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Recent advancement of immunotherapy targeting lung cancer

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Abstract. As one of the leading cause of deaths in all types of cancer, lung cancer has attracted public attention more than decades. Many chemotherapy and physical surgery therapies have been investigated and applied to lung cancer patients to increase the overall survival rate. As a more recently emerging therapy, immunotherapy is keep advancing in recent years and has achieved great success to complement the traditional therapy's weak point and even become the first line treatment against certain types of non-small cell lung cancer (NSCLC). The safety and overall survival improvement of immunotherapy drugs has been tested through multiple cycle of clinical trials, validating their potential for lung cancer treatment. Several clinical trials study the application of immunotherapy singly or in combination with chemotherapy has been established to target lung cancer many years ago. Here, this review will introduce the three most common immunotherapies against lung cancer, and both summarize their application and discuss their recent advancement based on multiple ongoing or finished clinical trials.

Keywords: Lung cancer, CAR-T therapy, cancer vaccine, immune checkpoint inhibitor.

1. Introduction

Cancer treatment is one of the hottest topics in the medical area, different from other diseases, cancer seems to be an original sin that haunts mankind. No matter of stage or wealth, cancer can always chase their victims and bring them suffering and death. Lung cancer caused 134,592 people died in 2021, which takes about 22% of all cancer leading death. The lung cancer causing death is showing a decreasing trend in recent years, the estimate number of people die from lung cancer is 127,070 in 2023. Even though the changing of environmental factors and living patterns are non-neglectable factors contribute to this decreasing tread, the advancement of treatments targeting lung cancer would also participating a vital role.

Lung cancer is a malignant tumor that develops in the bronchi or alveoli and begins with the uncontrolled growth of tissue cells. This unchecked proliferation of malignant cell would eventually take a large portion of energy and impair the normal function of lung. If left untreated, the tumor cells have a chance of being cleared by the immune system or get avoid the surveillance and metastasize to nearby tissues or other parts of the body and cause further damage. The most common primary malignancy of the lung is epithelial carcinoma, which can be roughly divided into small cell carcinoma (SCLC) and non-small cell carcinoma (NSCLC), the percentage for these two subtypes in lung cancer is about 20% to 80%. The NSCLC can further divide into squamous carcinoma, adenocarcinoma and large cell carcinoma. The etiology and pathogenesis for these multiple types of lung cancer indicate they

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need to be carefully identified and diagnosed to select the most suitable treatment for lung cancer patients. The most common symptoms of lung cancer are cough (including coughing up blood), weight loss, shortness of breath, and chest pain. In current days, lung cancer is the second most common cancer type in the US for both genders, it is also the leading cause of death among all types of cancers. Even though the rate of getting lung cancer is different for men and women, the same thing they both share is that the lung cancer causing death is even more than breast, prostate and colon cancer combined together [1]. The causes of cancer are so numerous and it is hard to enumerate them all, but a common sense is that due to industrialization and modernization, air pollution is contributing more to lung cancer, especially in the developing country. Smoking is another main contributing factor for lung cancer, which is also the factor that causes incidence variance between men and women. In recent years, the lung cancer rate has decreased in both men and women, but there is a lag for women's cancer incidence dropping which may attribute to the fact that women smoking is actually peaking at twenty years later than men [2]. Some other physical factors such as asbestos inhalation could also contribute to lung cancer development. The asbestos fibers can become airborne and lodged in the lung after inhalation, this mineral fiber cannot degrade by the human immune system and cause physical lesions. The asbestos can cause DNA damage by both inducing the production of reactive oxygen species and its physical features, eventually causing chronic inflammation and tumor immunity reduction [3]. A genetic study from a family with multiple members easily affected by lung, head or neck cancer shows a locus on chromosome 6q23-25, which indicates an inherited gene shared by a family could also contribute to the lung cancer development [4].

This review systematically introduces the current stage of multiple immunotherapies against lung cancer and discuss their application and limitation targeting different subtypes of lung cancer carrying multiple diagnostic biomarkers.

2. Immunotherapy efficacy predictor

Multiple factors can work together to contribute to lung cancer mutagenesis, which indicate there could also have many biomarkers useful to trace the induction and target the cancer cell. Lung cancer patients often bear a heavy mutation burden, multiple gene mutation could co-contribute to the neoantigens expressing on the cancer cells. Some peptides may express differently than normal cells due to the mutation that happens on cancer cells and become neoantigens, which are also called tumor specific antigens (TSA). Overexpression of certain peptides on cancer cells could also become tumor associate antigens (TAA), they can also be used to discriminate the cancer cells from normal cells.

Some genes that are highly related to the tumor development could be a biomarker to identify and classify the cancer types. Epidermal growth factor receptor (EGFR) is often highly expressed in most types of cancers, in lung cancers it is a common biomarker to identify NSCLC. EGFR is a transmembrane receptor which controls the signaling pathway for cell proliferation. Some studies show overexpression of EGFR could contribute to the cell malignancies, decreased patients' survival rate and with poor chemosensitivity. EGFR predominantly mutation could be a biomarker to indicate using immune therapy such as tyrosine kinase inhibitor against EGFR or CAR T cell therapy that target the EGFR overexpression genetic mutation can be useful to relief patients' syndrome and increase the overall survival rate.

PD-1 and PD-L1 is a receptor ligand system, PD-1 is a receptor expressed on many different lymphocytes, including T cells, B cell, monocytes, and natural killer cells. PD-L1 is a co-inhibitory factor which binds with PD-1 and activates like an immune checkpoint to inhibit the immune cell activation. This immune checkpoint can down regulate the immune system activation and contribute to self-tolerance. Some cancer cells including NSCLC also express PD-L1 on their plasma membrane and cytoplasm, which is induced by the pro-inflammatory molecule IFN-γ. The tumor microenvironment would also upregulate pro-inflammatory cytokine IFN-γ expression, thus further increasing the expression of PD-L1 on cancer cells [5]. The PD-L1 overexpression could be a biomarker for immune checkpoint inhibitors (ICI) against NSCLC and some of them already have significant clinical results.

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3. Immunotherapy against lung cancer

3.1. Cancer Vaccine

Vaccine is usually against viruses and infectious diseases by training the adaptive immune system and clearing the pathogens quickly during the second encounter. The identification of TAA or TSA from lung cancer cells makes using vaccines as an immunotherapy treatment platform become possible.

3.1.1. Cancer vaccine using TAA. There are four main types of cancer vaccine using TAA as antigens to target NSCLC, cell based, protein based, viral vector and gene based. Cell based vaccine is directly using living or dead tumor cells combined with several cytokines or stimulating factors to facilitate the immune system recognizing and clearing of the existing cancer cells. Belagenpumatucel-L is one of the tumor vaccines against NSCLC, it contains four NSCLC cell lines and transfected with transforming growth factor beta2(TGF-beta2). After administration, the vaccine plasmid can target the host NSCLC cells and express antisense RNA, which can suppress the tumor TGF-beta2 expression [6]. A phase II clinical study monitors the circulating tumor cell (CTC) and the overall survival, it shows a correlation with lower CTC count and improved survival, the higher dosage of Belagenpumatucel-L also shows significantly improved survival advantage [7]. A phase III clinical study using Belagenpumatucel-L to treat NSCLC patients shows the overall survival improved with those who completed chemotherapy or radiation within 12 months [6]. These two clinical studies both proved the safety and efficacy of using Belagenpumatucel-L, a cell-based cancer vaccine against NSCLC.

The outcome of protein-based vaccines are not as ideal as the cell based vaccine, four different epitope based cancer vaccines combining with adjuvants designed to trigger the antitumor response, none of them has significant advantage compared with the placebo group. MAGE-A3 cancer vaccine is a peptide cancer vaccine which uses recombinant MAGE-E3 protein as an immunostimulant to elicit the antitumor immune response. MAGE-A3 is a germline antigen expressed by 30-50% of NSCLC, it could be a potential target to identify the cancer cells. But the result is not ideal, there is no significant difference between the treatment and control groups in a phase III clinical trial, and then the study is terminated [8]. The reason for terminating CIMAvax-EGF, Racotumomab-alum and Tecemotide is the same, they do not show significant improvement on NSCLC patients overall survival rate.

Viral based cancer vaccine is using genetically edited virus that replicate within the cancer cells, it can stimulate the cancer cell apoptosis and upregulate the peptide loading on MHC I for better cytotoxic T cell targeting. Currently, virus-based vaccine targeting NSCLC is under better condition than the peptide-based vaccine, but there is still no FDA approved virus-based cancer vaccine. TG4010 is a viral based vaccine based on modified vaccinia of Ankara, it both expresses tumor antigen transmembrane glycoprotein mucin 1 (MUC1) and IL-2. A phase II clinical study using TG4010 combining with cisplatin and vinorelbine against NSCLC, the media survival in both groups is similar, but the responding patients in treatment groups have improved survival (23.3 vs. 12.5 mo) [9]. LV305 is a novel virus-based vaccine using genetically edited lentivirus to selectively transduce EY-ESO-1, a common cancer TAA, into the dendritic cell to stimulate the cytotoxic T cell targeting the cancer cells carrying EY-ESO-1. A phase 1 clinical trial has already proved its safety in patients with sarcoma, NSCLC and currently evaluating patients with melanoma (NCT02122861).

Gene based vaccines are using either DNA or RNA as the platform to deliver genes encoding tumor antigens to stimulate the antitumor immune response. Due to its composition stability, DNA vaccines are usually more stable and with higher safety than ordinary vaccines. The RNA vaccine platform was recently advancing due to the COVID vaccine development, which has more advantage than DNA vaccine on effectiveness and design because it does not need to be delivered into the nucleus and can skip the transcription step for activation. A phase 1 clinical study using particle-mediated epidermal delivery (PMED) delivers NY-ESO-1 plasmid DNA (pPJV7611) into the patients with tumor and historically proven express NY-ESO-1 or LAGE-1. By analyzing the patients receiving variable dosage of vaccine during a 13 weeks trial, the number of CD4+ T cells is generally increased in most patients and only a particle number of patients have CD8+ T cell increase (NCT00199849).

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3.1.2. Cancer vaccine using TSA. Neoantigens are generated through somatic hypermutation that happens in cancer cells; they have higher specificity and immunogenicity than TAAs. Neoantigens also have less off-target issue when designed as a cancer vaccine target. In recent years, with the advancement of second-generation genetic sequencing and complement of neoantigens library, the frequency of neoantigens in NSCLC is summarized and more neoantigens based cancer vaccines have registered on the US clinical trial website.

NEO-PV-01 is a personalized cancer vaccine currently under open-label, Phase IB study combining with adjuvant nivolumab for patients with melanoma, lung cancer or bladder cancer. The clinical trial has proved its safety and neoantigen-specific CD4+ and CD8+ T cell responses are both observed in the post-vaccinated patients. The neoantigen vaccine specific T cell cytotoxic potential is evaluated through the surface expression level of CD107a, a marker for T cell degradation, which is also used to evaluate immune cell antitumor activity. Among 71 CD4+ and CD8+ T cell epitopes tested, 58% of tested epitopes showed CD107a positive expression after vaccination [10].

RO7198457 is a RNA-Lipoplex neoantigen cancer vaccine, in a Phase IB clinical study combining with atezolizumab (anti-PD-L1) to stimulate the T cell immune response against NSCLC and melanoma. It is designed to deliver RNA to dendritic cells carried by lipoplex and then translate to present neoantigens to CD4 and CD8 T cells. The RNA in the dendritic cell would also be recognized by Toll like receptor (TLR) 7 and 8 to induce proinflammatory cytokines secretion to facilitate CD8+ T cells. By analyzing the proinflammatory cytokines level and CD4+ and CD8+ neoantigen specific T cell response, RO7198457 combining with atezolizumab is safely for patients and can successfully stimulate T cell immune response and the stimulated T cells can infiltrate the tumor cells [11]. Another ongoing Phase II clinical trial is studying RO7198457 combined with atezolizumab in patients with Stage II-II NSCLC (NCT04267237).

The main drawback of using TAA as the antigens to target the cancer cells is they already developed a strong tolerance in the immune system, since they are also expressed by normal cells, the lymphocytes against these antigens would get apoptosis during their maturation step. It would not be easy to induce an immune response against these self-expressing molecules, at the same time, a strong immune response induced by the cancer vaccine would also indiscriminately target all carriers and eventually develop into autoimmune disease [12]. Unlike TAA, TSA is a better target for cancer vaccine development, since it only expresses due to the cancer cell somatic hypermutation. Proteins expressing abnormally on cancer cells can be identified as neoantigens which trigger the adaptive immune response spontaneously and target by the cytotoxic T cell. Tumor mutation burden (TMA) is used to account for the genetic mutation that happens on cancer cell DNA. However, the mutation generated in NSCLC is highly variable, even those sharing the similar TMA level may have variable response to the same immunotherapy.

3.2. CAR-T therapy

Chimeric antigen receptor T (CAR-T) cell therapy is to genetically edit the patients' T cell to make it specifically targeting cancer cells which downregulate MHC I but expressing TAA or TSA. The edited CAR-T cells have enhanced targeting and cytotoxicity against cancer cells. CAR-T cell therapy is constitutively advancing from the time it was first developed. The first generation of CAR-T cell was only engineered to carry a single CD3ζ at the intracellular domain, then the second generation started carrying costimulatory domains such as CD28 and 4-1BB to improve the T cell proliferation and cytotoxicity. The third generation is combining multiple costimulatory domains together to both elongate the CAR-T cell persistence and cytotoxicity, but there is no difference on the efficacy between third and second generation. Currently, the fourth and fifth generation of CAR-T cell carrying costimulatory domain with constitutive or inducible cytokine expressing cassettes are undergoing testing for higher cancer treatment efficacy [13].

Multiple TAA and TAA targeting CAR-T cell therapies are undergoing clinical trials against lung cancer, including EGFR; mesothelin (MSLN); human epidermal growth factor receptor 2 (HER2); MUC1, etc. A phase 1 CAR-T cell clinical study targeting EGFR is applied to relapse or refractory

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NSCLC patients with >50% EGFR expression. By comparing the biopsied tumor tissues and the level of CAR-T-EGFR cells in the peripheral blood from patients in various dosing of CAR-T cells, CAR-T cells can specifically accumulate in the tumor tissue [14]. This clinical trial confirmed the ability of CAR-T-EGFR cells to traffic and accumulate at the EGFR positive tumor region. By evaluating the cytokine production level in CAR-T cell in vitro co-culture with EFDR positive tumor cells and patients' cytokine level during the treatment, the safety and specificity of CAR-T-EGFR cell treatment is also validated.

Mesothelin (MSLN) is an glycoprotein highly expressed in NSCLC and mesothelioma cells. In normal tissues, only certain mesothelial cells express small amounts of MSLN15. Compared with constitutively and highly expressed on certain tumor cells, MSLN can be identified as TAA to target cancer cells. An in vitro experiment has validated the target specificity of MSLN targeting CAR-T cell therapy against MSLN expressing HeLa cells and a follow up in vivo experiment in the mouse model further validated the CAR-T therapy targeting MSLN could inhibit the tumor progression [15]. However, the tumor growth rate eventually synchronized in both treatment and control groups, indicating CAR-T cell therapy still needs enhancement or combining with other therapy together against tumor. Until now, there has been no FDA approved MSLN targeting CAR-T therapy or significant tumor suppressing outcome from clinical trials. A phase I clinical trial is ongoing to test the safety dosage of MSLN-targeting CAR-T cells combining with anti-PD 1 component on patients with mesothelioma (NCT04577362).

HER2 is important in cell growth, survival and differentiation, the high expression level of HER2 in multiple cancers makes it receive great attention. Two clinical trials had been applied to test the toxicity of CAR-T-HER2 cell therapy against HER2 positive cancers, including lung cancers. However, the result of the two trials is not unified. One Phase I clinical trial (NCT01935843) proved its safety and feasibility by evaluating the common adverse effect and clinical response. Another Phase I clinical trial (NCT02713984) was withdrawn due to the safety concern. The HER2 targeting CAR-T research was once suspended due to a report of a lethal case in which a patient with metastatic colon cancer was treated with CAR-T-HER2 [16], until Nabil Ahmed made another research proved the safety of CAR-T-HER2 in 19 HER2-positive sarcoma patients.

MUC1 is a transmembrane macromolecular glycoprotein aberrantly highly expressed in 80% of NSCLCs. It is normally involved in cell signaling and protects cells from extreme conditions. In cancer cells, the overexpression of MUC1 participates in various aspects of cancer development, including cell growth, proliferation, apoptosis, etc. An ongoing phase I/II clinical trial (NCT02587689) is testing the effectiveness and adverse effect of CAR-T-MUC1 against relapsed or refractory solid tumors including NSCLC. Instead of testing the MUC1 targeting CAR-T cell therapy alone, another phase I/II clinical trial (NCT03525782) knockout immune checkpoint receptor PD-1 in the CAT-T-MUC1 cells to test the safety of this combination therapy. There were no severe adverse events and cytokine release syndromes observed during the treatment. After the PD-1 knockout CAR-T-MUC1 infusion, all patients' symptoms had significant improvement.

3.3. Immune checkpoint inhibitor (ICI)

The human immune system can detect and eliminate cancer cells by itself, the reason why the tumor would keep progressing is that it could inhibit the immune function through multiple pathways. Immune system is a double-edged sword, it could clear the pathogens and abnormally dividing cells, however, it would also induce auto-immune disease under certain conditions. To avoid against normal tissues, T reg cells can inhibit the effector cells function and immune cells express checkpoint receptors to control immune response. The immune system is maintained at a homeostasis stage, too strong would induce auto-immune disease, too weak would not be able to eliminate invading pathogens and abnormal cells.

Immune checkpoint inhibitors are currently one of the most prominent immunotherapy drugs against most types of cancer. In treating lung cancers, FDA has already approved several ICI drugs targeting PD-1, PD-L1 and CTLA-4, and more ICI clinical trials targeting these two immune checkpoints are ongoing. To reach a better efficacy, ICI drugs are sometimes not solely applied to patients, they also

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combine with other cancer treatments such as chemotherapy, radiation therapy and multiple ICI drugs together.

PD-1/PD-L1 is a contact-dependent immune checkpoint pathway. PD-1 is expressed on many immune cells, including activated T cell, B cell, natural killer T cells, regulatory T cells and dendritic cells. PD-L1 is an immune inhibitory receptor ligand normally expressed by host immune cells, cancer cells such as NSCLC cells also often upregulate the expression of PD-L1. The upregulation of PD-L1 from lung cancer can be identified as a biomarker to determine the ICI treatment suitable for patients. The basic mechanism of ICI is using monoclonal antibodies to block the PD-1/PD-L1 pathway and enhance the effector immune cell activation. Currently, there are three FDA approved PD-1 targeting and two PD-L1 targeting monoclonal antibody against lung cancer.

3.3.1. PD-1 targeting. Nivolumab is a PD-1 blocking human antibody that can be used to treat melanoma, NSCLC, real cell carcinoma and many other types of cancer. It was first approved by the FDA in Dec, 2014 for melanoma treatment. In the next year, FDA expanded the approval of nivolumab for lung cancer treatment. In the following research, nivolumab is combined with platinum chemotherapy, or ipilimumab together against NSCLC under different conditions.

Pembrolizumab is a humanized antibody targeting and blocking PD-1, it was first approved by the FDA in Oct 2015 for targeting advanced NSCLC. PD-L1 can be used as a biomarker for pembrolizumab application. It can be applied to patients by itself or combining with carboplatin and either paclitaxel or nab-paclitaxel for NSCLC treatment. In 2023, pembrolizumab is also approved as an adjuvant treatment following chemotherapy and physical removal of NSCLC. Pembrolizumab has become the only ICI approved by FDA as both metastatic and adjuvant treatment for NSCLC patients regardless of PD-L1 expression [17].

Toripalimab is a recombinant PD-1 targeting monoclonal whole antibody, it was first designed to treat melanoma and nasopharyngeal carcinoma. Recently, an ongoing clinical trial (NCT04158440) using toripalimab combined with chemotherapy against respectable NSCLC indicated its effectiveness on lung cancer treatment. The event free survival in toripalimab treatment group has significantly increased compared with the placebo group.

3.3.2. PD-L1 targeting. Atezolizumab is a PD-L1 targeting humanized monoclonal antibody which binds with PD-L1 located on cancer cells to block it from binding with PD-1. It was first approved by the FDA to treat specific metastatic lung cancer in Oct 2016. Two years later, atezolizumab combined with Avastin and chemotherapy acquired FDA approval for the initial treatment of metastatic NSCLC. With more in-depth research, it acquired more approval to target different types of lung cancer as monotherapy or combination with other treatments together.

Durvalumab is another PD-L1 targeting antibody, different from atezolizumab, it is a human antibody. Based on the result from a phase III clinical trial with 713 patients (NCT02125461), durvalumab treatment group patients showed significantly longer progression free survival [18]. Then it acquired its first approval from FDA to target unresectable stage III NSCLC in Feb 2018.

3.3.3 CTLA-4. Different from the inhibiting pathway of PD1/PD-L1 to prevent effector cell activation, CTLA-4 is preventing antigen presentation to activate the following step in adaptive immune response. CTLA-4 is to regulate T cell proliferation and has a distinct binding orientation with higher avidity than CD28 on T cells binding with CD80/86 on antigen presenting cells. Blocking the CTLA-4 located on T cells could increase the binding of tumor antigen presenting APC with CD28 on T cell, thus increasing the T cell activation against cancer cells.

Ipilimumab is a monoclonal antibody targeting CTLA-4, a phase III clinical trial (NCT02477826) has been started since 2015 to compare the treatment outcome of Nivolumab plus Ipilimumab with chemotherapy in patients with metastatic NSCLC. A five-year survival outcome has been compared with these two treatments indicating the nivolumab plus ipilimumab could significantly improve the NSCLC patients' survival length. To better analyze the outcome between these two different cancer treatments, the trial separates the NSCLC patients into two groups, one is expressing ≥ 1% PD-L1,

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another is expressing < 1%. The former groups treated with combined ICI have 24% overall survival rate, the chemotherapy treatment group only has 14% overall survival rate. In patients with < 1% PD-L1, it's 19% versus 7% overall survival rate for combined ICI treatment versus chemotherapy [19].

Tremelimumab is another CTLA-4 targeting human antibodies. It shows promising clinical activity in metastatic melanoma, but the overall survival and progression-free survival outcome in the NSCLC treatment clinical trial (NCT02453282) combined with durvalumab is not significant enough compared with durvalumab or standard of care chemotherapy alone. However, a more recent clinical trial (NCT03164616) shows different result, it assigned three different groups, treatment arm1 is tremelimumab, durvalumab and platinum based chemotherapy, arm 2 is durvalumab plus platinum based chemotherapy, arm 3 is platinum based chemotherapy alone. The treatment arm 1 shows significant improvement of overall survival than arm3 and acquired FDA approval for metastatic NSCLC treatment in November, 2022.

4. Conclusion

Immunotherapy is a quickly advancing cancer therapy that can either effect on patients by itself or combine with traditional chemotherapy and surgery. Using immunotherapy against lung cancer only emerges in a couple decades and still has many limitations. But the promising result of clinical trials using immunotherapy against lung cancer has proved its safety and validates it has great development prospects. Currently there are many ongoing clinical trials with promising initial results using immunotherapy platforms treating multiple subtypes of lung cancer, as these trials finish, they will provide more safety and efficacy validations to fill up the gap in this area. With in depth research, scientists are developing multiple platforms targeting the subunits in the immune pathway to suit lung cancer patients under multiple progressions. The biomarker diagnostic before treatment could also choose the most suitable immunotherapy against different types of lung cancer. The cost of immunotherapy could also become more affordable for most patients as they have wider applications and become industrialized. In general, as the immunotherapy develops, it could eventually replace the chemotherapy for lung cancer treatment as the first line therapy with less side effects and prolonged patients' survival length.

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