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Advancing Treatment in Non-Small Cell LungCancer: The Role of Immunotherapy and Pembrolizumab-Chemotherapy Combinations

[1]Sailee Swapnil Tawade

[1]Student
[1]Department of Medical Biotechnology
[1]Dr. D. Y. Patil Biotechnology & Bioinformatics Institute

Abstract: Non-small cell lung cancer (NSCLC) remains a major cause of cancer-related mortality globally. Recent advancements in immunotherapy, particularly immune checkpoint inhibitors (ICIs) like pembrolizumab, have transformed NSCLC treatment, improving survival in patients with advanced disease. However, many patients eventually develop resistance or experience progression on immunotherapy. This review focuses on the evolving role of pembrolizumab-chemotherapy combinations, exploring their mechanisms, efficacy, safety profiles, and the potential to overcome immunotherapy resistance. Emerging clinical trials show promising results, suggesting that combining pembrolizumab with chemotherapy can extend survival in patients who have progressed on prior therapies.

Index Terms **- Non-small cell lung cancer, pembrolizumab, immunotherapy, chemotherapy, immune checkpoint inhibitors, and combination therapy**

1. INTRODUCTION

Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancer cases and is a major contributor to cancer- related mortality worldwide. The aggressive nature of the disease, coupled with late-stage diagnoses, often limits treatment options, leading to poor patient outcomes. In recent years, the development of immune checkpoint inhibitors (ICIs) has marked a turning point in NSCLC therapy. These therapies, particularly those that target the programmed cell death protein 1 (PD-1) and its ligand (PD-L1) pathway, have significantly improved survival outcomes for patients with advanced NSCLC. Pembrolizumab, an anti-PD- 1 monoclonal antibody, has been a cornerstone of this therapeutic revolution, particularly benefiting patients whose tumors express high levels of PD-L1 ($\geqslant$50%). However, despite initial success with pembrolizumab monotherapy, many patients eventually develop resistance or experience disease progression. This underscores the need for novel therapeutic strategies that can provide sustained benefits. One promising approach is the combination of pembrolizumab with chemotherapy, which has shown encouraging results in extending survival and improving overall outcomes in patients with advanced NSCLC.

2. MECHANISMS OF IMMUNOTHERAPY AND PEMBROLIZUMAB

Immune checkpoint inhibitors like pembrolizumab have revolutionized the treatment of NSCLC by leveraging the body's immune system to more effectively target and destroy cancer cells. Pembrolizumab works by inhibiting the interaction between the PD-1 receptor on T cells and its ligand, PD-L1, which is often expressed on tumor cells. This interaction normally suppresses the immune response, allowing tumors to evade detection. By blocking the PD-1/PD-L1 pathway, pembrolizumab reactivates T cells, enhancing their ability to recognize and attack cancer cells. This immune reactivation is particularly effective in patients with high PD-L1 expression, making it a critical biomarker for identifying candidates most likely to benefit from this therapy. Pembrolizumab's ability to restore immune function and improve progression-free survival (PFS) and overall survival (OS) has been validated by landmark trials like KEYNOTE-024, particularly in patients with advanced NSCLC.

Additionally, pembrolizumab has been shown to influence the tumor microenvironment by promoting the infiltration of cytotoxic T cells, which further enhances its anti-tumor efficacy. It may also reduce the number of immunosuppressive cells, such as

regulatory T cells and myeloid-derived suppressor cells, within the tumor environment, allowing the immune system to remain activated against the tumor. Beyond immediate immune activation, pembrolizumab may help establish long-term immune memory, enabling the immune system to continue recognizing and attacking tumor cells even after initial treatment. These mechanisms contribute to durable responses in some patients, offering prolonged disease control. However, response to pembrolizumab can vary, and factors such as tumor mutational burden (TMB) and the composition of the tumor microenvironment play crucial roles in determining the overall effectiveness of the therapy.

3. RATIONALE FOR PEMBROLIZUMAB-CHEMOTHERAPY COMBINATIONS

While chemotherapy has long been a staple in the treatment of NSCLC, its benefits are often hampered by its toxicity and the limited duration of response. Chemotherapy works by targeting rapidly dividing cells, reducing tumor size, but it does not specifically target cancer cells, often leading to significant side effects. On its own, chemotherapy rarely offers long-term remission in advanced stages of NSCLC. However, when used in combination with pembrolizumab, chemotherapy offers a complementary mechanism of action that enhances the immune system's ability to fight the tumor. Chemotherapy can induce immunogenic cell death, releasing tumor antigens that were previously hidden from the immune system. This process exposes cancer cells to immune surveillance, allowing pembrolizumab to further potentiate the activity of T cells against these cancer cells.

This combination strategy seeks to overcome resistance mechanisms that may develop in patients who progress on immunotherapy alone. Chemotherapy may re-sensitize tumors to immune checkpoint blockade by modulating the tumor microenvironment, potentially increasing the likelihood of a sustained response to pembrolizumab. This rationale has driven numerous clinical trials to explore the synergistic potential of pembrolizumab and chemotherapy, with promising outcomes.

4. KEY CLINICAL TRIALS

4.1 BTCRC-LUN15-029 Trial

The BTCRC-LUN15-029 trial investigated the efficacy of combining pembrolizumab with chemotherapy in patients with advanced NSCLC who had previously progressed on PD-1/PD-L1 inhibitors. This phase II study enrolled patients who had already undergone treatment with immune checkpoint inhibitors but experienced disease progression, a challenging patient population with limited treatment options. The study aimed to determine whether adding pembrolizumab to next-line chemotherapy could extend PFS and OS. Results from the trial demonstrated that the combination of pembrolizumab with chemotherapy significantly improved PFS and OS compared to historical controls who received chemotherapy alone. Importantly, patients who had initially responded to immune checkpoint inhibitors but later developed resistance still derived benefits from the combination therapy. These findings suggest that continuing pembrolizumab, even after initial resistance, when paired with chemotherapy, can lead to meaningful clinical improvements.

4.2 KEYNOTE-189 Trial

The KEYNOTE-189 trial was another pivotal study that explored the use of pembrolizumab in combination with platinum-based chemotherapy in treatment-naive patients with metastatic NSCLC. This randomized phase III trial enrolled patients regardless of PD-L1 expression levels and demonstrated that the combination of pembrolizumab with chemotherapy significantly prolonged PFS and OS compared to chemotherapy alone. Importantly, the benefit was observed across all subgroups, including those with low or no PD-L1 expression, indicating that pembrolizumab combined with chemotherapy could be effective for a broader range of patients. The results of KEYNOTE-189 have had a profound impact on clinical practice, positioning pembrolizumab-chemotherapy combinations as a new standard of care for first-line treatment of metastatic NSCLC.

5. SAFETY AND TOXICITY

One of the primary concerns with combining pembrolizumab and chemotherapy is the potential for increased toxicity. Chemotherapy is known for causing side effects such as fatigue, nausea, anemia, and bone marrow suppression, while immune checkpoint inhibitors are associated with immune-related adverse events (irAEs), including pneumonitis, colitis, and endocrinopathies. However, data from trials such as BTCRC-LUN15-029 and KEYNOTE-189 suggest that pembrolizumab- chemotherapy combinations are generally well tolerated. Most adverse events are manageable with standard treatments, and severe irAEs are relatively rare. The incidence of treatment-related deaths in these trials was low, and most toxicities could be controlled with dose modifications or supportive care measures. This suggests that the combination therapy offers a favorable safety profile, making it a viable option for patients with advanced NSCLC. Nonetheless, careful patient selection and close monitoring are essential to minimize the risk of severe toxicities and ensure that patients can continue to benefit from treatment.

6. MECHANISTIC INSIGHTS INTO PEMBROLIZUMAB CONTINUATION AFTER PROGRESSION

Continuing pembrolizumab beyond disease progression is a relatively new concept that challenges the conventional approach of discontinuing a therapy once progression occurs. The rationale for this approach is based on several potential mechanisms. First, chemotherapy induces immunogenic cell death, which can expose previously hidden tumor antigens, allowing pembrolizumab to target these newly exposed antigens. Second, the interaction between tumors and the immune system is dynamic, meaning that tumors may acquire new vulnerabilities over time that can be exploited by continued PD-1 blockade. Finally, chemotherapy may alter the tumor microenvironment by depleting immunosuppressive cells such as regulatory T cells and myeloid-derived suppressor cells, thereby enhancing the ability of pembrolizumab to maintain its anti-tumor effects. These mechanisms provide a scientific

rationale for continuing pembrolizumab beyond progression in combination with chemotherapy, potentially offering additional survival benefits for patients.

7. CHALLENGES AND LIMITATIONS

While pembrolizumab-chemotherapy combinations have shown great promise, several challenges remain. Primary and acquired resistance to immune checkpoint inhibitors remains a significant hurdle. Some patients do not respond to pembrolizumab- chemotherapy combinations, and others may develop resistance after an initial period of response. Additionally, while PD-L1 expression is a commonly used biomarker for predicting response to pembrolizumab, it is not always reliable. Some patients with low or no PD-L1 expression still benefit from the therapy, suggesting that other factors, such as tumor mutational burden (TMB) or the composition of the tumor microenvironment, may play a critical role in determining treatment response.

Another challenge is the high cost of pembrolizumab and other ICIs, which can limit accessibility, particularly in healthcare systems without universal coverage. The financial burden of these treatments can be significant, both for individual patients and healthcare providers, underscoring the need for cost-effectiveness analyses and strategies to improve access to these life-saving therapies.

8. FUTURE DIRECTIONS

The future of NSCLC treatment lies in refining the use of immunotherapy combinations and addressing the limitations of current therapies. Ongoing research is focused on identifying more accurate biomarkers, such as TMB, to better predict which patients will benefit from pembrolizumab-chemotherapy combinations. Dual checkpoint blockade, which involves combining PD-1/PD-L1 inhibitors with other checkpoint inhibitors such as CTLA-4 inhibitors, is also being explored. Trials like CheckMate-227 have shown that dual checkpoint blockade can further enhance the immune response in certain subgroups of NSCLC patients, offering another potential avenue for improving outcomes.

Personalized immunotherapy, including neoantigen vaccines and adoptive T cell therapies, is another promising area of research. These approaches aim to tailor treatments to the specific characteristics of an individual's tumor, potentially leading to more durable responses. Additionally, combining immunotherapy with targeted therapies or radiation is being explored to further improve outcomes for patients with advanced or resistant NSCLC. As research progresses, pembrolizumab-chemotherapy combinations, along with other novel approaches, are likely to play an increasingly central role in the management of NSCLC.

9. CONCLUSION

The combination of pembrolizumab and chemotherapy represents a significant advancement in the treatment of advanced NSCLC, providing patients with improved survival and response rates, even after progression on prior immunotherapy. By leveraging the complementary mechanisms of both therapies, chemotherapy reduces tumor burden while pembrolizumab reactivates the immune system, allowing for a more robust and sustained anti-tumor response. Clinical trials such as BTCRC-LUN15-029 and KEYNOTE- 189 have demonstrated that this combination not only enhances progression-free survival (PFS) and overall survival (OS), but also offers a well-tolerated safety profile, making it a viable option for a broader range of patients, regardless of PD-L1 expression levels.

Despite these advancements, challenges such as resistance, high treatment costs, and variability in patient response remain key barriers to optimizing outcomes. The future of NSCLC treatment will likely focus on refining these combination strategies, identifying more precise biomarkers like tumor mutational burden (TMB), and personalizing treatments to better target individual tumor characteristics. Ongoing research into dual checkpoint blockade, personalized immunotherapy approaches, and novel combination therapies promises to further improve survival rates and quality of life for patients with advanced NSCLC, solidifying pembrolizumab-chemotherapy combinations as a cornerstone of modern lung cancer management.

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