure 4*) (47). Schmeel *et al.* (47) examined 2,729 patients for clinical trials of 22 kinds of solid tumors. The results showed that the average effective rate of CIKs against solid tumors was 39%, the OS was significantly increased, the quality of life was significantly improved, and the side effects were slight. CIKs may have considerable potential in improving tumor prognosis. Wang *et al.* (48) reported that compared with conventional treatment—

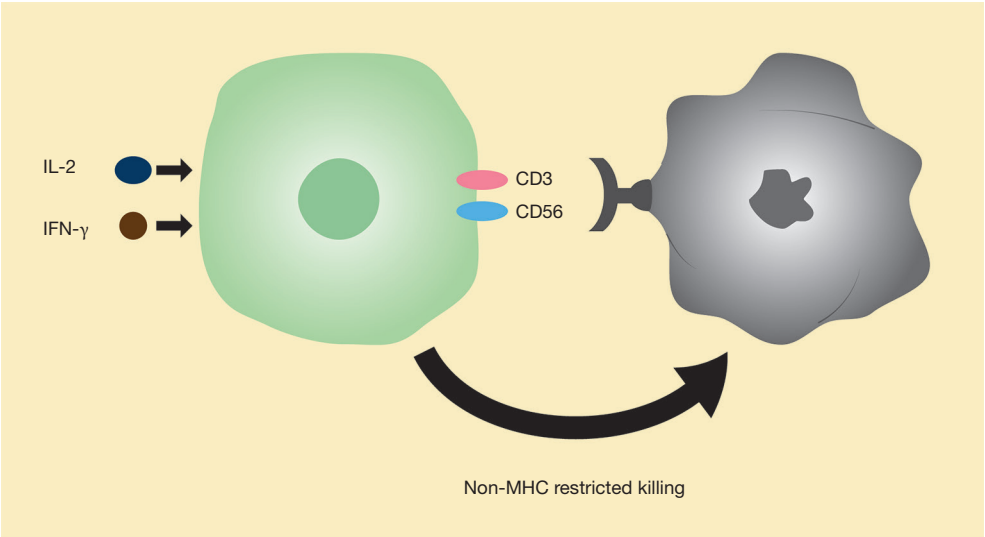

Figure 4 Activated T cells induced by IFN-γ and IL-2 *in vitro* can express both CD3 and CD56 markers, which can bind tumor cells with non-MHC-restricted cytotoxicity. IL-2, interleukin-2; IFN-γ, interferon-γ; MHC, major histocompatibility complex.

including chemotherapy—in patients with lung cancer, adoptive immunotherapy with adjuvant CIK cells yielded a significantly higher objective response rate (ORR) and OS. The percentage of $CD3^+$, $CD4^+$, $CD4^+CD8^+$, $CD3^+CD56^+$, and NK cells increased after CIK combined treatment, and CEA was more likely to decrease to normal levels. In Han *et al.*'s (49) study, patients with advanced NSCLC treated with CIK cells combined with PD-1 inhibitor had an ORR of 42.9%. In these patients, the T-cell level was significantly increased but not the incidence of adverse events. CIKs can be effectively expanded by peripheral blood mononuclear cell culture *in vitro* and are easy to obtain. CIK therapy is associated with a low incidence of graft versus host disease (GVHD), can strengthen the immune function of patients with lung cancer to help prevent cancer recurrence and metastasis, and can prolong the OS and PFS of these patients (50,51).

Some studies have shown that CIKs in combination with PD-1 blockade can enhance the efficacy of CIK therapy for patients with NSCLC, providing an experimental basis for clinical practice (52-54). Zhao *et al.* investigated the efficacy of PD-1 blockade combined with CIKs in patients with advanced NSCLC who failed at least two treatment regimens. They reported a disease control rate (DCR) of 85.7% and found this treatment to be safe and effective. Among the seven patients, two patients achieved PR and four patients experienced SD (55). Hui *et al.* reported clinical evidence that PD-1 blockade plus autologous CIK therapy was effective in treating patients with advanced squamous NSCLC and severe thrombocytopenia (56).

Notably, compared with the administration of DCs alone, the cocultivation of CIKs and DCs can significantly enhance the antitumor immunity and cytotoxic activity. Xiao *et al.* (57) examined 28 randomized controlled trials of DC-CIK therapy combined with chemotherapy in the treatment of NSCLC. The results showed that DC-CIK treatment could significantly increase the proportion of peripheral blood T-lymphocyte subsets. The antitumor effect was enhanced, and the ORR and DCR of the patients were effectively improved. DCs are by far the most powerful antigen-presenting cells, which are crucial to the host's immune response. CIKs exert stronger tumor-killing activity than do lymphokine-activated killer cells (LAKs). Therefore, DC-CIK therapy, which involves coculturing DCs and CIKs, has enormous potential for the targeted treatment of malignant tumors (58). One study demonstrated that PD-1 blockade–activated combined DC-CIK treatment in patients with advanced solid tumors was safe and effective (59). Despite these promising findings, patients treated with CIKs should be aware of issues such as recurrence, ineffective treatment, and unclear toxic effects (60).

TILs

TILs are a cell population that can exert antitumor activity. They can be obtained by stimulating and activating

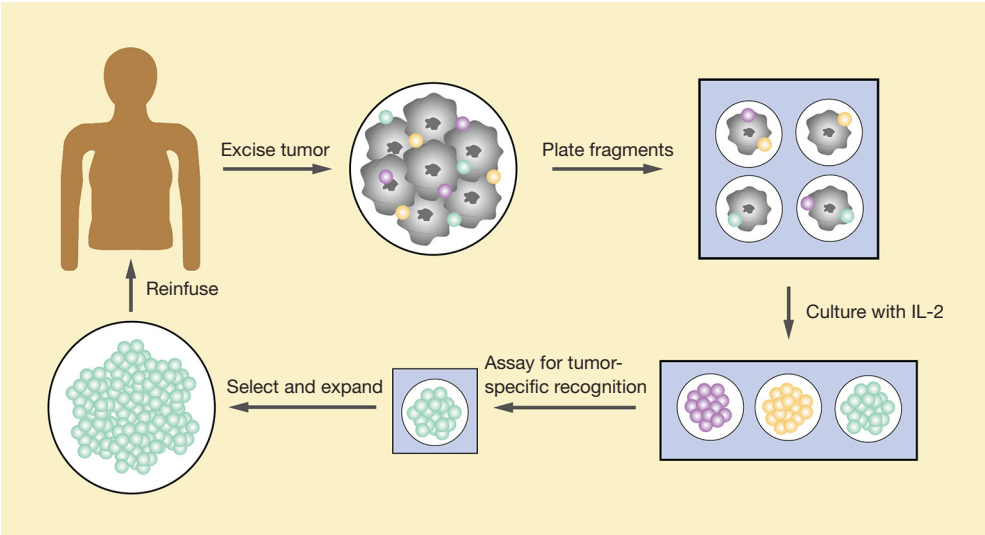

Figure 5 The tumor tissues isolated from patients are activated with IL-2 *in vitro*, and after tumor-specific recognition and selection, the cells with anti-tumor activity are expanded and then reinfused into patients. IL-2, interleukin-2.

infiltrating lymphocytes isolated from tumor tissues with IL-2 *in vitro* and further expansion after culture (*Figure 5*) (61). TILs were initially used to treat metastatic malignant melanoma and found to be capable of providing a good therapeutic effect (62). According to the relevant research, the remission rate of patients with malignant melanoma treated with TILs can reach 36% (63). Creelan *et al.* (64) conducted a phase I clinical trial in 20 patients with early progression of advanced NSCLC who were treated with nivolumab in PD-1 inhibitor monotherapy. Of these patients, 68.75% experienced tumor shrinkage after TIL treatment, and CR was achieved in two patients. Adverse effects of TIL include hypoproteinemia, nausea, hyponatremia, and diarrhea, but they can be effectively controlled in most patients. Iovance Biotherapeutics, a biotechnology company, opened a phase II, multicenter study (IOV-COM-202; NCT03645928) to evaluate autologous TILs in patients with solid tumors. After one cycle of LN-145 therapy, the overall response rate of 28 patients with metastatic NSCLC was 21.4%, one patient experienced CR, five patients experienced PR, and two patients had a PD-L1-negative response. Disease control was achieved in 64.3% of patients. Treatment-related adverse effects were fever, nausea, and cytopenia (65), and no unexpected adverse effects have been identified or encountered thus far. Additionally, Iovance has initiated another phase II trial (IOV-LUN-202; NCT04614103) to examine LN-145 in the second-line treatment of patients with metastatic NSCLC who progressed on previous ICI therapy and chemotherapy.

In recent years, the combination of TIL therapy with tumor-specific antigen (TSA) has provided a new direction in the development of TIL therapy. TSA, also known as neoantigen, is an abnormal protein produced by the somatic mutation of tumor cells (66). Achilles Therapeutics have begun the phase I–IIa CHIRON clinical trial to evaluate the safety, tolerability, and clinical activity of clonal neoantigen-reactive T cell (cNeT) therapy as a single dose in adult patients with advanced metastatic NSCLC. Among the eight enrolled patients, one experienced PR (56% tumor reduction maintained at week 36) and six experienced SD, with an overall durable clinical benefit at 12 weeks in 71% of evaluable patients (5/7) with advanced NSCLC. The safety and tolerability of cNeT therapy was observed to be better than those of standard TIL therapy, with the most common adverse events being lymphopenia and neutropenia (67).

Conclusions

Most of the research related to cell therapy for lung cancer thus far remains in the stages of preclinical or clinical trials. The United States National Library of Medicine clinical trials registered website lists almost 100 cell treatments for clinical trials in lung cancer (http://www.clinicaltrials.gov; accessed in April 2023). A substantial amount of clinical research data is required to support cell therapy for lung cancer before it can be widely applied in clinical

Table 2 Studies on conventional treatments combined with cell therapy for lung cancer

Conventional treatment	Cell therapy	Diseases	Number of patients	Results	Year	References
Surgery	TIL	Stage III NSCLC	24	The median survival was 14 months, and the 2-year survival was 40%	1995	Ratto *et al.* (68)
Chemotherapy	DC-CIK	Advanced NSCLC	60	The median survival time of was 13.8 months. More than two immunotherapies improved TTP and OS	2014	Zhong *et al.* (69)
	DC-CIK	Stage IB NSCLC	66	Patients in the DC-CIK therapy group had significantly longer OS and PFS	2015	Li *et al.* (70)
	CIK	Extensive stage NSCLC	44	The total response rate and PFS in the combined treatment group were longer than those of the control group	2017	Huang *et al.* (71)
	DC-CIK	Advanced NSCLC	135	The PFS and OS for DC-CIK plus chemotherapy were higher. The abundance $CD3^+$ T cells increased after immunotherapy	2019	Zhao *et al.* (72)
	CIK	Different progression stages NSCLC and SCLC	68	The median OS and the 3-year OS of patients in the CIK group were longer than those in the control group	2018	Chen *et al.* (73)
	DC-CIK	Locally advanced NSCLC	142	The OS and PFS in the DC-CIK group were superior to those in the chemoradiotherapy group	2020	Tian *et al.* (74)
	DC-CIK	Intermediate to advanced NSCLC	60	The overall cancer control rate of treatment in the DC-CIK immunotherapy plus chemotherapy group was higher	2021	Wang *et al.* (75)
	DC-CIK	Advanced NSCLC	507	Chemotherapy reduced the incidence of DTH in patients receiving DC-CIK therapy	2016	Zhang *et al.* (76)
Chemoradiotherapy	TIL	NSCLC	131	The 3-year survival was better for patients who underwent TIL therapy, especially for patients with stage IIIb NSCLC	1996	Ratto *et al.* (77)
Targeted therapy	R-CIK	Advanced NSCLC	7	Partial remission was achieved in two patients and stable disease in four patients, one patient experiencing progressive disease. The median TTP was 4.8 months	2018	Zhao *et al.* (55)
	CIK	NSCLC	1	The patient achieved a near-complete response. No adverse events occurred during treatment	2018	Wang *et al.* (78)

TIL, tumor-infiltrating lymphocyte; NSCLC, non-small cell lung cancer; DC, dendritic cell; CIK, cytokine-induced killer cell; TTP, time to progression; OS, overall survival; PFS, progression-free survival; SCLC, small cell lung cancer; R-CIK, RetroNectin-activated CIK; DTH, delayed-type hypersensitivity.

practice. Despite the progress made in this area, there are critical challenges that need to be overcome, including the complexity of preparation technology, high cost, tolerability to immunotherapy, insufficient antitumor activity in solid tumors, the high heterogeneity of tumors, unclear side effects, and adverse reactions.

Nonetheless, cell therapy represents a novel option for patients with lung cancer and has favorable potential in the treatment of lung cancer. Moreover, cell therapy, while not a substitute for conventional means of treatment, can complement these therapies (details in *Table 2*). Cell therapy can be administered to postoperative patients with a small tumor burden to remove small residual lesions, prevent tumor recurrence and metastasis, and thus improve the cure rate (17,46,68). Many studies have shown that for patients undergoing chemotherapy, combination with cell therapy can enhance the immune function of patients, prolong OS and PFS, improve the quality of life of patients, reduce the incidence of adverse reactions, and inhibit tumor progression (38,69-76,79,80). Ratto *et al.* (77) reported that compared with chemoradiotherapy alone, TIL therapy combined with chemoradiotherapy could significantly improve the survival rate of patients with stage III NSCLC. Targeted therapy combined with cell therapy is considered to be a safe and effective treatment method, which can exert strong antitumor activity and improve the control rate of the disease (55,78,81). Thus far, cell therapy has shown good antitumor activity in lung cancer, especially in NSCLC. Due to the lack of understanding in SCLC regarding the molecular mechanism underlying rapid progression, tumor genetic heterogeneity, and treatment resistance, good efficacy has not been achieved for this disease type.

Cell therapy has been applied in the treatment of lung cancer and has been used in combination with conventional methods to provide new solutions in clinical practice. Many relevant issues, including finding stably expressed sites, reducing off-target toxicity, mitigating cytokine storm, understanding the mechanism of cell therapy, and developing a clinical application strategy, still need to be researched further. In the future, studies into cell therapy can examine their combination with traditional methods in the treatment of lung cancer to improve the efficacy of drugs and reduce the occurrence of adverse reactions, thus providing a more effective treatment of lung cancer.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1015/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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