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REVIEW ON THE ROLE OF IMMUNOTHERAPY IN LUNG CANCER

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ABSTRACT

The management of lung cancer has been significantly reshaped by immunotherapy, particularly immune checkpoint monoclonal antibodies (mAbs), which restore antitumor immune activity by overcoming tumor-induced immunosuppression. Late-phase clinical trials in advanced lung cancer have demonstrated superior outcomes compared with standard chemotherapy in metastatic non-small cell lung cancer (NSCLC), leading to FDA approval of two checkpoint inhibitors in the second-line setting. Early-phase studies have also shown encouraging activity in small cell lung cancer (SCLC) and with checkpoint inhibitor combinations in NSCLC. Despite their clinical benefit, these agents produce a distinct spectrum of immune-related toxicities compared with conventional cytotoxic therapies. As immune checkpoint mAbs become integrated into routine lung cancer care, optimizing patient selection, refining response evaluation, and developing rational combination strategies will be essential to enhance response rates and prolong durable clinical benefit.

KEYWORDS: CTLA-4; immune checkpoint inhibitors; immunotherapy; NSCLC; PD-1; PD-L1; SCLC; TMB; Btmb.

INTRODUCTION

Lung cancer remains one of the leading causes of cancer-related morbidity and mortality worldwide, accounting for a significant proportion of new cancer diagnoses and deaths each year. Despite advances in surgery, chemotherapy, and radiotherapy, the overall survival of patients with advanced lung cancer has historically remained poor. Non–small cell lung cancer (NSCLC) constitutes approximately 85% of all lung cancer cases, while small cell lung cancer (SCLC) is characterized by aggressive behavior and early metastasis. These challenges have driven the search for novel therapeutic strategies with improved efficacy and tolerability.

Immunotherapy has emerged as a revolutionary approach in the management of lung cancer by harnessing the patient's own immune system to recognize and eliminate tumor cells. Tumor cells often evade immune surveillance through inhibitory pathways known as immune checkpoints, such as programmed cell death protein-1 (PD-1) and its ligand PD-L1, as well as cytotoxic T-lymphocyte–associated antigen-4 (CTLA-4). Immune checkpoint inhibitors targeting these pathways have demonstrated remarkable clinical benefits, including durable responses and prolonged survival in selected patients with lung lung cancer treatment, offering new hope for improved outcomes and long-term disease control cancer.

In recent years, immunotherapeutic agents have become integral to the treatment landscape of both NSCLC and SCLC, used as monotherapy or in combination with chemotherapy and radiotherapy. Biomarkers such as PD-L1 expression and tumor mutational burden have further refined patient selection, enabling a more personalized approach to treatment. As ongoing research continues to expand indications and optimize combinations, immunotherapy represents a paradigm shift in.

IMMUNOTHERAPY IN LUNG CANCER – DISEASE DETAILS

1. Definition

Immunotherapy is a cancer treatment that stimulates or restores the body's immune system to recognize and destroy lung cancer cells.

2. Types of Lung Cancer Treated

Non-Small Cell Lung Cancer (NSCLC) – most common; responds well to immunotherapy

Small Cell Lung Cancer (SCLC) – immunotherapy used mainly in advanced stages.

3. Mechanism of Action

Lung cancer cells evade immunity by activating immune checkpoints

Immunotherapy drugs block checkpoints like PD-1, PD-L1, and CTLA-4

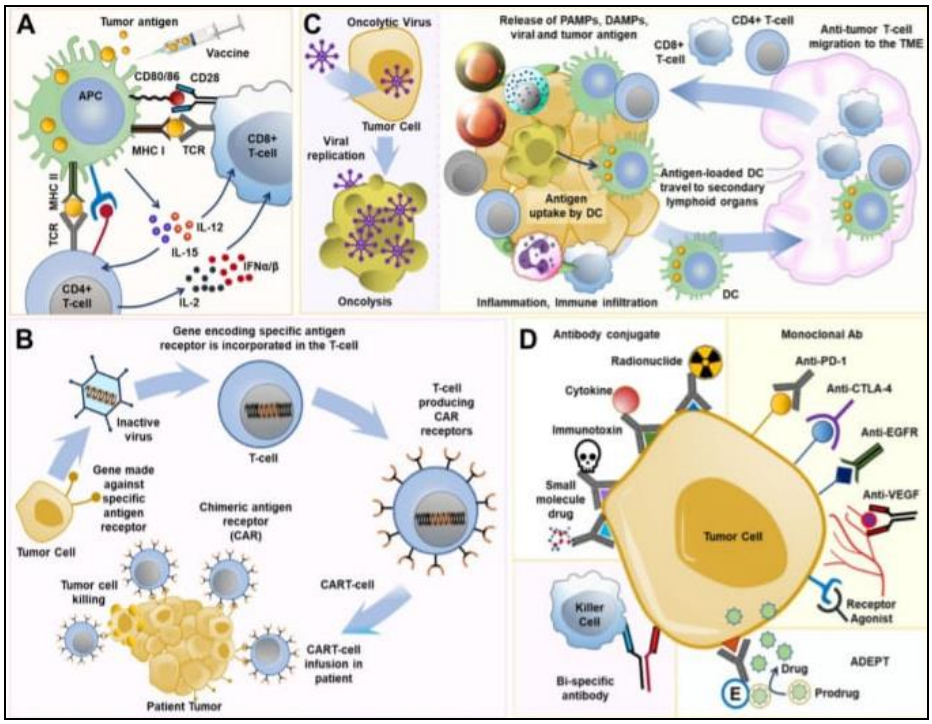
This reactivates T-cells to attack cancer cells.

4. Common Immunotherapy Drugs

PD-1 inhibitors: Nivolumab, Pembrolizumab

PD-L1 inhibitors: Atezolizumab, Durvalumab

CTLA-4 inhibitors: Ipilimumab (often in combination)



CURRENT ROLE OF IMMUNOTHERAPY IN LUNG CANCER

The relentless nature of any cancer is often attributed to its vast mutational repertoire equipping the cancer cells with mechanisms to develop resistance to commonly used treatment strategies. It is not surprising that lung cancer, with its major histologic subtypes, is among the top five tumor types carrying the highest number of somatic mutations.[3] In the first decade of 21st century, of median OS patients diagnosed with advanced NSCLC and SCLC was one year. The discovery of actionable driver genomic alterations and development of targeted therapies led to striking improvement in OS of a subset of NSCLC patients. The survival of the vast majority of patients with NSCLC without an actionable genomic driver and virtually all patients with SCLC remained limited and platinum-based chemotherapy was the mainstay of first-line therapy for these patients.

The discovery of immune checkpoints and subsequent development of Nobel Prize winning ICIs have brought in a radical revolution in the therapeutic landscape of lung cancer, specifically NSCLC.[4,5] Of the several known immune checkpoints utilized by the tumor to evade host immune system, the best known and farthest along in clinical application is programmed cell death protein-1/programmed cell death ligand-1(PD-1/PD-L1) and cytotoxic T lymphocyte antigen-4 (CTLA-4) pathways. Inhibition of these pathways enables priming and anti-tumor activity of cytotoxic T-cells, the essential steps that are otherwise inhibited by the expression of B7-1/2 and PD-L1 by the antigen presenting cells carrying tumor associated antigens and tumor cells, respectively.[4]

The first breakthrough in the utility of ICIs in treatment of lung cancer was in the form of PD-1 inhibitor nivolumab as second-line therapy for patients with advanced NSCLC, when randomized phase III trials showed superior objective response rate (ORR) and OS with nivolumab compared to docetaxel in patients with advanced squamous and non-squamous NSCLC following progression on atezolizumab were approved by platinum-based chemotherapy.[6,7] Shortly thereafter, another PD-1 inhibitor pembrolizumab and PD-L1 inhibitor the US FDA for the same indication, based on superior efficacy of these agents compared to docetaxel in second-line setting.= The success of ICIs in second-line setting paved the way for their use in first-line treatment of advanced NSCLC. A plethora of phase III clinical trials reported over the past five years, showing durable responses and unprecedented improvement in OS with ICI or ICI plus platinum-based chemotherapy compared to chemotherapy alone, have rapidly expanded first-line treatment options for patients with advanced NSCLC not harboring sensitizing EGFR mutations or ALK translocations. These options include pembrolizumab, atezolizumab, cemiplimab, nivolumab plus CTLA-4 inhibitor ipilimumab, pembrolizumab plus platinum-based chemotherapy, atezolizumab plus platinum-based chemotherapy with or without bevacizumab (for non-squamous histology), and nivolumab plus ipilimumab plus two cycles of platinum-based chemotherapy.[10–17] The choice of therapy in clinical practice is largely determined by PD-L1 expression, burden of disease, and tumor mutation profile. Besides the improvement in response rates and OS, one of the most fascinating aspects of using ICI-based therapies in NSCLC is the durability of survival benefit. For example, recently reported 5-year outcomes of landmark KEYNOTE-024 trial comparing pembrolizumab with chemotherapy as first-line treatment for patients with advanced NSCLC harboring PD-L1 expression of ≥50% demonstrated unprecedented 5-year OS of 32% with pembrolizumab.[18] Randomized trials

comparing nivolumab with docetaxel in second-line treatment of advanced NSCLC have also reported that a subset of patient derive prolonged and clinically meaningful survival benefit with ICI.[19]

The success march of ICI in NSCLC has expanded to unresectable stage III and more recently to resectable stage II-IIIA disease. In a randomized phase III trial comparing PD-L1 inhibitor durvalumab with placebo in patients with unresectable stage III NSCLC who had non-progressive disease following concurrent chemoradiation, durvalumab showed superior progression free survival (PFS) and OS which were sustained at 5-year follow up, further affirming the durability of anti-tumor activity of ICI in NSCLC.[20,21] Another phase III trial comparing atezolizumab with best supportive care in patients with resectable stable IB-IIIA NSCLC following complete surgical resection and adjuvant platinum-based chemotherapy showed superior disease-free survival (DFS) with atezolizumab which led to recent FDA approval of the agent for adjuvant therapy for patients with resected stage II-IIIA disease with positive PD-L1 expression.[22]

Signs and symptoms

Common symptoms seen in lung cancer patients include

- Persistent cough
- Shortness of breath (dyspnea)
- Chest pain
- Hemoptysis (coughing up blood)
- Fatigue
- Unexplained weight loss
- Loss of appetite
- Recurrent respiratory infections
- Bone pain or headache (if metastasis present)
- Hoarseness of voice

CAUSES

* Lung cancer cells evade immunity by activating PD-1/PD-L1 immune checkpoint pathways.

* High tumor mutation burden (especially in smokers) increases tumor immunogenicity.

* Overexpression of PD-L1 on tumor cells suppresses T-cell activity.

* Immunosuppressive tumor microenvironment inhibits effective immune response.
* Resistance or limited response to chemotherapy and radiotherapy.
* Chronic lung inflammation due to smoking or pollutants alters immune regulation.

TREATMENT

1. Immune Checkpoint Inhibitors (ICIs)

These drugs enhance the immune system's ability to recognize and attack cancer cells by targeting immune checkpoints.

a) PD-1 Inhibitors

Pembrolizumab (Keytruda)

Used in: Non-small cell lung cancer (NSCLC), often for tumors expressing PD-L1 ≥1%

Mechanism: Blocks PD-1 receptor on T-cells, preventing tumor-induced T-cell inhibition

Nivolumab (Opdivo)

Used in: Advanced NSCLC and small cell lung cancer (SCLC) after chemotherapy

Mechanism: Similar PD-1 blockade enhancing T-cell response.

b) PD-L1 Inhibitors

Atezolizumab (Tecentriq)

Used in: NSCLC, SCLC, often combined with chemotherapy

Mechanism: Blocks PD-L1 ligand on tumor cells, preventing T-cell inactivation

Durvalumab (Imfinzi)

Used in: Stage III NSCLC after chemoradiation

Mechanism: PD-L1 inhibition, enhancing anti-tumor immunity.

c) CTLA-4 Inhibitors

Ipilimumab (Yervoy)

Sometimes combined with PD-1 inhibitors (like nivolumab)

Mechanism: Blocks CTLA-4 receptor, enhancing T-cell activation early in immune response

2. Combination Therapies

Often used in metastatic NSCLC with high tumor mutational burden (TMB)

Combines PD-1 and CTLA-4 blockade for stronger immune activation

Atezolizumab + Chemotherapy

Standard first-line therapy for many advanced NSCLC cases

3. Other Investigational/Targeted Immunotherapies

Cancer Vaccines: Stimulate immune system to recognize lung cancer antigens (under research) sponse Oncolytic Viruses: Engineered viruses that selectively infect tumor cells and trigger immune response.

PHARMACOLOGICAL ACTION

1. Immune Checkpoint Inhibition

Lung cancer cells often express PD-L1, which binds to PD-1 receptors on T-cells, suppressing T-cell activity.

Drugs (e.g., Pembrolizumab, Nivolumab, Atezolizumab) block PD-1/PD-L1 interaction.

Effect: Reactivation of T-cells → T-cells recognize and kill tumor cells.

2. CTLA-4 Blockade

CTLA-4 on T-cells inhibits early T-cell activation in lymph nodes.

Ipilimumab blocks CTLA-4.

Effect: Enhances T-cell priming and proliferation → stronger anti-tumor response.

3. T-cell Activation

Some immunotherapies involve agonists of co-stimulatory molecules (e.g., OX40, CD137).

Effect: Amplifies T-cell proliferation and cytokine production → improved tumor killing.

4. Antibody-Dependent Cellular Cytotoxicity (ADCC)

Some monoclonal antibodies bind tumor antigens and recruit immune effector cells (NK cells, macrophages).

Effect: Direct lysis of tumor cells via immune-mediated cytotoxicity.

5. Cancer Vaccines & Oncolytic Viruses

Stimulate immune system by presenting tumor antigens or inducing tumor cell lysis.

Effect: Initiates a targeted immune response against cancer-specific antigens.

CONCLUSION

Immunotherapy has revolutionized the management of lung cancer by offering durable clinical responses and improved survival outcomes beyond conventional chemotherapy. Immune checkpoint inhibitors targeting PD-1, PD-L1, and CTLA-4 pathways have become integral in the treatment of both NSCLC and SCLC across various disease stages. The use of

predictive biomarkers such as PD-L1 expression and tumor mutational burden has enabled a more personalized treatment approach. Despite challenges such as immune-related adverse effects and variable response rates, ongoing research and combination strategies continue to refine and expand the role of immunotherapy, making it a cornerstone of modern lung cancer treatment.

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