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SHORT REPORT

Current front-line treatment strategies in EGFR-mutated advanced NSCLC: Balancing efficacy with risks of interstitial lung disease and venous thromboembolism

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ABSTRACT

Current front-line treatment strategies in EGFR-mutated advanced NSCLC: Balancing efficacy with risks of interstitial lung disease and venous thromboembolism

The therapeutic landscape for patients with previously untreated epidermal growth factor receptor (EGFR)-mutated advanced non-small cell lung cancer (NSCLC) has significantly evolved, with novel treatment options now available beyond osimertinib monotherapy. The addition of platinum-pemetrexed chemotherapy to osimertinib has demonstrated improved progression-free survival, particularly in patients with central nervous system metastases. Recently, amivantamab-lazertinib combination has shown superior overall and progression-free survival compared to osimertinib monotherapy in the MARIPOSA trial. However, these efficacy improvements are accompanied by increased toxicity. Interstitial lung disease (ILD) remains a class effect across EGFR-targeted therapies, whereas venous thromboembolism (VTE) has emerged as a notable safety concern specifically associated with amivantamab-lazertinib combination. Although prophylactic strategies can reduce the risk of these complications, their impact on patients' quality of life and the ability to continue treatment must be carefully considered. Individualized treatment decisions, based on clinical features such as CNS involvement, tumor burden, and patient frailty, are essential to optimize therapeutic outcomes while minimizing adverse effects. This article highlights the evolving first-line treatment strategies in EGFR-mutated advanced NSCLC, with a particular focus on ILD and VTE risks.

Key words: Non-small cell lung cancer; first-line therapy; toxicity; interstitial lung disease; venous thromboembolism

ÖZ

EGFR mutasyonu taşıyan ileri evre küçük hücreli-dışı akciğer kanserinde güncel birinci basamak tedavi seçenekleri: Etkinlik ve tedavi ilişkili interstisyel akciğer hastalığı ve venöz tromboemboli riskleri

Daha önce sistemik tedavi almamış, EGFR mutasyonu taşıyan ileri evre küçük hücreli dışı akciğer kanseri (KHDAK) hastalarında tedavi seçenekleri artmış ve osimertinib monoterapisinin ötesine geçmiştir. Osimertinibe platin-pemetreksed kemoterapisi eklenmesiyle, özellikle santral sinir sistemi metastazı olan hastalarda progresyonsuz sağkalım süresinin uzadığı görülmüştür. Diğer yandan, MARIPOSA çalışmasında amivantamab-lazertinib kombinasyonu, osimertinib monoterapisine kıyasla hem genel sağkalım hem de progresyonsuz sağkalım açısından üstünlük göstermiştir. Ancak bu etkinlik artışı, belirgin bir toksisite yükü ile birlikte gelmektedir. EGFR hedefli tedavilerde interstisyel akciğer hastalığı (İAH) sınıf etkisi olarak görülürken, venöz tromboemboli (VTE) özellikle amivantamab-lazertinib kombinasyonunda önemli bir tedavi ilişkili toksisite olarak öne çıkmaktadır. Profilaktik yaklaşımlar bu komplikasyonların riskini azaltabilse de, hastaların yaşam kalitesi ve tedaviye devamlılık üzerindeki etkileri dikkatle değerlendirilmelidir. Santral sinir sistemi tutulumu, tümör yükü ve kırılabilirlik gibi klinik özelliklere dayalı bireyselleştirilmiş tedavi kararları, tedavi etkinliğini artırırken yan etkileri en aza indirmek için hayati öneme sahiptir. Bu makale, EGFR mutasyonu taşıyan ileri evre KHDAK hastalarında güncel birinci basamak tedavi stratejilerini, özellikle İAH ve VTE risklerine odaklanarak özetlemektedir.

Anahtar kelimeler: Küçük hücreli dışı akciğer kanseri; birinci basamak tedavi; toksisite; interstisyel akciğer hastalığı; venöz tromboemboli

INTRODUCTION

Patients with activating mutations in the epidermal growth factor receptor (EGFR) gene account for approximately 13% to 49% of advanced non-squamous non-small cell lung cancers (NSCLC) (1). As EGFR mutations are highly prevalent and targetable alterations, the therapeutic landscape of previously untreated EGFR-mutated advanced NSCLC has evolved in recent years. Current options for first-line treatment of advanced NSCLC include osimertinib monotherapy, osimertinib combined with platinum-pemetrexed chemotherapy, and the combination of amivantamab with lazertinib (2-5). In the phase III FLAURA trial, osimertinib demonstrated superior efficacy compared to erlotinib or gefitinib, with significantly improved progression-free survival (PFS) and overall survival (OS), along with a favorable safety profile (2,3) (Table 1). However, the eventual development of resistance to osimertinib monotherapy has driven the need for novel first-line treatment approaches. Osimertinib was the global first-line standard of care until the addition of platinum-pemetrexed chemotherapy to osimertinib significantly reduced the risk of disease progression or death by 38% compared to osimertinib monotherapy in the FLAURA2 trial [median PFS: 25.5 vs. 16.7 months; HR 0.62 (95% CI: 0.49-0.79); $p < 0.001$] (4). At the second interim analysis of FLAURA2, a trend toward improved OS was reported (41% data maturity), with post-progression outcomes also favoring the combination of osimertinib with platinum-pemetrexed chemotherapy (6). The benefit of adding platinum-pemetrexed chemotherapy to osimertinib was more

pronounced in patients with central nervous system (CNS) metastases at baseline [median PFS: 24.9 vs. 13.8 months; HR 0.47 (95% CI: 0.33-0.66)]. Although efficacy improved, the addition of chemotherapy to osimertinib led to a higher rate of grade ≥ 3 adverse events (64% vs. 27%), primarily due to chemotherapy-related hematologic toxicities. These findings highlight the importance of individualized treatment decisions, particularly in patients with high-risk features such as CNS involvement. On the other hand, increased toxicity associated with the combination of osimertinib and chemotherapy makes osimertinib monotherapy preferable for many patients, particularly those with lower tumor burden or clinical frailty.

Recently, the phase III MARIPOSA trial reported that the combination of amivantamab and lazertinib improved both PFS and OS compared to osimertinib monotherapy in patients with previously untreated EGFR-mutated advanced NSCLC [median PFS: 23.7 vs. 16.6 months; HR 0.70 (95% CI: 0.58-0.85); $p < 0.001$; median OS: not estimable vs. 36.7 months; HR 0.75 (95% CI: 0.61-0.92); $p < 0.005$] (5,7). This combination has the potential to extend median OS beyond four years, offering more than a one-year survival advantage compared to osimertinib monotherapy (5). Although this combination is the first and only first-line treatment option to significantly reduce the risk of death compared to osimertinib in patients with EGFR-mutated advanced NSCLC, this efficacy comes at the cost of markedly increased toxicity. In MARIPOSA trial, grade ≥ 3 adverse events occurred in 75% of patients receiving amivantamab plus lazertinib, compared to 43% of those receiving

Table 1. Comparison of survival outcomes and incidence rates of ILD and VTE in pivotal clinical trials

	FLAURA		FLAURA2		MARIPOSA*	
Target population	Previously untreated, EGFR-mutated advanced NSCLC		Previously untreated, EGFR-mutated advanced NSCLC		Previously untreated, EGFR-mutated advanced NSCLC	
Treatment protocols	Osimertinib 80 mg once daily	Gefitinib 250 mg or erlotinib 150 mg once daily	Osimertinib 80 mg once daily plus 4 cycles of pemetrexed (500 mg/m ²) and either cisplatin (75 mg/m ²) or carboplatin (AUC 5 mg/mL/min) Q3W, then maintenance with osimertinib 80 mg once daily plus pemetrexed 500 mg/m ² Q3W	Osimertinib 80 mg once daily	Amivantamab 1050 mg (1400 mg if ≥80 kg) weekly for the first four weeks, then every two weeks, plus lazertinib 240 mg once daily	Osimertinib 80 mg once daily
Number of patients	n= 279	n= 277	n= 279	n= 278	n= 429	n= 429
Median PFS	18.9 months (95% CI 15.2-21.4)	10.2 months (95% CI 9.6-11.1)	25.5 months (95% CI 24.7-NC)	16.7 months (95% CI 14.1-21.3)	23.7 months (95% CI 19.1-27.7)	16.6 months (95% CI 14.8-18.5)
	HR 0.46 (95% CI 0.37-0.57), p< 0.001		HR 0.62 (95% CI 0.49-0.79), p< 0.001		HR 0.70 (95% CI 0.58-0.85), p< 0.001	
Median OS	38.6 months (95% CI 34.5-41.8)	31.8 months (95% CI 26.6-36.0)	NR (95% CI 38.0-NC)	36.7 months (95% CI 33.2-NC)	NE (95% CI 42.9-NE)	36.7 months (95% CI 33.4-41.0)
	HR 0.80 (95% CI 0.64-1.00), p= 0.046		HR 0.75 (95% CI 0.57-0.97)**		HR 0.75 (95% CI 0.61-0.92), p< 0.005	
Grade ≥3 adverse events	42%	47%	64%	27%	75%	43%
ILD						
Any grade	4%	2%	3%	4%	3%	3%
Grade ≥3	1%	1%	<1%	1.8%	1%	1%
VTE						
Any grade	Not reported	Not reported	Not reported	Not reported	37%	9%
Grade ≥3	3%	0.7%	2.9%	1.8%	11.2%	3.5%

CI: Confidence interval, HR: Hazard ratio, ILD: Interstitial lung disease, NC: Not calculable, NE: Not estimable, NR: Not reached, NSCLC: Non-small cell lung cancer, OS: Overall survival, PFS: Progression-free survival, VTE: Venous thromboembolic event.

*Data for the lazertinib monotherapy arm are not provided in the table.

**41% maturity.

osimertinib (7). The most prominent adverse events in the amivantamab-lazertinib arm were skin side effects, infusion-related reactions, and venous thromboembolic events, which can be reduced with appropriate prophylactic approaches (5,7). The percentage of treatment-related adverse events leading to discontinuation of all trial agents was 10% in the amivantamab-lazertinib arm and 3% in the osimertinib arm (7). Despite the improved efficacy and avail-

able prophylactic strategies, the substantial toxicity burden of amivantamab-lazertinib combination may limit its widespread use in the real-world population.

The management of treatment-related pulmonary side effects is particularly challenging in lung cancer patients, whose baseline respiratory function is frequently diminished by tumor mass and concurrent pulmonary disorders. Interstitial lung disease (ILD) has been recognized as a class effect across EGFR

tyrosine kinase inhibitors (TKIs), arising from the suppression of alveolar epithelial repair pathways, resulting in inflammatory cell infiltration and parenchymal injury (8). In FLAURA trial, osimertinib, a third-generation, irreversible EGFR-TKI, was associated with an ILD incidence of 4%, with severe (grade ≥ 3) cases reported in approximately 2% of patients (2). Similarly, FLAURA2 trial reported an ILD and pneumonitis incidence of 4% in osimertinib arm (grade ≥ 3 : 1.8%) and 3% in osimertinib plus chemotherapy arm (grade ≥ 3 : $<1\%$) (4). In the MARIPOSA trial, the incidence of ILD or pneumonitis in patients receiving amivantamab-lazertinib was approximately 3%, comparable to that observed with osimertinib monotherapy (7). Grade ≥ 3 ILD events were infrequent across treatment arms (1% vs. 1%) (7). This suggests that the ILD risk is predominantly related to EGFR pathway inhibition rather than any synergistic increase from the combination. Management strategies generally involve symptomatic supportive treatment, drug discontinuation, and/or corticosteroid therapy (9). Venous thromboembolism (VTE), however, emerged as a notable safety signal associated with the amivantamab-lazertinib regimen (7). VTE events were reported in 37% of patients treated with amivantamab-lazertinib compared with 9% in those receiving osimertinib (7). Pulmonary embolism was reported in 17% of patients treated with amivantamab-lazertinib, whereas the incidence was 5% in the osimertinib arm (7). Notably, only 5% of the patients across both groups were on anticoagulation at baseline, with just 1% in the amivantamab-lazertinib group receiving anticoagulants at the time of their first VTE event (7). Since more than 60% of VTE events in the amivantamab-lazertinib group occurred within the first 4 months of therapy, prophylactic anticoagulation during this period is now recommended (7,10). Risk factors for VTE include age ≥ 60 years, ECOG performance status of 1 (vs. 0), and partial or better response to therapy, leading to the hypothesis that rapid tumor-cell death from amivantamab-lazertinib may induce a transient prothrombotic state (7,10). Despite the increased VTE risk with amivantamab-lazertinib combination, most thromboembolic events were non-fatal and manageable with standard anticoagulation, underscoring the impor-

tance of early intervention and vigilant monitoring. In contrast, osimertinib has not been shown to exert a direct pro-thrombotic effect. The few thromboembolic events reported in clinical trials are more likely attributable to cancer-associated hypercoagulability or individual patient risk factors, rather than a drug-specific mechanism. An analysis of 17 prospective and retrospective studies involving patients with NSCLC treated with osimertinib reported a thromboembolic event incidence of 2.4%, with no significant difference compared to the control arms [RR: 1.45 (95% CI: 0.56-3.78); $p=0.45$] (11).

In conclusion, the decision of first-line treatment for EGFR-mutated advanced NSCLC should be individualized based on a range of patient-specific characteristics. Due to its ease of use as an oral agent and favorable safety profile, osimertinib monotherapy continues to be regarded as the standard of care for a substantial proportion of patients. Patients with high-risk features, such as CNS involvement, derive greater benefit from the addition of platinum-pemetrexed chemotherapy to osimertinib, albeit with a higher incidence of grade ≥ 3 adverse events. Although the amivantamab-lazertinib combination improves therapeutic outcomes, the associated risks of dermatologic adverse effects, infusion-related reactions, and VTE must be effectively prevented and managed to preserve patients' quality of life. Treatment-related pulmonary side effects, including ILD and VTE, require close monitoring during EGFR-targeted therapy.

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CONFLICT of INTEREST

The authors declare that they have no conflict of interest.

AUTHORSHIP CONTRIBUTIONS

Concept/Design: All of authors

Analysis/Interpretation: All of authors

Data acquisition: All of authors

Writing: All of authors

Clinical Revision: All of authors

Final Approval: All of authors

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