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SHORT REPORT

Re-evaluating perioperative and neoadjuvant immunotherapy in early-stage lung cancer: Current evidence and discussions

Enes ERUL(ID)

Division of Medical Oncology, Department of Internal Medicine, Ankara University Faculty of Medicine, Ankara, Türkiye

ABSTRACT

Re-evaluating perioperative and neoadjuvant immunotherapy in early-stage lung cancer: Current evidence and discussions

Early-stage lung cancer remains a challenging disease with a significant risk of recurrence despite treatment. In recent years, there has been growing interest in the application of neoadjuvant and perioperative immunotherapies. The success of immune checkpoint inhibitors in advanced stages has prompted their investigation in earlier disease stages. This editorial examines clinical trials comparing the efficacy of perioperative and neoadjuvant immunotherapies, focusing on their impact on survival, pathological response rates, and toxicity profiles. Furthermore, ongoing debates and the importance of patient-centered decision-making are discussed.

Key words: *Early-stage lung cancer; neoadjuvant immunotherapy; perioperative treatment; immune checkpoint inhibitors; non-small cell lung cancer*

ÖZ

Erken evre akciğer kanserinde perioperatif ve neoadjuvan immünoterapinin yeniden değerlendirilmesi: Mevcut kanıtlar ve tartışmalar

Erken evre akciğer kanseri, tedaviye rağmen tekrarlama riski taşıyan karmaşık bir hastalıktır. Son yıllarda neoadjuvan ve perioperatif immünoterapilerin kullanımına yönelik ilgi artmıştır. İmmün kontrol noktası inhibitörlerinin ileri evre hastalıklardaki başarısı, bu tedavilerin daha erken evrelerde uygulanabilirliğini gündeme getirmiştir. Bu editoryal, perioperatif ve neoadjuvan immünoterapilerin etkinliğini karşılaştıran klinik çalışmaları; bu yaklaşımların sağkalım, patolojik yanıt oranları ve toksisite profilleri üzerindeki etkilerini incelemektedir. Ayrıca tedaviye ilişkin mevcut tartışmalar ile hasta merkezli karar verme sürecinin önemi ele alınmaktadır.

Anahtar kelimeler: *Erken evre akciğer kanseri; neoadjuvan immünoterapi; perioperatif tedavi; İmmün kontrol noktası inhibitörleri; küçük hücreli olmayan akciğer kanseri*

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Address for Correspondence

Dr. Enes ERUL

Division of Medical Oncology,
Department of Internal Medicine,
Ankara University Faculty of Medicine,

ANKARA-TÜRKİYE

e-mail: eneserul@hotmail.com

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Re-evaluating perioperative and neoadjuvant immunotherapy in early-stage lung cancer

Lung cancer remains the leading cause of cancer-related mortality in both men and women. However, three-year survival rates have improved from 22% for patients diagnosed between 2004 and 2006 to 33% for those diagnosed between 2016 and 2018. This notable improvement is likely due to advancements in surgical techniques, the development of medical therapies such as immunotherapy and targeted treatments, and the increased detection of early-stage lung cancer through enhanced screening programs (1). The introduction of immune checkpoint inhibitors, particularly monoclonal antibodies targeting PD-1, PD-L1, and CTLA-4, has fundamentally transformed treatment algorithms for non-small cell lung cancer (NSCLC). Progression-free survival and overall survival (OS) benefits demonstrated in randomized controlled trials for advanced-stage NSCLC have shifted the focus towards exploring the use of immunotherapy in earlier stages of the disease (2-4). The occurrence of recurrence even in early resectable stages of lung cancer highlights the unmet need for effective treatment strategies. The availability of numerous distinct therapeutic scenarios has further fueled debates regarding the optimal treatment choice.

Previous neoadjuvant approaches using chemotherapy, such as preoperative administration of carboplatin and paclitaxel in early-stage cases, failed to demonstrate a significant difference in disease-free survival compared to postoperative adjuvant chemotherapy (5). However, with the CheckMate 816 trial, the addition of three cycles of nivolumab to platinum-based neoadjuvant chemotherapy introduced the concepts of major pathologic response, pathological complete response (pCR), and residual viable tumor (RVT) (6). The combination of three cycles of nivolumab and chemotherapy prior to surgery demonstrated a significant benefit compared to chemotherapy alone, with a hazard ratio (HR) of 0.68 [95% confidence interval (CI), 0.48-0.93] for disease progression or death. Based on the outcomes achieved with preoperative therapy, discussions have begun to focus on treatment escalation and de-escalation strategies, as well as the potential use of circulating tumor DNA for monitoring and guiding therapy (6,7). While OS is commonly used as an endpoint in oncology, its evaluation often requires longer follow-up. Therefore, event-free survival (EFS) has been increasingly utilized in lung cancer studies. It is well-established that preoperative therapies achieving pCR and reduced RVT are associated with improved EFS outcomes (7).

A significant challenge in clinical trials evaluating neoadjuvant or perioperative (neoadjuvant-adjuvant immunotherapy) approaches lies in the heterogeneity of the study populations. This heterogeneity arises from variations such as the inclusion of different stages (ranging from IB to IIIA in some trials and II to III in others) and discrepancies in staging methods, with some studies using the tumor, node, metastasis (TNM) 7th edition and others employing the TNM 8th edition (6,8-15) (Table 1). Unfortunately, the debate surrounding perioperative, neoadjuvant, or adjuvant treatment approaches continues to rely on indirect findings and comparisons. This is primarily due to the lack of a randomized, three-arm trial directly comparing neoadjuvant immunotherapy combined with chemotherapy, neoadjuvant chemotherapy alone, and a perioperative approach within the same study.

The intact interaction between the primary tumor and its draining lymph nodes is thought to favor neoadjuvant immunotherapy strategies. This approach is supported by the hypothesis that lymph node resection may limit the efficacy of immunotherapy by reducing the activation of anti-tumor T-cell responses (16). Another hypothesis favoring the neoadjuvant approach is the concern that adjuvant immunotherapy may increase toxicity. In an indirect meta-analysis including perioperative approaches from trials such as KEYNOTE-671, Neotorch, AEGEAN, and NADIM II, compared to chemotherapy alone, and CheckMate 816, which involved only neoadjuvant immunotherapy, no significant differences were observed in EFS (HR, 0.90; 95% CI, 0.63-1.30; p= 0.59) or OS (HR, 1.18; 95% CI, 0.73-1.90; p= 0.51). However, treatment-related adverse events of any grade were significantly higher in the perioperative approach, where adjuvant immunotherapy was included (relative risk, 1.08; 95% CI, 1.00-1.17; p= 0.04) (17).

An individual patient-level data analysis of CheckMate 77T and CheckMate 816 was conducted to assess the contribution of the adjuvant phase in the perioperative nivolumab treatment regimen. The analysis demonstrated a benefit in EFS [HR (95% CI): Unweighted, 0.59 (0.38-0.92)]. However, the carry-over effect of the initial neoadjuvant immunotherapy component

Table 1. Overview of clinical trials evaluating neoadjuvant, adjuvant and perioperative approaches in lung cancer

Trial	Timing	Size	Agent I/O	Cycles, n	Inclusion	Stage IB+II/III, %	Primary endpoint	Chemotherapy	EGFR/ALK
IMpower010[8]	Adjuvant	1.005	Atezolizumab (PD-L1)	16	Completely resected IB (>4 cm)-IIIA (7^{th})	59/41	DFS hierarchical	Cisplatin doublet	Included (15%)
KEYNOTE-091[9]	Adjuvant	1.177	Pembrolizumab (PD-1)	18	Completely resected IB (>4 cm)-IIIA (7^{th})	72/28	DFS, DFS in PD-L1 ≥50%	Platinum doublet encouraged	Included (7.4%)
BR.31[10]	Adjuvant	1.415 (477)	Durvalumab (PD-L1)	12	Completely resected IB (>4 cm)-IIIA (7^{th}) ESTS	71/39	DFS, PD-L1 ≥25%, EGFR/ ALK WT	Platinum doublet if not eligible	Included
CheckMate-816[6]	Neoadjuvant	358	Nivolumab (PD-1)	3	Resectable IB (>4 cm)-IIIA (7^{th})	36/64	pCR, EFS	Platinum doublet	No documented mutation
AEGEAN[11]	Perioperative	802	Durvalumab (PD-L1)	16	Resectable II-IIIB (8^{th}) by lobectomy	29/71	pCR, EFS	Platinum based	WT: Asia
Neotorch[12]	Perioperative	500	Toripalimab (PD-1)	17	Resectable II-IIIB (8^{th})	20/80	MPR, EFS	Platinum based	No documented mutation
KEYNOTE-671[13]	Perioperative	797	Pembrolizumab (PD-1)	13	Resectable II-IIIB (8^{th})	30/70	EFS, OS	Cisplatin doublet	WT
CheckMate-77T[14]	Perioperative	461	Nivolumab (PD-1)	16	Resectable II-IIIB/ (8^{th})	35/65	EFS	Platinum doublet	No EGFR, no documented ALK
RATIONALE-315[15]	Perioperative	453	Tislelizumab (PD-1)	12	Resectable II-IIIA (8^{th})	41/59	EFS, MPR	Platinum doublet	WT

OS: Overall survival, EFS: Event-free survival, pCR: Pathological complete response, DFS: Disease-free survival, WT: Wild-type, PD-1: Programmed death-1, PD-L1: Programmed death-ligand 1, EGFR: Epidermal growth factor receptor, ALK: Anaplastic lymphoma kinase, MPR: Major pathologic response.

cannot be entirely ruled out. Additionally, although PD-L1 is known to be an imperfect biomarker, the observed benefit was significant in PD-L1-negative patients [PD-L1 <1%, HR: 0.51 (0.28-0.93)] while showing overlap in PD-L1-positive patients [PD-L1 ≥1%, HR: 0.86 (0.44-1.70)], continuing to raise questions and uncertainties (18). Nonetheless, the strongest hypothesis supporting the perioperative approach is that the KEYNOTE-671 trial, with its extended follow-up duration, is the only study demonstrating an OS benefit (13). In the perioperative study of pembrolizumab, the KEYNOTE-671 trial, the relationship between pathological regression and EFS revealed that when more than 60% RVT remained, the pembrolizumab and placebo arms showed overlapping results (19). This finding raises critical questions such as: Is postoperative adjuvant therapy truly necessary? Should we persist with adjuvant therapy in cases where neoadjuvant treatment has failed to elicit a response?

Amidst all these ongoing debates, a fundamental principle in oncology remains unchanged: Treatment selection should consider patient's preference, financial toxicity, shared decision-making, and drug availability. Until more definitive evidence emerges, personalized decision-making based on the patient's preference will be the most appropriate approach.

CONFLICT of INTEREST

The author have no conflict of interest to declare.

AUTHORSHIP CONTRIBUTIONS

Concept/Design: EE

Analysis/Interpretation: EE

Data acqusition: EE

Writing: EE

Clinical Revision: EE

Final Approval: EE

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