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IMMUNOTHERAPY IN LUNG CANCER: EFFICACY AND PROSPECTS OF THE USE OF IMMUNE CHECKPOINT INHIBITORS

IMMUNOTHERAPY IN LUNG CANCER: EFFICACY AND PERSPECTIVES OF IMMUNE CHECKPOINT INHIBITORS USE

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SUMMARY:

Lung cancer, especially non-small cell lung carcinoma (NSCLC), is the leading cause of cancer-related death worldwide and represents a major public health challenge. In recent years, the introduction of immune checkpoint inhibitors, such as anti-PD-1 and anti-PD-L1 antibodies, has revolutionized the treatment of this neoplasm, particularly in patients with advanced or metastatic disease. These agents block immune checkpoints, allowing a more effective immune response against the tumor. This study aims to review the recent literature on the efficacy of immune checkpoint inhibitors in the treatment of lung cancer, analyzing the main advances achieved, as well as the challenges and future perspectives. Ten studies were selected from the PubMed and ScienceDirect databases, which included clinical trials, systematic reviews and meta-analyses published between 2019 and 2023. The results indicate that immunotherapy offers a significant improvement in the response rate and survival of patients, especially when combined with other therapeutic modalities, such as chemotherapy and radiotherapy. However, treatment resistance and adverse effects remain important challenges to be overcome. Identifying biomarkers that can predict treatment response is a priority area of research, essential to optimize patient selection and personalize therapeutic approaches. Thus, future studies should focus on overcoming treatment resistance and personalizing immunotherapy to maximize clinical benefits.

Keywords: Lung cancer. Immunotherapy. Immune checkpoint inhibitors. PD-1. PD-L1.

ABSTRACT:

Lung cancer, particularly non-small cell lung cancer (NSCLC), is the leading cause of cancer-related deaths worldwide, posing a significant challenge to public health. In recent years, the introduction of immune checkpoint inhibitors, such as anti-PD-1 and anti-PD-L1 antibodies, has revolutionized the treatment of this neoplasm, especially in patients with advanced or metastatic disease. These agents block immune checkpoints, allowing for a more effective immune response against the tumor. This study aims to review recent literature on the efficacy of immune checkpoint inhibitors in the treatment of lung cancer, analyzing key advances, challenges, and future perspectives. Ten studies were selected from PubMed and ScienceDirect databases, including clinical trials, systematic reviews, and meta-analyses

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published between 2019 and 2023. The results indicate that immunotherapy significantly improves response rates and patient survival, particularly when combined with other therapeutic modalities, such as chemotherapy and radiotherapy. However, treatment resistance and adverse effects remain significant challenges. Identifying biomarkers that can predict treatment response is a priority research area, essential for optimizing patient selection and personalizing therapeutic approaches. Therefore, future studies should focus on overcoming treatment resistance and personalizing immunotherapy to maximize clinical benefits.

Keywords: Lung cancer. Immunotherapy. Immune checkpoint inhibitors. PD-1. PD-L1.

1. INTRODUCTION

Lung cancer is the leading cause of cancer-related deaths worldwide, and is one of the most common types of cancer and a major public health challenge. Among the subtypes of lung cancer, non-small cell lung carcinoma (NSCLC) accounts for approximately 85% of diagnosed cases, and patient survival largely depends on the stage at which the disease is identified, with the chances of a cure being more limited when the diagnosis is made in advanced stages (Ernani*et al.*, 2019).

In recent years, there has been a revolution in the treatment of lung cancer with the advent of immunotherapy, especially with immune checkpoint inhibitors, such as anti-PD-1 and anti-PD-L1 antibodies. These agents block the immune checkpoints that normally limit the immune system's response, resulting in a more effective antitumor response. Compared to conventional treatments, such as chemotherapy, which are generally unselective and highly toxic, immune checkpoint inhibitors offer a more targeted approach and a more tolerable adverse effect profile (Kang*et al.*, 2021).

However, not all patients benefit from immunotherapy, and resistance to treatment is a frequent problem. Therefore, it is essential to understand the mechanisms of resistance and identify biomarkers that can predict which patients are most likely to respond to treatment (Dantoing*et al.*, 2021).

The aim of this study is to comprehensively review the recent literature on the efficacy of immune checkpoint inhibitors in the treatment of lung cancer, analyzing the main advances regarding survival and tumor response, as well as the associated challenges, such as treatment resistance and adverse effects. In addition, it aims to

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identify future perspectives to optimize the use of these agents, considering the possibility of combined treatments and the importance of biomarkers that can help select patients most likely to benefit from immunotherapy.

2. MATERIAL AND METHOD

To conduct this systematic review, a comprehensive search was conducted in the PubMed and ScienceDirect databases, using a specific search strategy to identify studies related to the use of immunotherapy in patients with lung cancer. The search key used included the terms: ('lung cancer' OR 'NSCLC') AND ('immunotherapy' OR 'immune checkpoint inhibitors' OR 'PD-1' OR 'PD-L1'), ensuring broad coverage of relevant topics published between 2019 and 2024. The choice of this time range aimed to ensure that only recent and pertinent evidence was included, with an emphasis on randomized clinical trials, systematic reviews and meta-analyses.

Initially, 5,876 articles were identified. Study selection was performed in stages. The first stage consisted of screening titles and abstracts in order to exclude duplicate studies and those that did not fit the objective of the review. Studies were then selected based on previously defined inclusion criteria, such as: studies conducted in humans, publications in English, and approaches that evaluated the efficacy of immune checkpoint inhibitors in specific subgroups of patients, such as those with brain metastases or early-stage NSCLC. In addition, studies that analyzed the combination of immunotherapy with other treatment modalities, such as chemotherapy and radiotherapy, were included.

At the end of the screening and application of the inclusion criteria, ten studies were selected for further analysis. Data extracted from each study included patient characteristics, interventions performed, outcomes related to the efficacy and safety of immunotherapy, and information on biomarkers predictive of response. All selected studies were assessed for methodological quality, using appropriate tools to ensure the validity of the results and minimize selection biases.

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and analysis. Table 1 presents the details of the selected articles, including authors, journals and thematic considerations.

Table 1. Works included.

Database	**Title**	**Authors**	**Periodical (vol, no, page, year)**	**Considerations Themes**
PubMed	Management of Brain Metastases in Non-Small-Cell Lung Cancer	Ernani *et al.*	**J Oncol Pract**, v. 15, no. 11, p. 563-570, 2019	Management of cerebral metastases in patients with NSCLC
PubMed	Neoadjuvant immunotherapy for non-small cell lung cancer: State of the art	Kang *et al.*	**Cancer Common (Lond)**, v. 41, n. 4, p. 287-302, 2021	Effectiveness from the immunotherapy neoadjuvant for NSCLC
PubMed	Tumor Immunology and Immunotherapy of Non-Small-Cell Lung Cancer	Cascone *et al.*	**Cold Spring Harb Perspect Med**, v. 12, n. 5, p. a037895, 2022	Response immunological and effectiveness from the immunotherapy for NSCLC
PubMed	Combined treatment of non-small cell lung Cancer using radiotherapy and immunotherapy: challenges and updates	Shang *et al.*	**Cancer Common (Lond)**, v. 41, n. 11, p. 1086-1099, 2021	Combination of immunotherapy and radiotherapy node treatment of NSCLC

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PubMed	Anti-PD1/PD-L1 Immunotherapy for Non-Small Cell Lung Cancer with Actionable Oncogenic Driver Mutations	Dantoing*et al.*	**Int J Mol Sci**, v. 22, n. 12, p. 6288, 2021	Effectiveness from the immunotherapy in NSCLC with mutations oncogenic actionable
PubMed	Intratumoral plasma cells predict outcomes to PD-L1 blockade in non-small cell lung cancer	Patil*et al.*	**Cancer Cell**, v. 40, n. 3, p. 289-300.e4, 2022	Contribution of the cells plasma for effectiveness of the blocking of PD-L1 in NSCLC

Source: own authorship, 2024.

3. RESULTS AND DISCUSSION

Immune checkpoint inhibitors have demonstrated significant efficacy in the treatment of patients with advanced NSCLC, providing a higher response rate and overall survival compared to conventional chemotherapy. Reviewed studies indicate that the use of anti-PD-1 and anti-PD-L1 antibodies is particularly beneficial for patients in more advanced stages of the disease, improving quality of life and increasing progression-free survival (Kang*et al.*, 2021).

The results of studies on the combination of immunotherapy with other treatment modalities, such as chemotherapy and radiotherapy, have shown that there is a synergistic effect when these treatments are combined. In one of the studies analyzed, the combination of radiotherapy with checkpoint inhibitors resulted in a high objective response rate, since radiotherapy promotes the release of tumor antigens, increasing the immunogenicity of the tumor and enhancing the immune response (Shang*et al.*, 2021).

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These results suggest that combination approaches may represent a promising path for patients who do not respond well to immunotherapy alone (Shang *et al.*, 2021).

Despite the positive results, resistance to immune checkpoint inhibitor treatment remains a significant challenge. Primary resistance, in which patients do not initially respond to treatment, and acquired resistance, in which patients lose their response over time, are recurring problems. Studies indicate that actionable oncogenic mutations may be associated with primary resistance, making it essential to identify these molecular profiles before starting treatment (Dantoing *et al.*, 2021). Thus, the integration of biomarker analysis into the therapeutic decision-making process can contribute to a better selection of patients who will benefit most from immunotherapy (Dantoing *et al.*, 2021).

Furthermore, the presence of intratumoral plasma cells has been suggested as a predictive biomarker of good response to PD-L1 blockade. Patients with a high density of these cells presented better outcomes in terms of response to treatment, suggesting a relevant role of plasma cells in modulating the immune response to the tumor (Patil *et al.*, 2022). These findings reinforce the need to identify and validate biomarkers that can help personalize treatment and increase the effectiveness of immunotherapy (Patil *et al.*, 2022).

Finally, the adverse effects associated with immune checkpoint inhibitors are generally less severe than those seen with chemotherapy, but they can still impact patients' quality of life. Among the most common adverse events are autoimmune reactions, such as colitis, pneumonitis, and endocrinopathies. It is essential that healthcare professionals are prepared to identify and manage these effects appropriately, aiming to ensure continuity of treatment and patient safety (Cascone *et al.*, 2022).

FINAL CONSIDERATIONS

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Immune checkpoint inhibitors represent a significant advance in the treatment of lung cancer, especially in patients with advanced NSCLC. Immunotherapy has been shown to be effective in increasing response rates and survival, particularly when combined with other treatment modalities such as chemotherapy and radiotherapy, showing promising synergistic effects (Shang*et al.*, 2021). These combinations have been shown to be effective in optimizing tumor control and minimizing the risks of disease progression (Kang*et al.*, 2021).

Despite the clear benefits, treatment resistance remains a significant barrier for many patients, making it essential to identify predictive biomarkers that can help select patients most likely to respond to immunotherapy (Dantoing*et al.*, 2021). Resistance, both primary and acquired, challenges the efficacy of immunotherapy and highlights the importance of a personalized approach in the treatment of lung cancer (Patil*et al.*, 2022).

Therefore, future studies should focus on identifying specific biomarkers and developing strategies that can overcome treatment resistance. Implementing more personalized approaches that consider the individual characteristics of each patient will be essential to maximize the benefits of immunotherapy and improve clinical outcomes in a larger number of lung cancer patients (Cascone*et al.*, 2022).

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