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EGFR突变肺腺癌耐药后双靶治疗致急性间质性肺炎1例并文献复习

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摘　要

目的：探究双靶治疗在晚期EGFR突变阳性的非小细胞肺癌患者中的疗效及安全性，不良反应的处理及下一步治疗方案。方法：收集并整理1例携带EGFR敏感突变的晚期肺腺癌患者在TKI耐药后接受双靶向药物联合治疗过程中出现急性间质性肺炎的临床资料，包括患者的基本信息、病史、临床表现、辅助检查、治疗经过及转归；同时，利用PubMed检索国内外相关文献对类似病例的报道及研究进展进行系统分析。结果：患者在应用伏美替尼联合克唑替尼靶向治疗3个月后发生急性间质性肺炎，及时停用靶向药物并给予全身糖皮质激素治疗1周后病情好转，后线加用全身化疗及小分子多靶点药物，取得生存获益，OS为60个月。结论：针对晚期EGFR突变阳性的NSCLC患者，在二线靶向治疗耐药后选择双靶治疗方案可能会引发严重的药物相关间质性肺疾病。因此，我们需要及时识别、调整靶向药物种类或剂量并进行积极对症支持，这对于提高患者后续生存质量至关重要。

关键词

肺腺癌，EGFR突变，靶向治疗，药物相关间质性肺疾病

Acute Interstitial Pneumonia Caused by Dual-Target Therapy in Resistant EGFR-Mutated Lung Adenocarcinoma: A Case Report and Literature Review

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Abstract

Objective: To investigate the efficacy and safety of dual-targeted therapy in patients with advanced EGFR mutation-positive non-small cell lung cancer (NSCLC), as well as the management of adverse reactions and next-step treatment strategies. Methods: We collect and organize the clinical data of a case of advanced lung adenocarcinoma harboring an EGFR-sensitive mutation who developed drug-induced interstitial lung disease (DI-ILD) during dual-targeted combination therapy following TKI resistance, including demographic characteristics, medical history, clinical manifestations, auxiliary examinations, treatment course, and outcomes; concurrently, conduct a systematic analysis of domestic and international literature on similar reported cases and research advances using PubMed. Results: The patient developed acute interstitial pneumonia three months after initiation of furmonertinib combined with crizotinib targeted therapy. Immediate discontinuation of targeted agents and administration of systemic glucocorticoids for one week resulted in clinical improvement. Subsequent-line therapy integrating systemic chemotherapy and a small-molecule multi-target agent provided survival benefits, achieving an overall survival (OS) of 60 months. Conclusion: For patients with advanced EGFR mutation-positive NSCLC, the selection of dual-targeted therapeutic regimens after resistance to second-line targeted therapy may precipitate severe DI-ILD. Therefore, prompt recognition, adjustment of targeted agent types or dosages, and implementation of aggressive supportive measures are required to optimize post-treatment quality of life, which is critical for long-term clinical outcomes.

Keywords

Lung Adenocarcinoma, EGFR Mutation, Targeted Therapy, Drug-Induced Interstitial Lung Disease

1. 背景

近年来，非小细胞肺癌(Non-small cell lung cancer, NSCLC)精准靶向治疗取得了显著进展，显著延长了驱动基因阳性的非小细胞肺癌患者的生存期[1]。表皮生长因子受体酪氨酸激酶抑制剂(Epidermal growth factor receptor-Tyrosine kinase inhibitor, EGFR-TKI)是 NSCLC 靶向治疗的一个重要里程碑，然而，耐药性是不可避免的。一线靶向治疗耐药后可根据基因检测结果选择合适的二线靶向治疗，EGFR-T790M 突变是第一代 EGFR-TKI 治疗后出现的最主要的耐药形式，在 AURA 系列研究[2]-[4]的支持下，奥希替尼成为出现 EGFR-T790M 突变后标准的二线治疗方案。然而，二线靶向治疗耐药后的标准治疗方案相关临床资料亟待补充，双药靶向联合治疗仍处于摸索阶段，其疗效与安全性仍需进一步验证。多份病例报告[5]-[7]显示吉非替尼/厄洛替尼联合奥希替尼对携带 T790 M 和 C797 S 反式突变的 EGFR 突变 NSCLC 患者有效。一项回顾性研究[8]报告了克唑替尼联合奥希替尼在 MET 扩增的肺腺癌患者中，ORR 为 100%，中位 PFS 为 6.2 个月。另一项回顾性研究[9]显示 6 例接受克唑替尼联合 EGFR-TKI 治疗的患者中 2 例出现了 3 级转氨酶升高。多数患者发生的 EGFR-TKI 相关的不良反应可以通过药物减量来建立耐受，但仍有 5.7% 的患者会发生 EGFR-TKI 相关间质性肺疾病(Interstitial lung disease, ILD) [10]。药物相关间质性肺疾病

(Drug-induced Interstitial lung disease, DI-ILD)的临床表现具有异质性，可以从轻微的气促、咳嗽等呼吸道症状急剧进展为致命性的急性呼吸衰竭[11]。DI-ILD 缺乏特异性的临床、实验室、影像学或病理学特征，疾病诊断为排除性诊断，存在明确致肺毒性药物的接触史，并排除 ILD 的其他潜在致病因素[12]。及时识别并停用致病药物是临床诊疗的关键，疾病表现为重症或进展性时则应用全身性糖皮质激素治疗。据统计，约 58% EGFR-TKI 治疗相关的死亡病例是因为发生了急性间质性肺炎(acute interstitial pneumonia, AIP) [13]。ILD 很少变现为 AIP，然而，AIP 一旦发生，90%患者即可出现进行性呼吸困难，大部分在数日内需行气管插管和机械通气。我们本次报道的患者在联合应用伏美替尼和克唑替尼后出现了严重 AIP，该病例进一步补充完善了有关双靶治疗相关不良反应的证据。同时，我们还对 NSCLC 患者联合应用靶向治疗的临床疗效和安全性进行了文献综述，旨在进一步丰富临床证据。

2. 病例回顾

患者女性，45 岁，2018 年 12 月因“胸背部疼痛 2 月余”入院。胸部增强 CT 示右肺上叶前段胸膜下结节，大小约 13 mm × 10 mm；右侧胸腔积液。随后患者完善右肺穿刺活检，病理示中分化腺癌，免疫组化 PD-L1 (SP263) (+，约 5%)，基因检测示 EGFR-19-Del (19 外显子)阳性(突变)。骨扫描示胸骨转移。初步诊断为右肺腺癌并多处转移(T4N2M1b，IV 期)，EGFR-19-Del 突变。ECOG 体能状态(performance status, PS)评分 1 分。给予埃克替尼靶向治疗，疾病进展(progressive disease, PD)后，行 NGS 检测提示新增 EGFR-20-T790M 耐药突变(突变频率 14.98%)，换用奥希替尼行二线靶向治疗。21 个月后疾病再次进展，基因检测提示 EGFR-19-del 突变、EGFR-20-T790M-C797S 顺式突变、ROS1 突变、TP53 突变阳性，给予患者伏美替尼联合克唑替尼双靶向治疗。

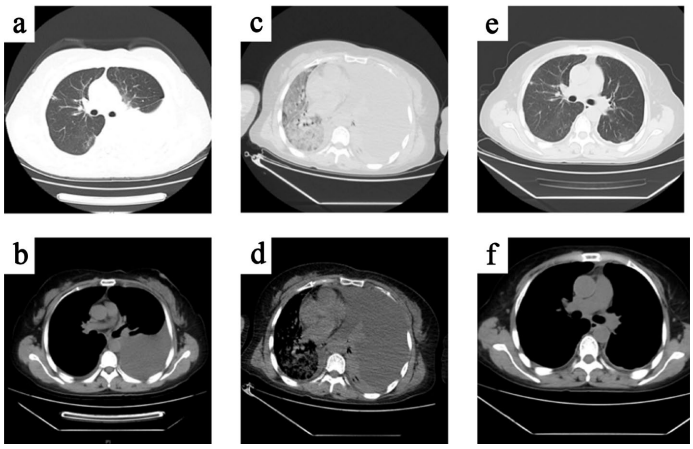

Figure 1. Chest CT findings at different time points during the diagnosis and treatment of the case. (a) (b) Prior to combination therapy, massive left pleural effusion is observed ((a) lung window; (b) mediastinal window). (c) (d) Three months post-combination therapy, diffuse pulmonary lesions with interlobular septal thickening in the right lung and persistent left pleural effusion are noted ((c) lung window; (d) mediastinal window). (e) (f) One week after treatment, near-complete resolution of right lung patchy consolidations and ground-glass opacities, along with marked reduction of left pleural effusion ((e) lung window; (f) mediastinal window)

图 1. 病例在诊断和治疗中不同时间节点的胸部 CT 表现。(a) (b) 患者联合治疗前，左侧大量胸腔积液((a) 肺窗；(b) 纵隔窗)；(c) (d) 联合治疗 3 个月后，右肺弥漫性病变伴小叶间隔增厚、左侧大量胸腔积液((c) 肺窗；(d) 纵隔窗)；(e) (f) 治疗 1 周后，右肺片状高密度影及磨玻璃影基本吸收，左侧胸腔积液明显减少((e) 肺窗；(f) 纵隔窗)

双靶向治疗 3 个月后患者因“呼吸困难进行性加重”入院，胸部 CT (见图 1)示原发灶较前相仿(7 mm × 5 mm)、右肺弥漫性病变伴小叶间隔增厚、左侧大量胸腔积液；血气分析示 PH：7.43，氧分压：40.00 mmHg，二氧化碳分压：30.00 mmHg，氧饱和度：78.8%；血常规示：WBC：17.05 × 10^9/L，中性粒细胞：

15.24 × 10^9/L，淋巴细胞：1.10 × 10^9/L，单核细胞：0.66 × 10^9/L；C 反应蛋白：33.06 mg/L，降钙素原：1.22 ng/ml；细菌培养及鉴定、抗酸菌检测、X-pert 未见明显异常；支气管肺泡灌洗液(BAL)检测出 94%淋巴细胞，2%的单核细胞，提示非感染性炎症反应；胸腔积液较前增加可能与原发病有关，实验室检查和影像学(见表 1)均没有证据支持肿瘤进展或肺部感染等其他加重症状的原因，考虑患者出现 DI-ILD，根据 CTCAE 5.0 评估为 4 级不良反应。立即停用靶向治疗，给予患者高流量湿化氧疗、应用全身糖皮质激素抗炎(甲泼尼龙：2 mg/kg)及营养支持等对症支持治疗。1 周后复查胸部 CT 示肺间质性病变较前好转，改鼻导管吸氧可维持血氧饱和度 98%左右，尽管缺乏病理证据，但双靶治疗后患者进行性呼吸困难加重，CT 示新发弥漫性磨玻璃影，并且激素治疗 1 周后病变明显吸收，在排除了其他可能的原因后可临床诊断 DI-ILD。激素逐渐停用后改为奥希替尼联合安罗替尼靶向治疗，患者疾病进展缓慢，行积极抗肿瘤治疗未再发生 AIP。于 2023 年 12 月患者原发病进展去世，0S 为 60 个月，见图 2。

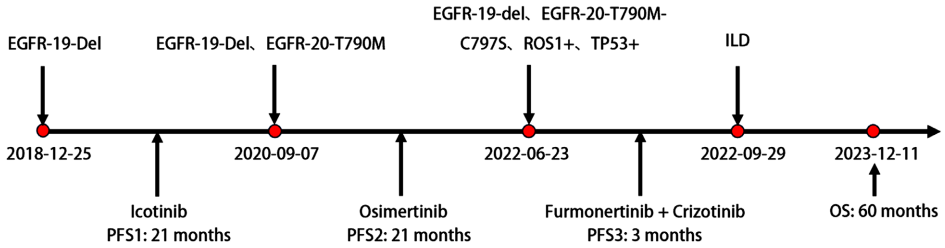

Figure 2. The genetic testing results and treatment regimens at different time points during diagnosis and therapy in the case
图 2. 病例在诊断和治疗中不同时间节点的基因检测结果及治疗方案等

Table 1. Clinical manifestations, laboratory findings, imaging studies, and primary treatment regimens before and after the onset of AIP and post-treatment in the case
表 1. 病例在发生 AIP 前后及 AIP 治疗后的临床表现、实验室检查、影像学检查及主要治疗方案

	发生 AIP 前	发生 AIP 后	AIP 治疗后
临床表现	胸闷	呼吸困难进行性加重	呼吸困难明显缓解
血气分析	PH：7.40，PaO_2：97.20 mmHg，$PaCO_2$：42.20 mmHg，SaO_2：96.8%	PH：7.42，PaO_2：40.00 mmHg，$PaCO_2$：30.00 mmHg，SaO_2：78.8%	PH：7.43，PaO_2：96.40 mmHg，$PaCO_2$：40.70 mmHg，SaO_2：97.2%
血常规	白细胞：4.27 × 10^9/L，中性粒细胞：2.17 × 10^9/L，淋巴细胞：1.58 × 10^9/L，单核细胞：0.39 × 10^9/L	白细胞：17.05 × 10^9/L，中性粒细胞：15.24 × 10^9/L，淋巴细胞：1.10 × 10^9/L，单核细胞：0.66 × 10^9/L	白细胞：4.27 × 10^9/L，中性粒细胞：1.92 × 10^9/L，淋巴细胞：0.79 × 10^9/L，单核细胞：0.46 × 10^9/L
风湿四项	无	ASO < 50 IU/ml，RF < 11.30 IU/ml，CRP 76.06 mg/L，A-CCP < 8.00 U/ml	无
降钙素原	<0.05 ng/ml	1.22 ng/ml	<0.05 ng/ml
影像学	2022-08-23 胸部 CT：原发灶 7 mm × 5 mm，左侧大量胸腔积液	2022-09-29 胸部 CT：原发灶 7 mm × 5 mm，右肺弥漫性病变伴小叶间隔增厚，左侧大量胸腔积液	2022-10-04 胸部 CT：原发灶 7 mm × 5 mm，右肺片状高密度影及磨玻璃影基本吸收，左侧胸腔积液明显减少
支气管肺泡灌洗液	无	淋巴细胞 94%，单核细胞 2%	无
细菌培养及鉴定、抗酸菌检测、X-pert	阴性	阴性	无
治疗	伏美替尼联合克唑替尼	高流量湿化氧疗、糖皮质激素、营养支持	鼻导管吸氧、糖皮质激素

3. 讨论

EGFR 突变肺癌患者应用 EGFR TKI 的中位无进展生存期(progression-free survival, PFS)为 10 到 14 个月[14]。我们报道的病例无论一线治疗还是在一线耐药后的奥希替尼治疗中，PFS 均超过了 14 个月。然而，DI-ILD 阻碍了疗效。关于 DI-ILD 的发生、治疗与预后，尚且需要进一步讨论。

耐药后旁路突变的治疗尚缺乏大型的临床研究，特别是针对 EGFR 突变后合并 ALK 等突变。我们收集了既往报道过的 18 例联合应用不同 TKI 药物治疗 NSCLC 的案例报道(见表 2)。18 例患者均未出现 DI-ILD，无论 EGFR-TKI 联合 ALK-TKI 或其他类型 TKI 均未增加治疗相关的不良反应，其中 11 例在联合治疗后能够达到部分缓解，多数不良反应在靶向药物减量后可得到缓解，1 例因出现严重口腔炎而停药。在伏美替尼联合克唑替尼治疗的病例中，PFS 为 6 个月到 12 个月，且没有观察到不良事件的发生率和严重程度增加[9] [15]。不排除大多数联合应用靶向治疗的患者暂未出现严重不良反应，但我们报道的患者在联合治疗 3 个月后出现了危及生命的严重不良反应，TKIs 联合应用治疗 NSCLC 患者安全性仍需要更多的临床数据，我们在选择 TKI 耐药后出现可治疗的新靶点时的后续治疗方案仍需谨慎。

Table 2. Case analysis of combined TKIs therapies in NSCLC. NA denotes “not mentioned”, adverse reactions not documented in this study were considered absent
表 2. 联合应用不同 TKI 药物治疗 NSCLC 的案例分析。NA 指未提及，本文认为未提及的不良反应为无

序号	年龄	性别	吸烟史	首次基因检测	新增突变	治疗阶段	联合治疗方案	疗效评价	PFS (月)	不良反应	OS (月)
1 [16]	52	女	NA	EGFR 19del	EGFR T790、C797S	三线	奥希替尼、吉非替尼	PR	8	腮腺炎、皮疹	39
2 [17]	56	男	无	BRAF V600E、TP53、PD-L1	NA	一线	达拉非尼、曲美替尼	PR	3	NA	NA
3 [18]	65	女	无	EGFR 19del	EGFR T790M、EGFR L858R、TP53、BRAF V600E	三线	奥希替尼、维罗非尼	PR	NA	NA	14.3
4 [18]	51	男	有	EGFR 19del、EGFR T790M、BRAF V600E	无	三线	奥希替尼、维罗非尼	NA	4.5	NA	21.3
5 [19]	69	男	无	EGFR T790M	EGFR 19del、EML4-ALK 融合	四线	奥希替尼、阿来替尼	PR	NA	无	NA
6 [20]	81	女	NA	EGFR 19del、TP53	无	三线	卡博替尼、奥希替尼	PR	NA	2~3 级腹泻	25
7 [21]	48	男	有	EGFR 19del	T790M、C797S、G724S	六线	阿美替尼、阿法替尼	PR	NA	NA	NA
8 [22]	54	女	无	EGFR L861Q	Met	三线	阿法替尼、克唑替尼	PR	10	无	NA
9 [23]	64	女	NA	EGFR 19del	BRAF V600E	四线	奥希替尼、达拉非尼、曲美替尼	NA	NA	1~2 级皮疹、食欲下降、发热	NA
10 [24]	55	男	无	EGFR L858R、MET	无	二线	奥希替尼、克唑替尼	PR	7	NA	NA
11 [25]	39	男	无	EGFR 19del、ALK-EML4	无	四线	奥希替尼、色瑞替尼	PR	NA	NA	NA
12 [26]	63	女	无	EGFR L861Q、G719D	CUX1-Met 融合	四线	伊科替尼、克唑替尼	PR	NA	NA	NA
13 [27]	61	女	无	EGFR 19del	EGFR T790M、MET	三线	克唑替尼、奥希替尼	NA	19	2 级乏力、呕吐和食欲下降、贫血、下肢水肿	NA

续表

14 [28]	69	男	无	EGFR 19del	EGFR T790M、cis-C797S、ERBB2	七线	阿法替尼、阿帕替尼	PR	10	NA	80
15 [29]	65	女	NA	野生型	无	三线	阿帕替尼、厄洛替尼	NA	15.4	NA	NA
16 [30]	63	男	有	EGFR 19del	EGFR T790M、BRAF V600E	三线	奥希替尼、达拉非尼、曲美替尼	SD	9	低热、甲沟炎	NA
17 [31]	62	女	NA	EGFR L858R	EGFR T790M	三线	奥希替尼、吉非替尼	NA	NA	3 级口腔炎(停药)	NA
18 [32]	50	男	无	EGFR 19del	EGFR T790M、LMNA-NTRK1 融合	三线	奥希替尼、恩曲替尼	NA	5	NA	92

DI-ILD 的发病率在不同情况下差异显著，这取决于药物种类、剂量以及病例报告的准确性等。严重的 DI-ILD 在单药靶向治疗时发生率相对较低。EGFR-TKI 引起的 DI-ILD 的发病率为 1.1%~1.6%，3 级以上不良反应的发病率为 0.49%~0.9% [10]。三代 EGFR-TKI 药物研究中，对 19 例在应用 EGFR-TKI 耐药后出现 EGFR-T790M 突变阳性的 NSCLC 患者进行奥希替尼靶向治疗，4 例发生 1~3 级 DI-ILD [33]。仅有相关个案报道了克唑替尼治疗后发生的 4 级药物性间质性肺炎[34] [35]。国内曾有过晚期 NSCLC 患者接受克唑替尼联合奥希替尼治疗后发生早发性间质性肺炎的案例报道，该病例在及时停药并应用全身性糖皮质激素等对症支持治疗后症状得到缓解[36]。EGFR-TKI 药物的肺毒性机制尚不清楚。表皮生长因子受体(Epidermal growth factor receptor, EGFR)在 II 型肺泡上皮细胞中表达，并参与肺泡壁损伤修复过程。有观点[36]认为 EGFR-TKI 的应用可能通过抑制 EGFR 信号通路，破坏肺泡上皮细胞损伤修复，从而诱发肺损伤。也有研究[37]表明 EGFR-TKI 诱导上皮细胞的慢性炎症从而修复气道，同时可能会促进肺损伤。在一项临床研究[38]中认为肺纤维化与 TGF-β 信号传导通路有关，TGF-β 信号通路激活下游产生的 IL-6 可能导致急性肺损伤。此外，有体外实验[39]表明 EGFR-TKI 上调了肿瘤细胞 IL-6 的表达，增加了肺成纤维细胞中胶原蛋白和 α-肌动蛋白的表达，可能诱导间质性肺炎的发生。日本一项回顾性研究表明遗传易感性被认为是 DI-ILD 发病的独立风险因素[11]。此外，有研究表明吸烟史、既往肺纤维化或慢性阻塞性肺病病史、合并肺部疾病感染等因素都会增加 EGFR-TKI 治疗相关 ILD 发生的风险[14]。总之，DI-ILD 的发病机制尚不完全清楚。我们报道的这例患者既往无吸烟史及肺部其他基础疾病，联合伏美替尼联合克唑替尼双靶向治疗可能是 ILD 发生的主要原因。一般来说，早期发现并停用致病药物通常与良好的预后相关，延迟诊断可能导致快速进展性急性呼吸窘迫综合征(Acute respiratory distress syndrome, ARDS)或肺纤维化[11]。然而，对于肺癌患者停药后肿瘤不可避免会出现进展，是否继续应用相同药物或换用其他靶向治疗需要仔细考虑风险和获益比。值得注意的是，仍有部分重度 DI-ILD 缓解后再次应用靶向治疗获益的临床报告[40] [41]。

小分子多靶点药物被认为在靶向治疗耐药后续治疗具有重要作用，安罗替尼是一种新型多靶点的 TKI，对血管内皮生长因子受体、血小板衍生生长因子受体、成纤维细胞生长因子受体、c-Kit 等多个通路均有封闭作用，显著提高晚期 NSCLC 患者的生存期[42]。而抗纤维化药物尼达尼布同样是一种多靶点 TKI，通过抑制多种受体酪氨酸激酶，包括血管内皮生长因子受体、血小板衍生生长因子受体和成纤维细胞生长因子受体，阻滞胞内信号传导，抑制成纤维细胞的增殖、迁移和转化[43]。在作用靶点方面，二者具有共同的作用通路。因此，我们在患者出现严重 ILD 后，及时停药并给予全身糖皮质激素治疗后 AIP 得到控制。后续逐渐停用激素，加用安罗替尼后抗肿瘤的同时，患者肺间质纤维化同样得到进一步控制，患者进一步获得了生存获益。因此，DI-ILD 出现后停用靶向药物是确定的，应用全身糖皮质激素治疗对

病情缓解有重要作用。但是，根据患者病情变化，适时减量激素、及时加用小分子多靶点药物继续抗纤维化和抗肿瘤靶向治疗，对患者的整体预后有重要意义。

4. 结论

疾病进展时的基因检测、了解药物的安全性对指导非小细胞肺癌患者在联合应用两种靶向药物时至关重要。而我们报道的 1 例联合应用靶向药物后出现间质性肺炎的病例表明并非所有患者都适合应用联合治疗，我们应谨慎对待靶向治疗耐药突变后患者的治疗方案并警惕不良反应的发生，在不良反应发生后应该及时调整相应治疗方案。探索晚期非小细胞肺癌联合应用两种靶向治疗出现不良反应人群的临床特点，找到能够预测可能出现不良反应的临床指标，找出最适合联合应用靶向治疗的人群特点，都是指导药物联合应用必不可少的探索过程。

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