

Immunotherapy in Non-Small Cell Lung Cancer (NSCLC): Chance and Challenge

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Abstract. Non-small cell lung cancer (NSCLC) is the major type of lung cancer, accounting for 85%. The common options for treatment include surgery, radiotherapy, chemotherapy, immunotherapy, and molecularly targeted therapy depending on the stage, histology, genetic changes, and health condition of patients. Sadly, just 15% of individuals with stage III NSCLC are still alive after five years, which indicates a bad outlook. Because of the use of PD-1 and CTLA-4 immune checkpoint inhibitors (ICIs), immunotherapy has unquestionably made the most progress in the field of NSCLC. This article offers a comprehensive exploration of NSCLC, encompassing its epidemiological characteristics, pathological processes of different classification, and the diverse treatment modalities available. It emphasizes the pivotal role of immunotherapy, particularly immune checkpoint inhibitors (ICIs) for treatment some classification of patients. The article discusses challenges and prospects, such as identifying patient populations that benefit most from immunotherapy and addressing issues like immune-related adverse events (irAEs) and immune resistance. Through this analysis, the article underscores the significant strides made in NSCLC treatment and the ongoing efforts to improve patient outcomes.

Keywords: Immunotherapy; non-small cell lung cancer (NSCLC); Immune checkpoint inhibitors (ICIs); TCR-T cell.

1. Introduction

NSCLC is a worldwide health issue. The prevalence of NSCLC varies greatly by region, with greater rates in affluent nations where cigarette use is more pervasive. The prevalence of lung cancer is thought to be lower in less developed nations like Central and South America and much of Africa. One of the reasons is many lung cancer cases go unreported which results from the fact that many developing nations lack centralized reporting systems, hiding the true prevalence of the disease [1]. The common options for treatment include surgery, radiotherapy, chemotherapy, immunotherapy, and molecularly targeted therapy depending on the stage, histology, genetic changes, and health condition of patients [2].

To treat both localized and distant micro-metastatic illness, concomitant chemoradiation therapy has been the chosen treatment for unresectable stage III NSCLC for the past ten years. Sadly, just 15% of individuals with stage III NSCLC are still alive after five years, which indicates a bad outlook. Because of the use of PD-1 and CTLA-4 immune checkpoint inhibitors (ICIs), immunotherapy has unquestionably made the most progress in the field of NSCLC in 2013, according to the magazine Science, which named immunotherapy the scientific breakthrough of the year.

This article delves into the multifaceted landscape of NSCLC, offering insights into its epidemiology, classification, and underlying pathological processes. Furthermore, the article simply introduced the diverse treatment modalities available for different classification patients, with a specific focus on the pivotal role of immunotherapy, such as ICIS, TCR-T cells, CAR-T and cancer vaccines. Importantly, ICIs have revolutionized NSCLC treatment, significantly improving patient outcomes in recent years. However, the article also addresses the challenges that persist in this field, such as identifying the ideal patient populations for immunotherapy, managing immune-related adverse events, and overcoming issues of immune resistance.

2. Pathological Classification and Characteristics

Non-small cell lung cancer (NSCLC) is the major type of lung cancer, accounting for 85%, which classified three types of adenocarcinomas, squamous cell carcinoma, and large cell carcinoma.

2.1. Adenocarcinoma

The most typical NSCLC is adenocarcinoma with largest proportion (40% in lung cancer), which are original from mutation of alveolar cells in the smaller airway epithelium, typically expressing immunohistochemical markers including TTF-1 and napsin A. It is more common in non-smokers and women. Adenocarcinoma contains 4 subtypes which are MIA, AIS, invasive adenocarcinoma, and variants of adenocarcinoma [3]. The outcomes of MIA and AIS are better when identified earlier. It mainly influences local tissue and organs including pericardium, bronchi, pleura or diaphragm in early phase of disease, and then it affects other organs in the chest with cancer cells spreading to the neighboring lobe, trachea, esophagus, mediastinum, major arteries, and spinal column at the advanced stage.

2.2. Squamous Cell Carcinoma (SqCLC)

This type typically is associated with a history of smoking. SqCLC often develops in the center of the lung, commonly starting in the proximal bronchi and in the first stages of flat cells that line the interior of the lung airways. Because of its central location, sqCLC is more prone to infect bigger blood arteries, and important mediastinum structures, and restrict bronchial passages. Additionally, cases of sqCLC that are peripherally situated typically show up after the tumor has gotten bigger and infiltrated the chest wall. Additionally, more than 80% of cavitating tumors have been found to have the sqCLC squamous histologic subtype [4].

Adenocarcinoma can be distinguished from sqCLC according to its microscopic characteristics. SqCLC presents intercellular bridges in the areas of keratinization, whereas gland development and papillary structures are often seen in adenocarcinoma. Adenocarcinoma could be present if the tumor cells exhibit characteristics of both the adenocarcinoma and sqCLC histologic subtypes, each accounting for at least 10% of the tumor cells [4]. Immunohistochemical analysis can be done in conjunction with morphological assessment to help determine the histologic subtype-squamous cell carcinoma with the two main markers of p63 and p40.

2.3. Large Cell Carcinoma

Large cell carcinoma is a broad category and can include different subtypes, such as basaloid, clear cell, and giant cell variants. Each variant may have unique histological characteristics. These subtypes may have varying clinical behaviors and prognoses. Unlike adenocarcinoma, large cell carcinoma typically lacks the glandular or tubular structures seen in adenocarcinoma. The cytoplasm of large cell carcinoma cells may be abundant and eosinophilic (pink staining), giving them a distinct appearance under the microscope.

Immunohistochemistry can be used to identify specific markers and proteins that help differentiate large cell carcinoma from other lung cancer subtypes. The expression of markers such as cytokeratin, TTF-1, and p63 may be used to aid in the diagnosis. Large lung cell carcinoma may exhibit genetic and molecular alterations similar to other NSCLC subtypes, such as mutations in genes like EGFR, KRAS, and ALK. Molecular testing is becoming increasingly important in guiding treatment decisions for large cell carcinoma patients, particularly when actionable mutations are identified.

The prognosis for individuals with large cell carcinoma in NSCLC can vary widely depending on the stage at diagnosis, genetic/molecular characteristics, and response to treatment. Early-stage cases that are successfully treated with surgery have the best prognosis, with a potential for cure. Locally advanced and advanced-stage cases have a less favorable prognosis compared to some other NSCLC subtypes, but advances in targeted therapies and immunotherapies have improved outcomes for some patients.

3. The Important Roles of Immunotherapy

Positive and negative regulators function at different points in the cancer-immunity cycle to keep immune system activity the acceptable range. So, by up-regulating the activating signals or down-regulating the inhibiting signals, the therapeutic goal was attained. ICIs are most advanced and frequently utilized approach against NSCLC because they target the signaling of negative immunological checkpoints. A group of immunosuppressive molecules, such as CTLA-4 and PD-1, prevent the T cells activation [5].

The CTLA-4 on T cells binding with B7 on APCs is capable of downregulation of IL-2 synthesis, thus inhibiting T cell growth, whereas the blockers of CTLA-4 are able to halt this reduction. Additionally, a number of recent data have found that this kind of inhibitors specifically eliminate Treg cells via an Fc-dependent mechanism in tumor tissue [5], which is how they exert their anticancer action.

The PD-1 expressed on activated T cells recognized PD-L1, which can be expressed on the surface of immunological and cancer cells, resulting in the following effects: encouraging T cell death, decreasing cytokine production in the TME, and inhibiting T cell proliferation [5].

In addition to these two kinds of inhibitors, other immunological inhibitory molecular included CD244, TIGIT, VISTA, TIM-3, and LAG-3. These immunological checkpoints can stop T cells from carrying out their function through adhering to specific ligands on certain cells, such as APCs and cancer cells. For example, T cell recognized its ligands FGL1 and LAG-3, which mainly expressed on some activated immune cells like NK cell, resulting in inhibition of its activity. T and NK cells are the primary surfaces on which TIGIT is expressed. Cell function is inhibited by attaching to its ligands, CD122 and CD55. To improve the anticancer action, these immunological checkpoints can be blocked to reactivate T cells and NK cells [5].

4. NSCLS Immunotherapeutic Methods

Data from different clinical trials showed that the patient survival with locally advanced NSCLC improved after using immunotherapy. For example, in PACIFIC, a randomized phase III clinical trial, the overall survival ratio of patients in unresectable stage III NSCLC had a strikingly increased who received a programmed cell death protein ligand (PD-L1) inhibitor, durvalumab (2 weeks per injection) as consolidation therapy after 1 year of chemoradiation compared to placebo group [2]. Besides, durvalumab was tolerable in a manner consistent with earlier investigations. As a result, it was approved by the FDA for stage III NSCLC which was unresectable.

Whether monotherapy or combined immunotherapy, nowadays is the first choice to treat advanced NSCLC, if the patient does not have the gene mutation which can be targeted by molecular therapy. The ICIs include pembrolizumab and nivolumab against PD-1, durvalumab and atezolizumab against PDL-1, and ipilimumab against CTLA-4 [2].

In addition to the use of ICIs, there are other two reliable immunotherapy methods for NSCLC patients, which are the cancer vaccine and ACT.

TCR T-cell treatment, TIL therapy, and CAR T-cell therapy are three representatives of ACT which attempts to rewire immune cells to improve the detection and elimination of tumor cells [5]. Cancer vaccines come in two primary categories: preventative vaccinations and therapeutic vaccines. Oncovirus-related cancers can be prevented by preventive vaccines, but other cancer-causing factors including environmental chemicals and genetics are unaffected. T In order for therapeutic vaccinations to work, the immune system must be prompted to attack cancer cells. They have been shown to be successful in treating it. The cells and antigens that make up each person's tumor are distinctive. Therapeutic vaccinations must therefore be tailored specifically for each patient [6].

5. Current ICI agents for the treatment of NSCLC

Pembrolizumab and nivolumab are both human IgG4 antibodies targeting PD-1, with respective half-lives of 25 and 22 days, administered intravenously. No dosage adjustments are needed for mild to moderate kidney or liver impairment [7].

Atezolizumab and durvalumab, humanized IgG1 antibodies targeting PD-L1, have half-lives of 27 and 18 days, administered intravenously. Mild or moderate liver or kidney impairment does not significantly affect atezolizumab compared to durvalumab [7].

Ipilimumab, a fully human anti-CTLA-4 antibody with IgG1 kappa subtype, has a 15.4-day half-life when given intravenously. Factors like age, gender, performance status, mild liver impairment, and renal impairment do not substantially impact ipilimumab clearance [7].

The use of ICIs has significantly advanced NSCLC treatment over the last ten years. Firstly, ICIs are now used in a variety of clinical situations in addition to their original second-line therapy role. Besides, ICI therapy has evolved from monotherapy to combination therapy, combining several ICI types, or combining ICIs with radiograph or chemotherapy with an antibody targeting VEGF. Also, a number of new ICIs that target LAG-3, TIM-3, or VISTA are processing clinical studies to assess their therapeutic potential with obvious effectiveness and optimal safety without serious adverse effects after treatment tumor patients like NSCLC [5].

There are several different scenarios for ICI monotherapy or combined therapy being focused in this review.

5.1. Treat Advanced NSCLC

The ICIs monotherapy for the second-line treatment of advanced NSCLC have been approved by FDA/NMPA since all of them improved patients' survival after addition to other therapeutic methods from data of clinical trials [5], although both pembrolizumab and atezolizumab improved significantly overall survival compared to chemotherapy while nivolumab did not show obvious improvement of survival when as first line treated strategies according to the results of clinical trials.

5.2. Treat Early-stage Resectable NSCLC

In addition, ICIs will probably be crucial to the management of early-stage resectable NSCLC because of the encouraging statistics data from clinical research, demonstrating its optimistic efficacy as neoadjuvant therapy for NSCLC. Numerous studies have shown that ICIs have greater potential than chemotherapy in the context of neoadjuvant monotherapy, with higher MPR and pCR [5]. However, ICIs haven't received approval for neoadjuvant treatment to use in clinical patients until now.

Similar to neoadjuvant immunotherapy, numerous phase II and phase III trials investigated the therapeutic effects as adjuvant immunotherapy using in patients of early-stage resectable NSCLC, showing significant improvement of survival without obvious side effects. In a phase III IMpower010 trial evaluating the safety and effectiveness of atezolizumab, atezolizumab significantly improved DFS (36 months: 60.0% against 48.2%) compared to BSC. Efficacy results from two major adjuvant therapy experiments using nivolumab and pembrolizumab which are against PD-1, have not yet been made public [5]. in patients with resected stage from IB to IIA NSCLC.

5.3. Treat Unresectable Stage III NSCLC

Patients with stage III NSCLC that were unresectable were included in the phase III trial PACIFIC and were given either consolidative durvalumab or a placebo following concomitant chemoradiotherapy. In a cohort study, the median progression-free survival (PFS) increased significantly in durvalumab treatment group compared to placebo group (16.8 months vs. 5.6 months), indicating an optimistic prospective using this antibody treated this stage patients (HR=0.51, 95% CI between 0.41 and 0.63), eventually this ICIs was approved by FDA/NMDA application as

consolidation therapy for this stage patients. PACIFIC published its most recent efficacy results in 2021. Durvalumab was estimated to have a 4-year OS rate of 49.6% compared to a placebo's 36.3%, and a 4-year PFS rate of 35.3% as opposed to 19.5% [5].

6. Challenges and prospectives of immunotherapy

6.1. ICI in Patients with Targetable Molecular Mutation

Patients with NSCLC who have mutations amenable to target therapy generally respond to ICIs less favorably. KRAS and BRAF were found to have RRs of 26% and 24%, respectively, in the IMMUNOTARGET registry, compared to EGFR's RR of 12% and ALK's RR of 0%. There were more prolonged responses in the MET (23.4%) and KRAS (25.6%) groups. PFS (Progressive Free Survival) was connected to smoking in BRAF and HER2 as well as PD-L1 expression in KRAS and EGFR [8].

To solve this problem, one possible method is doing a genetic screening before providing ICI immunotherapy to patients with NSCLC. If they have mutations amenable to targeted therapy, then they should be prioritized for targeted therapy. If not, ICI immunotherapy can be provided.

6.2. Screening of Potential Benefit Population

At present, there are no perfect indicators available for predicting which patients will experience favorable outcomes from immunotherapy. Despite lots of data from clinical experiments and research studies, a relative limited proportion of this kind of cancer patients exhibit positive responses to these antibodies of ICIs and derive lasting advantages from it [5].

6.3. irAEs of Normal Tissue

Even though immunotherapy is safer and more successful than chemotherapy in treating a variety of cancer types, unanticipated side effects have been noted that are probably connected to its mode of action. These treatments typically function is to restart immune cells like the cytotoxic T to kill tumor cells in peripheral tissues and lymph nodes, which enhances these cells to active and proliferate, thus probably destructing normal cells with expressing similar antigens and inducing local inflammation or autoimmune responses that result in immune-related adverse events (irAEs). Clinically, irAEs can present diverse symptoms depending on the organ involved, the pattern of development, and the intensity. These symptoms can cause serious, even life-threatening consequences in patients, necessitating the early discontinuation of a treatment that would otherwise be beneficial. It's interesting to note that irAEs may be idiosyncratic because various medications and dosages used to treat various malignancies may cause various adverse effects with variable severity [9].

6.4. Immune Resistance of ICIs

Immune resistance is seen in some patient subsets with the therapeutic application of ICIs in NSCLC which has become more widespread over time. Some people do not respond to the inhibitors at all, and of those who do, a sizeable percentage eventually relapse with fatal medication-resistant disorders months or years after receiving ICIs [5].

There is yet no accepted remedy for this issue because immunotherapy has intricate pathways of resistance. Combination therapy is currently the most efficient method for reversing or reducing immunological resistance. This includes combining ICIs of different types, for instance, using PD-1 inhibitor and CTLA-4 inhibitor at the same time. As an example, a promising approach involves the combination of ipilimumab with nivolumab in the initial treatment of advanced NSCLC because of their collaboration to create a synergistic impact to recovery functions of immune cells. They enhance T cell production by blocking CTLA-4 at the onset of the inflammatory response and also renew T cell functionality by averting PD-1/PD-L1 binding, thereby preventing T cell depletion and aiding in

the eradication of tumor cells [5]. Besides, combining ICIs with other regular therapeutic strategies in cancer is another method.

7. Conclusion

The management of NSCLC has witnessed remarkable advancements these years, particularly with the advent of immunotherapy, including ICIs. This article has outlined the complex landscape of NSCLC, from its epidemiology and classification to the various treatment modalities available. While the potential of ICIs is clear, there are ongoing obstacles, such as the necessity to identify the patient groups most likely to benefit and effectively manage immune-related side effects. Additionally, strategies to address immune resistance are actively being explored.

In conclusion, NSCLC treatment is at an exciting crossroads, with ongoing research and clinical trials aimed at refining the use of immunotherapy to offer patients better outcomes and an improved quality of life. As science continues to unravel the mysteries of this formidable disease, the hope is that NSCLC patients will continue to benefit from the relentless pursuit of better, more effective treatments.

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