The Immune-related Adverse Events of Immunotherapy in Lung Cancer

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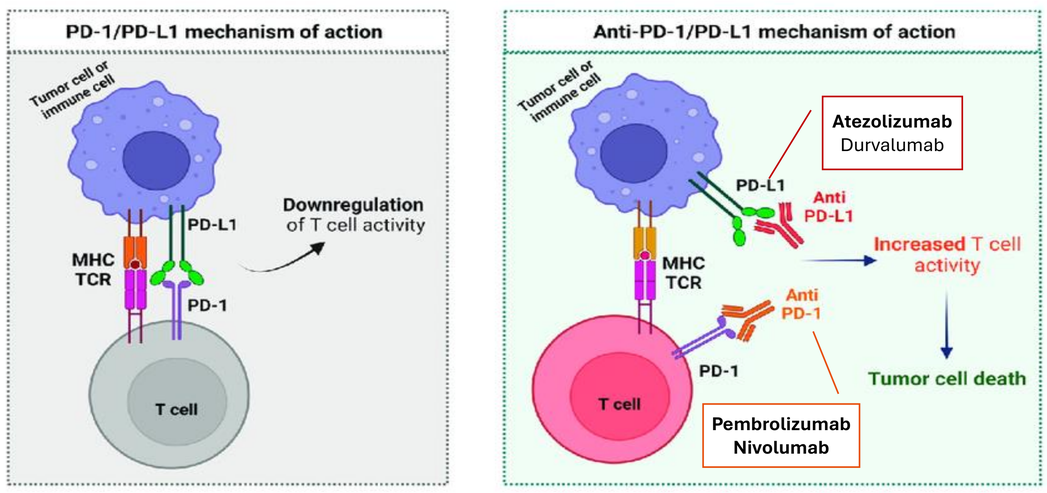
Introduction

Lung cancer is the leading cause of cancer-related mortality. Recent advancements in understanding the complex interplay between tumors and the immune system have paved the way for **immunotherapy**, revolutionizing the treatment paradigm for **lung cancer**, notably in non-small cell lung cancer (NSCLC) which accounts for 80-85% of all lung cancer cases and, to a lesser extent, small cell lung cancer (SCLC). Various immunotherapeutic modalities aim to target the evasion potential of cancer cells by harnessing the power of the immune system. One key approach is the use of **immune checkpoint inhibitors (ICIs),** including PD-1/PD-L1 inhibitors currently **available in Algeria (pembrolizumab, nivolumab and atezolizumab)**. These drugs enhance the immune system's ability to combat cancer by **blocking pathways that suppress T-cell activation and contribute to immune evasion**. However, because ICIs broadly stimulate the immune system, they can inadvertently affect normal tissues and organs, leading to a spectrum of complications known **as immune-related adverse events (irAEs)** that require careful monitoring and management.

Objective

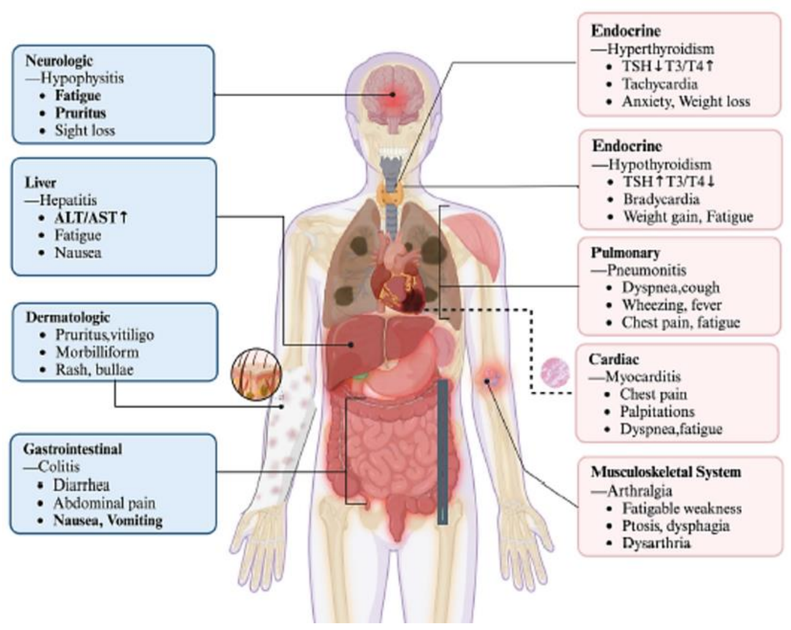
To highlight the spectrum of irAEs associated with the use of the ICIs in the treatment of lung cancer and to offer insights into effective management strategies to mitigate these complications.

ICIs Mechanism of action



Immune checkpoints : **PD-1**: is a regulatory protein on T cells that, when bound to PD-L1, inhibits T-cell activation, prevent them from attacking the body's own cells including cancer cells (prevent autoimmunity). **PD-L1**: is a ligand that can be expressed on cancer and other cells, binding to PD-1 on T cells to suppress immune responses and enable tumor evasion. The interaction between PD-1 and PD-L1 is a mechanism that tumors use to protect themselves from the immune system. **ICIs** can block these checkpoints (either PD-1 or PD-L1) enabling T cells to attack and kill cancer cells. Two (02) **anti-PD-1** are commercialized in Algeria: **Pembrolizumab and Nivolumab**. One **anti-PD-L1** is available in Algeria: **Atezolizumab.** These ICIs have demonstrated considerable efficacy in treating lung cancer. In NSCLC, they significantly enhance overall survival rates, particularly as first-line treatments for patients with high PD-L1 expression. In SCLC, their use as second-line therapy has shown potential in improving outcomes for patients whose disease has progressed after initial treatments.
Pembrolizumab is the 1st immunotherapy to be used for lung cancer. By June 2024, this anti-PD-1 has received its 40th approval and due to its potential for treating various types of cancer, it is listed on the WHO's list of essential medicines.

Spectrum of irAEs associated with ICIs



ICIs block immune regulation: deactivating immune checkpoints and leading to an uncontrolled immune response that mistakenly attack the body's own tissues. **Expansion of autoreactive clones**: This unregulated immune activity results in the expansion of T- and B-cell populations that produce harmful autoantibodies and inflammatory cytokines, causing tissue damage. **Tumor cell release of self-antigens**: Following cytotoxic attacks on tumors, cancer cells release self-antigens that can provoke immune responses against both tumor and normal tissues, resulting in cross-reactivity.
Skin toxicities are often common irAEs with the earliest onset. Rash and pruritus are the most common irAEs associated with ICI treatment.

Management of irAEs in Patients Treated With ICIs

Before Treatment initiation

Conducting a baseline physical examination, laboratory tests, and imaging before starting immunotherapy provides a reference point for any AE that may arise during treatment. Establishing an immunotherapy baseline checklist before initiating ICI therapy is crucial

Patient and their family caregivers should receive thourough education about immunotherapies, their mechanism of action, and the clinical profile of possible irAEs before initiating therapy and throughout treatment course, and should be encouraged to report any new symptom they may observe

Grade 1	Minimal or no symptoms	In general, immunotherapy should be continued with close monitoring, except for some neurologic, hematologic, and cardiac toxicities
Grade 2	Mild to moderate symptoms	• Hold ICI for most grade 2 toxicities • Resume ICI when symptoms and/or laboratory values revert ≤ grade 1. • Corticosteroids (initial dose of 0.5-1 mg/kg/day of prednisone or equivalent) may be administered.
Grade 3/4	Severe or life-threatening symptoms	**Grade 3 :** • Hold ICI • Initiate high-dose corticosteroids (prednisone 1-2 mg/kg/d or equivalent). • Taper corticosteroids over the course of at least 4-6 weeks. • If symptoms do not improve with 48-72 hours of high-dose steroid, infliximab may be offered for some toxicities. • When symptoms and/or laboratory values revert ≤ grade 1, rechallenging with ICI may be considered; however, caution is advised, especially in those patients with early-onset irAEs. Dose adjustments are not recommended. **Grade 4 :** • Permanent discontinuation of ICI, except for endocrinopathies that have been controlled by hormone replacement (e.g. thyroid hormones in case of hypothyroidism).

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