Immunotherapy in Non-Small Cell Lung Cancer

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Cancer is a disease where cells mutate and grow uncontrollably. These cancer cells can even spread to new parts of the body. The immune system, a network of cells, tissues, and organs, fights against infections to protect healthy cells. Ideally, the immune system is supposed to recognize cancer cells as harmful and eliminate them to prevent the cancer from spreading. However, cancer cells can sometimes evade the immune system by hiding, suppressing immune responses, or mimicking normal cells by altering the expression of certain proteins on their surface**.** Immunotherapy is a type of treatment that utilizes the immune system to fight cancer. Rather than targeting all cells indiscriminately, as traditional treatments like chemotherapy and radiation often do, immunotherapy strengthens your immune system to better recognize and terminate cancer cells. This unique approach makes immunotherapy an attractive option to overcome cancer's ability to evade immune responses. This review examines current immunotherapy treatments and future directions for non-small cell lung cancer (NSCLC) treatment.

Lung cancer is the leading cause of cancer-related deaths worldwide[1], with NSCLC representing about 85 percent of cases[3]. NSCLC is divided into three different subtypes: adenocarcinoma, squamous cell carcinoma, and large cell carcinoma[1]. Symptoms of NSCLC include chest pain or discomfort, a cough that stays or worsens, trouble breathing, wheezing, coughing up blood, hoarseness, loss of appetite, unexpected weight loss, tiredness, difficulty swallowing, and swelling in the face or the vein in the neck[3]. NSCLC can be classified into five different stages of cancer – stage 0, I, II, III, and IV – each varying in degree, which can help determine treatments for patients[3]. Tests to diagnose NSCLC include laboratory tests, chest X-rays, CT scans, biopsies, sputum cytology, thoracoscopy, and thoracentesis[3]. Patients with NSCLC can be treated with surgery (section, lobectomy, or lung resection), radiofrequency ablation (RFA), radiation therapy, chemotherapy (systemic or regional), targeted drug therapy (monoclonal antibodies or tyrosine kinase inhibitors), and immunotherapy (checkpoint inhibitors including medications like pembrolizumab, cemiplimab, and atezolizumab)[3]. Known risk factors include, but are not limited to, smoking (tobacco), drinking alcohol, asbestos, radon, arsenic, chromium, nickel, exposure to secondhand smoke, pollution, radiation, and polycyclic aromatic hydrocarbons[1]. Individuals with pulmonary fibrosis and human immunodeficiency virus (HIV) are at higher risk of developing NSCLC, independent of smoking[1]. Lung cancer incidence is directly related to the rate of smoking tobacco in a population[1]. For example, the age-adjusted mortality rate in the United States is expected to drop about 79% from 2015 to 2065 due to the decreased use of tobacco[1]. Certain mutations of cancer can guide treatment decisions for patients. Approximately 30% of NSCLC cases have a mutation of the *Kirsten rat sarcoma (KRAS)* oncogene, making it the most common mutation found in NSCLC[2]. Other common mutations include *epidermal growth factor receptor (EGFR), MET, anaplastic lymphoma kinase (ALK),*

c-ROS oncogene 1 (ROS1), v-raf murine sarcoma viral oncogene homolog B (BRAF), neurotrophic tyrosine receptor kinasƒae (NTRK), human epidermal growth factor 2 (HER2), neuregulin-1 (NRG1), and *rearranged during transfection (RET)*[2]. The five-year survival rate for individuals with NSCLC without localized tissue or lymph node spread is 63%[3]. The regional five-year survival rate, where it has spread from the lungs to nearby tissue or lymph nodes in the individual, is 35%[3]. The metastatic five-year survival rate, where it has spread from the lungs to the brain or bones, is 7%[3].

NSCLC can evade the human immune system from being attacked in the pre-invasive lesions to the later, main NSCLC histotypes[5]. The two main pre-invasive lesions are adenocarcinoma (LUAD) and squamous cell carcinoma (LUSC), which can avoid the immune system by reducing antigen presentation, experiencing loss of heterozygosity at the Human Leukocyte Antigen (HLA), silencing neoantigens, activating immune checkpoints, changing TH1/TH2 cytokine ratios, and evolving in immune contexture[5]. The immune escape methods continue to change and develop as the cancer progresses, which can make NSCLC resistant to immunotherapy such as Immune Checkpoint Blockade (ICB)[5]. Cells that are often dysregulated in NSCLC are T cells (regulatory and dysfunctional), Natural Killer (NK) cells, dendritic cells (DC), macrophages, myeloid-derived cells, B cells, and neutrophils[5]. Cancer cells can avoid the immune system when expressing T-lymphocytes-associated antigen 4 (CTLA-4), programmed death 1 (PD-1), and programmed death ligand 1 (PD-L1)[4]. Patients with NSCLC benefit the most from immune checkpoint inhibitors (ICI), which is also the most commonly used immunotherapy, generally targeting either PD-1, PD-L1, or CTLA-4[4]. Specific types of ICIs include nivolumab, pembrolizumab, ipilimumab, atezolizumab, cemiplimab, durvalumab, and tremelimumab. Immunotherapy tends to be combined with other treatments such as surgery, chemotherapy, radiation, etc[4]. Many patients have a survival benefit and improved quality of life with immunotherapy, but only a small percentage of patients experience prolonged anti-tumor growth[4]. ICIs can even be called a “cure” in long-term responders to immunotherapy[4]. Not all patients respond to immunotherapy and few have long-term survival[4]. There are immune-related adverse effects (irAEs), especially when combining different approaches[4]. IrAEs are autoimmune conditions that can affect organ systems in the body after starting ICIs[4]. While ICIs can lead to improved survival and quality of life in some patients, immune-related adverse effects (irAEs) affect over 20% of patients, rising above 50% when combined with other therapies[4]. These irAEs, including potentially severe autoimmune reactions, underscore the need for careful patient selection and monitoring[4]. There have been a couple of different types of immunotherapies that have gained FDA approval in NSCLC, specifically many ICIs including nivolumab, pembrolizumab, ipilimumab, atezolizumab, and durvalumab[4]. There have been targeting therapies approved by the FDA including six mAb targeting PD-1/PD-L1 and one mAb targeting CTLA4[4]. In the future, advances in therapeutics will likely combine with diagnostics to improve patient selection for immunotherapy[4]. Continued development of effective

immunotherapy combinations and expansions into earlier stage NSCLC will likely increase the number of patients that respond to ICIs[4].

There have been two recent and ongoing immunotherapy clinical trials testing combination therapies on NSCLC. One trial explores the impact of combining statins with immunotherapy and the other investigates neoadjuvant Sintilimab with chemotherapy for EGFR-mutant NSCLC. The first trial is testing the combination of statin with PD-1/PD-L1 inhibitors in treating advanced non-small cell lung cancer. Patients need a diagnosis of stage IIIB or IV NSCLC that can't be removed surgically or by radiotherapy. The inclusion criteria include being 18-80 years old, not being able to use EGFR/ALK/ROS1 targeted therapy, having a measurable target lesion within 4 weeks prior to randomization, never receiving PD-1/PD-L1/CTLA-4 inhibitors treatment for this phase of NSCLC, having an indicator for statins, ECOG PS score (a performance status metric) 7 days prior to the first use of the drug is 0 or 1, having an expected lifetime over 12 weeks, and the main organ function works well. The exclusion criteria include there being other active malignancies within 5 years prior, currently participating in clinical research treatment, having received other research drugs, having used research devices within 4 weeks prior to the first administration, having an active autoimmune disease requiring treatment within 2 years prior to the first administration, receiving immunosuppressive therapy within 7 days prior to first administration, having a history of allogeneic organ transplantation and allogeneic hematopoietic stem cell transplantation, having contraindications with the use of statin, being allergic to a part of the drug, and having multiple factors affecting oral medicine. The study is examining the PD-1/PD-L1 expression on T-cells, which if lowered by statin would reduce immune evasion of PD-1/PD-L1. This study addresses the earlier limitations of evaluating the efficiency and safety of combining statin with immunotherapy in a controlled setting. Future research includes using larger-scale clinical trials to determine the optimal statin therapy to use with immunotherapy, as well as identifying suitable patient populations for this treatment. Similarly, the second trial focuses on combination treatments but in EGFR-mutant NSCLC. It is testing neoadjuvant (pre-surgical treatment) Sintilimab (a PD-1 inhibitor) with chemotherapy in EGFR-mutant stage II-IIIB non-small cell lung cancer. The inclusion criteria include being 18-75 years old, ECOG score of 0-1, having an expected survival over 3 months, having a measurable target lesion, meeting criteria for the main organ function, voluntarily joining the study, and providing informed consent. The exclusion criteria include having stage I or IV NSCLC, driver mutations, histologically confirmed SCLC, previously used anti-tumor drugs or radiotherapy, a history of active bleeding within 6 months prior to enrollment, underlying diseases that may affect the patient's prognosis, gastrointestinal abnormalities, being a pregnant or lactating woman, and not complying with the study guidelines. The study is examining the PD-1/PD-L1 expression on T-cells, which if lowered by neoadjuvant Sintilimab would reduce immune evasion of the PD-1/PD-L1. This study addresses the earlier limitations of finding treatment options for EGFR-mutant stage II-IIIB NSCLC due to the challenges in managing the immune evasion of cancer. Future research will focus on

large-scale trials to refine statin and immunotherapy combinations, as well as expanding neoadjuvant Sintilimab and chemotherapy strategies for EGFR-mutant cases, targeting specific patient profiles for optimal outcomes.

NSCLC, the most common and deadliest form of lung cancer in the world, has seen advances in immunotherapies shown to provide benefits to patients suffering from this disease. These immunotherapies for NSCLC help boost the immune system of the body and inhibit PD-1, PD-L1, and CTLA-4 to kill the cancer cells. ICIs are the main immunotherapies used in treating NSCLC, and they have been very impactful and game-changing, providing many benefits to patients, such as increased lifespan. The people in the field of treating NSCLC with immunotherapies are currently working on decreasing the amount of immune-related adverse effects (irAEs), which are autoimmune conditions that can affect organ systems after beginning ICIs. In the future, the use of immunotherapy in NSCLC should enhance survival rates through personalizing treatment and using a combination of therapies, which are likely to boost efficacy and potentially minimize side effects, addressing current limitations in NSCLC treatment. New research aims to iron out problems and increase the efficiency and survival of all patients.

References

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