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Clinical Review on Perioperative Immunotherapy Patterns for Non-Small Cell Lung Cancer

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Abstract: The application scope of immunotherapy has gradually expanded from advanced non-small cell lung cancer to the perioperative stage, with three core clinical application forms progressively established: neoadjuvant therapy, adjuvant therapy, and comprehensive management combining neoadjuvant and adjuvant approaches. Recent clinical studies have demonstrated that all three treatment modalities can achieve improvements in pathological response and event-free survival. However, consensus remains elusive regarding the characteristics of beneficiary populations, efficacy differences among various treatment strategies, and perioperative-specific safety risks. By integrating recent clinical research findings and systematically reviewing evidence-based data for each therapeutic approach, this review aims to provide evidence-based support for rational clinical treatment selection.

Keywords: Non-small cell lung cancer; Perioperative period; Immunotherapy; Treatment modality; Immune-related adverse reactions

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1. Introduction

Lung cancer ranks as the most prevalent and lethal malignant tumor globally, with non-small cell lung cancer (NSCLC) accounting for over 80% of cases. Radical surgery remains the standard treatment for resectable cases, yet high recurrence rates persist postoperatively, and conventional perioperative chemotherapy demonstrates limited efficacy in improving long-term survival outcomes. The advent of immune checkpoint inhibitors has introduced novel therapeutic approaches, with multiple studies validating their significance in perioperative applications. Critical challenges in current clinical practice include rational selection among neoadjuvant therapy, adjuvant therapy, and neoadjuvant-consolidation regimens, precise identification of

high-risk populations, and effective management of perioperative-specific adverse reactions.

2. Evidence-based foundations of three models for perioperative immunotherapy

2.1. Research evidence on neoadjuvant immunotherapy regimens

Wang Changli (2022) conducted a systematic review of key studies in this field. As the first Phase III clinical trial, CheckMate816 demonstrated improved pathological complete response rates and event-free survival following neoadjuvant nivolumab combined with chemotherapy. Hao Zhuohong (2024) analyzed trials such as NADIM and NADIMII, revealing that patients in Phase IIIIA maintained high primary pathological response rates after receiving combined immunotherapy and chemotherapy regimens. Hong Wenyuan (2024) discussed NEOSTAR study data, indicating that the dual immunotherapy regimen combining nivolumab and ipilimumab holds promising potential for improving pathological responses. Xu Yuanyuan (2024) investigated early-stage studies on immunotherapy monotherapy, with CheckMate159 trial data confirming that neoadjuvant immunotherapy monotherapy achieves pathological response without affecting surgical procedures.

2.2. Research evidence on adjuvant immunotherapy modalities

Adjuvant immunotherapy can be utilized to eliminate minimal residual disease postoperatively and reduce the likelihood of tumor recurrence [1]. Wang Changli (2022) reviewed the results of two Phase III studies, IMpower010 and KEYNOTE-091, demonstrating that atezolizumab application in programmed death ligand 1-positive patient populations prolongs disease-free survival, while pembrolizumab exhibits positive effects on overall disease-free survival across the entire study cohort. Xu Yuanyuan (2024) analyzed the inclusion criteria and key observation indicators of both studies, noting that the adjuvant chemotherapy followed by a sequential immunotherapy regimen adopted in IMpower010 has become the current mainstream clinical approach [2]. Hong Wenyuan (2024) highlighted in his discussion that patients without prior adjuvant chemotherapy in the KEYNOTE-091 study showed no significant benefit from pembrolizumab treatment, thereby validating the clinical value of prior adjuvant chemotherapy.

2.3. Research evidence on the “sandwich cake” perioperative whole-process treatment model

The “sandwich model” represents a comprehensive treatment strategy integrating neoadjuvant immunotherapy, surgery, and adjuvant immunotherapy [3]. Fang Yujia (2024) published findings from the AEGEAN study, demonstrating that perioperative application of davolizumab can prolong event-free survival and improve pathological complete response rates. Hong Wenyuan (2024) analyzed data from multiple Phase III trials, including KEYNOTE-671, Neotorch, and RATIONALE-315, revealing that the pembrolizumab group exhibited superior outcomes compared to the placebo group in both event-free survival and primary pathological response rates [4]. Hao Zhuohong (2024) elucidated the event-free survival benefits observed in the netreplisumab group within the Neotorch study and identified correlation data between perioperative tislelizumab administration and primary pathological response rates in the RATIONALE-315 trial. Wang Chenming (2025) synthesized these research findings to establish core evidence for perioperative treatment, with this model consistently demonstrating therapeutic benefits across multiple clinical studies.

3. Screening of beneficiary populations for different treatment modalities

3.1. The predictive value and controversies of PD-L1 expression levels

The expression of programmed death ligand 1 (PD-L1) demonstrates robust predictive efficacy during the neoadjuvant therapy phase. Wang Changli (2022) reported in the CheckMate816 study that there is a strong correlation between patient treatment benefit and PD-L1 expression levels, with increased PD-L1 levels correlating with greater treatment efficacy. However, the predictive value of this biomarker in adjuvant therapy remains controversial. Liu Xuehui (2025) systematically reviewed these discrepancies, noting that IMpower010 data suggest higher treatment benefits in high-PD-L1 expression populations, whereas the KEYNOTE-091 study failed to demonstrate statistical significance in the endpoint metrics of the high-PD-L1 subgroup [5]. Xu Yuanyuan (2024) proposed that the KEYNOTE-091 study revealed a survival advantage shift in the control cohort, which may have directly obscured the statistical differences between groups [6]. The expert consensus led by Xie Qichao (2022) concluded that the reference value of PD-L1 expression levels for adjuvant immunotherapy benefits has not yet reached a unified consensus, underscoring the need for further clinical studies for validation.

3.2. Impact of clinical staging and pathological type on therapeutic efficacy

Wang Changli (2022) mentioned in the CheckMate816 study that patients in stage III achieved higher benefits after neoadjuvant immunotherapy compared to those in stage IB-II. Liu Xuehui (2025) analyzed subgroup data from the AEGEAN study, demonstrating improved pathological responses in both stage II and stage III patients following neoadjuvant immunotherapy, though no definitive conclusion was reached regarding the benefits across stages. At the pathological type level, existing studies have not reached a unified conclusion. Liu Xuehui (2025) reviewed multiple studies, revealing that the Neotorch study showed superior event-free survival benefits in squamous cell carcinoma patients compared to non-squamous cell carcinoma, while the CheckMate816 study demonstrated more pronounced benefits in non-squamous cell carcinoma. However, long-term follow-up data from this study showed no statistically significant difference in overall survival between squamous cell carcinoma and non-squamous cell carcinoma.

3.3. The potential of ctDNA-MRD as a novel biomarker

The clearance status of circulating tumor DNA (ctDNA) is closely associated with immunotherapy efficacy. Wang Changli (2022) observed in the CheckMate816 study that the clearance rate of ctDNA under neoadjuvant immunotherapy combined with chemotherapy was higher than that of chemotherapy alone, with patients achieving clearance demonstrating superior pathological complete response rates. Xu Yuanyuan (2024) validated through the PROSPECTIVE LUNGCA-1 study data that postoperative molecular residual disease positivity serves as a key prognostic indicator for recurrence risk, with positive groups exhibiting significantly higher recurrence rates compared to negative groups. Liu Xuehui (2025) proposed that cases maintaining negative postoperative ctDNA molecular residual disease demonstrate potential cure characteristics, where adjuvant therapy may yield limited additional benefits. Xie Qichao (2022) suggested in a relevant expert consensus that populations with detection capabilities could utilize dynamic molecular residual disease monitoring to guide treatment planning, emphasizing that even late-stage cases should receive adjuvant therapy despite negative molecular residual disease results.

4. Key issues in selection of perioperative immunotherapy regimens

4.1. Consideration of neoadjuvant therapy cycles and surgical timing

The optimal number of cycles for neoadjuvant immunotherapy remains inconclusive. Wang Changli (2022), incorporating findings from the neoSCORE study, demonstrated that a three-cycle regimen combining immunotherapy and chemotherapy achieved superior primary pathological response rates compared to the two-cycle group. Extending treatment cycles neither increased surgical risks nor postoperative complication rates, while longer treatment durations correlated with higher pathological response rates. Currently, most Phase III studies adopting preoperative neoadjuvant immunotherapy combined with chemotherapy employ three-or four-cycle regimens. Regarding surgical timing, Xu Yuanyuan (2024) synthesized multiple studies to recommend performing surgery approximately one month after the final dose of neoadjuvant immunotherapy, as prolonged intervals may induce fibrosis that elevates surgical difficulty and risks. Hong Wenyuan (2024) similarly highlighted the increased incidence of hilar fibrosis following neoadjuvant immunotherapy, leading to a higher proportion of thoracoscopic-to-open thoracotomy transitions and placing greater demands on surgical expertise and experience.

4.2. Controversies in adjuvant therapy decision-making for pCR patients

Whether to initiate subsequent adjuvant therapy for patients achieving pathological complete response (PCR) after neoadjuvant therapy has become a central issue in clinical discussions [7]. Liu Xuehui (2025) systematically reviewed relevant controversies, noting that patients achieving PCR in the NADIM study demonstrated superior progression-free survival outcomes. Long-term follow-up data from the CheckMate816 study also corroborated that the overall survival rate in the PCR group was superior to that in the non-PCR group, suggesting potential exemption from subsequent adjuvant therapy for these patients. In contrast, the KEYNOTE-671 study observed that the survival benefit in the perioperative immunotherapy group was not influenced by the status of PCR [8]. Wang Chenming (2025), based on a meta-analysis of neoadjuvant chemotherapy phases, proposed that patients achieving PCR still carry certain mortality risks and that PCR should not be equated with disease cure. In clinical practice, individualized treatment plans are often formulated in conjunction with circulating tumor DNA (ctDNA) residual lesion detection results.

4.3. Comparison of safety among different treatment modalities

The overall safety of perioperative immunotherapy is controllable, with variations in the spectrum of adverse reactions across different modalities. Wang Changli (2022) reported that in the CheckMate816 study, the incidence of serious treatment-related adverse events was comparable between neoadjuvant immunotherapy combined with chemotherapy and chemotherapy alone. Hong Wenyuan (2024) demonstrated that in the KEYNOTE-671 trial, the incidence of serious adverse events was slightly higher in the pembrolizumab group compared to the placebo group, yet remained within a manageable range. Fang Yujia (2024) noted that the mortality rate of perioperative immunotherapy was slightly higher than that of chemotherapy alone, underscoring the importance of identifying appropriate patient populations for benefit. Xu Yuanyuan (2024) analyzed the impact of neoadjuvant immunotherapy on surgical outcomes, indicating that severe adverse reactions may delay surgical timing, necessitate surgical modality conversion, or even result in missed surgical opportunities. Ni Jun (2021) emphasized the critical importance of standardized baseline assessment and continuous monitoring in clinical practice recommendations.

5. Management strategies for immune-related adverse reactions during the perioperative period

5.1. Prevention and baseline assessment of irAEs

The prevention of immune-related adverse reactions relies on comprehensive evaluation before treatment initiation. Ni Jun (2021) explicitly outlined in relevant clinical guidelines that baseline assessment should encompass multiple components, including medical history collection, physical examination, laboratory testing, and imaging screening. Special populations such as those with autoimmune diseases, organ transplantation history, or chronic viral infections require careful benefit-risk assessment. Endocrine-related indicators, including thyroid function, adrenal function, and pituitary function, must be evaluated before treatment commencement. Pulmonary function tests and cardiac function assessments can assist in predicting perioperative potential risks. Patients should be informed about possible adverse reactions to immunotherapy before treatment initiation and establish a protocol for timely symptom reporting.

5.2. Graded diagnosis and treatment principles for common irAEs

The hierarchical diagnosis and treatment of immune-related adverse reactions form the core of standardized management. According to Ni Jun's (2021) clinical recommendations referencing domestic and international guidelines, adverse reactions are classified into four grades with corresponding management strategies: Grade I reactions require no suspension of immunotherapy but should be closely monitored; Grade II necessitates treatment suspension with consideration of local or systemic medium-dose glucocorticoids [9]; Grades III and above demand hospitalization with high-dose systemic glucocorticoids, followed by gradual dose reduction after symptom relief. The total treatment course typically lasts several weeks. During glucocorticoid therapy, vigilance is required for complications such as opportunistic infections and osteoporosis. For refractory cases unresponsive to glucocorticoid therapy, immunomodulators like infliximab or tocilizumab may be added.

6. Conclusion

Perioperative immunotherapy for non-small cell lung cancer has evolved from exploratory approaches to established practice, with three modalities, neoadjuvant therapy, adjuvant therapy, and comprehensive therapy, each supported by evidence-based rationale and applicable scenarios. The comprehensive "sandwich" model has demonstrated superior event-free survival benefits in multiple studies, though overall survival data require long-term follow-up validation. Key strategies for maximizing perioperative immunotherapy efficacy include precise identification of beneficiary populations, optimization of treatment cycles and surgical timing, and rational management of immune-related adverse reactions.

Disclosure statement

The authors declare no conflict of interest.

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