Pembrolizumab Reduces Pulmonary AEs vs Chemotherapy in NSCLC

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> Pulmonary adverse events (AEs) represent a significant concern in the management of advanced non-small cell lung cancer (NSCLC), particularly with systemic therapies. The choice of first-line treatment impacts not only efficacy but also the safety profile. Recent data indicate that pembrolizumab monotherapy may offer a more favorable pulmonary safety profile compared to traditional platinum-based chemotherapy in this patient population.1

KEY TAKEAWAYS

- The Pivot: Pembrolizumab monotherapy is associated with a lower rate of pulmonary adverse events compared to platinum-based chemotherapy.
- The Data: The incidence of all-grade pulmonary AEs was 13.3% with pembrolizumab versus 23.9% with chemotherapy.
- The Action: Clinicians should consider pembrolizumab's pulmonary safety profile when selecting first-line therapy for advanced NSCLC patients, especially those with pre-existing pulmonary comorbidities.

The management of advanced non-small cell lung cancer (NSCLC) has evolved significantly with the introduction of immune checkpoint inhibitors. While these therapies have demonstrated superior efficacy in many settings, their distinct adverse event profiles, particularly immune-related adverse events (irAEs), necessitate careful consideration. Pulmonary irAEs, such as pneumonitis, are a known complication of PD-1/PD-L1 inhibitors, yet a comprehensive comparison of overall pulmonary adverse event burden between pembrolizumab and chemotherapy has been a focus of recent analysis.

Background and Clinical Rationale

NSCLC accounts for approximately 85% of all lung cancers, and a significant proportion of patients present with advanced or metastatic disease. Historically, platinum-based chemotherapy regimens formed the backbone of first-line treatment for these patients. However, chemotherapy is associated with a range of systemic toxicities, including myelosuppression, gastrointestinal disturbances, and fatigue, which can significantly impact patient quality of life and treatment adherence. Pulmonary complications, such as chemotherapy-induced pneumonitis, opportunistic infections due to immunosuppression, and exacerbation of underlying lung conditions, also represent a substantial burden. The advent of immune checkpoint inhibitors, particularly pembrolizumab, a humanized monoclonal antibody that blocks the PD-1 receptor, has revolutionized NSCLC treatment, especially in patients with high PD-L1 expression or in combination with chemotherapy regardless of PD-L1 status. Understanding the full spectrum of adverse events, beyond just immune-related toxicities, is crucial for informed clinical decision-making and patient management.

Comparative Pulmonary Safety Profile

A pooled analysis of several pivotal trials, including KEYNOTE-024, KEYNOTE-042, and KEYNOTE-189, evaluated the incidence of pulmonary adverse events in patients with advanced NSCLC receiving first-line pembrolizumab monotherapy or pembrolizumab in combination with chemotherapy, compared to chemotherapy alone. The analysis specifically focused on events classified as pulmonary, respiratory, thoracic, and mediastinal disorders.

The methodology involved a systematic review of adverse event data from these large, randomized, controlled trials. KEYNOTE-024 enrolled patients with previously untreated, advanced NSCLC with PD-L1 tumor proportion score (TPS) ≥50%. KEYNOTE-042 included patients with advanced NSCLC and PD-L1 TPS ≥1%. KEYNOTE-189 evaluated pembrolizumab plus platinum-pemetrexed chemotherapy in patients with metastatic non-squamous NSCLC, regardless of PD-L1 expression. The patient populations across these trials were generally representative of advanced NSCLC patients, encompassing various histological subtypes (primarily non-squamous and squamous) and performance statuses. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0. The pooled analysis allowed for a robust comparison of safety profiles across a large cohort of patients, providing a comprehensive overview of pulmonary toxicity.

The data revealed that pembrolizumab monotherapy was associated with a lower incidence of all-grade pulmonary adverse events compared to platinum-based chemotherapy. In patients receiving pembrolizumab monotherapy, the incidence of all-grade pulmonary AEs was 13.3%. In contrast, patients treated with platinum-based chemotherapy experienced an incidence of 23.9% for all-grade pulmonary AEs. This difference was statistically significant (P 0.001). When considering Grade 3-5 pulmonary adverse events, the rates were also lower with pembrolizumab monotherapy, at 2.8%, compared to 5.2% for chemotherapy (P 0.01). The most common pulmonary adverse events reported in the chemotherapy arm included dyspnoea, cough, and pneumonia. While pneumonitis is a known irAE associated with pembrolizumab, its overall contribution to the total pulmonary AE burden was lower than the collective pulmonary events observed with chemotherapy.

The combination of pembrolizumab with chemotherapy also showed a numerically lower, though not statistically significant, rate of all-grade pulmonary AEs (20.1%) compared to chemotherapy alone (23.9%). For Grade 3-5 events, the combination arm reported 4.1%, compared to 5.2% for chemotherapy alone.

These findings suggest that while immune-related pneumonitis is a specific concern with pembrolizumab, the broader spectrum of pulmonary adverse events, including those related to myelosuppression and infection commonly seen with chemotherapy, contributes to a higher overall pulmonary toxicity burden in the chemotherapy arm. The mechanism for the observed reduction in pulmonary AEs with pembrolizumab monotherapy versus chemotherapy is multifactorial, likely involving differences in direct lung toxicity, immunosuppression leading to infection, and exacerbation of pre-existing lung conditions.

Limitations and Future Directions

Despite the robust nature of this pooled analysis, certain limitations warrant consideration. The analysis relied on adverse event reporting from individual trials, which may have inherent variability in assessment and documentation. While the NCI CTCAE provides standardized grading, subjective interpretation can still occur. Furthermore, the specific etiologies of all pulmonary adverse events were not always definitively established, making it challenging to precisely differentiate between immune-related, infection-related, or chemotherapy-induced events in all cases. The pooled analysis also

combined data from trials with slightly different patient selection criteria and chemotherapy regimens, which could introduce heterogeneity. Future research could involve prospective studies specifically designed to compare pulmonary toxicity profiles with detailed adjudication of event etiologies. Real-world data analyses could also provide further insights into the long-term pulmonary safety of these treatments in broader patient populations, including those with significant comorbidities often excluded from clinical trials.

For a comprehensive overview of respiratory conditions and their management, including treatment-related pulmonary complications, consult the invaluable Oxford Handbook of Respiratory Medicine.

CLINICAL IMPLICATIONS

This analysis provides a clear signal that pembrolizumab monotherapy offers a pulmonary safety advantage over platinum-based chemotherapy in advanced NSCLC. For clinicians, this means that when selecting first-line therapy, particularly for patients with pre-existing pulmonary comorbidities such as COPD or interstitial lung disease, pembrolizumab may be the preferred option to mitigate the risk of exacerbating respiratory function. The data underscore the importance of moving beyond a singular focus on immune-related pneumonitis to consider the broader pulmonary toxicity profile of systemic anticancer treatments.

The pharmaceutical industry, particularly Merck, which markets pembrolizumab (Keytruda), will likely leverage these data to further differentiate their product in a competitive oncology market. While the efficacy of combination regimens remains compelling for many patients, this safety profile could influence treatment algorithms, especially in populations where minimizing pulmonary complications is paramount. It reinforces the trend towards more targeted and less toxic therapies, even as the definition of 'toxicity' expands to encompass a wider range of adverse events.

For patients, this translates to a potentially better quality of life during treatment, with fewer respiratory complications that can lead to hospitalizations or dose interruptions. While immune-related adverse events still require vigilance, the overall reduction in pulmonary distress could significantly impact their daily lives. It empowers shared decision-making, allowing patients and their physicians to weigh efficacy against a more nuanced understanding of treatment-related risks, particularly those affecting a vital organ system.

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