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非小细胞肺癌中EGFR-TKI联合疗法的间质性肺疾病风险研究进展

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摘　要

非小细胞肺癌(NSCLC)患者中，表皮生长因子受体酪氨酸激酶抑制剂(EGFR-TKI)已成为一线治疗方案。但联合治疗时，间质性肺疾病(ILD)风险备受关注。单药治疗时，不同代际EGFR-TKI的ILD风险特征各异，第一代在亚洲人群风险较高，第三代与剂量、治疗阶段及患者基线肺功能状态关联。联合治疗中，免疫检查点抑制剂增加重度ILD发生率，抗血管生成药物或序贯放疗可降低风险。临床管理策略如风险分层、剂量调整及跨代换药等逐步完善，提升了ILD防控效率。未来需大规模前瞻性研究明确不同药物组合及治疗顺序对ILD风险的长期影响。本文旨在综述EGFR-TKI不同代际及联合治疗的ILD风险研究现状。

关键词

非小细胞肺癌，表皮生长因子受体酪氨酸激酶抑制剂，间质性肺疾病，联合治疗，药物毒性

Advances in the Study of Interstitial Lung Disease Risk in Non-Small Cell Lung Cancer with EGFR-TKI Combination Therapy

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Abstract

In patients with non-small cell lung cancer (NSCLC), epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) have become first-line therapeutic agents. However, the risk of interstitial lung disease (ILD) during combination therapies has attracted significant attention. For monotherapy, different generations of EGFR-TKIs exhibit distinct ILD risk profiles: first-generation drugs show higher risks in Asian populations, while third-generation agents demonstrate correlations with dosage, treatment phases, and patients' baseline pulmonary function status. In combination therapies, immune checkpoint inhibitors increase the incidence of severe ILD, whereas anti-angiogenic agents or sequential radiotherapy may mitigate risks. The optimization of clinical management strategies—including risk stratification, dosage adjustments, and cross-generation drug substitution—has progressively enhanced ILD prevention and control. Future large-scale prospective studies are required to clarify the long-term impacts of various drug combinations and treatment sequences on ILD risk. This review aims to summarize current research on ILD risks associated with different EGFR-TKI generations and their combination therapies.

Keywords

Non-Small Cell Lung Cancer, Epidermal Growth Factor Receptor-Tyrosine Kinase Inhibitor, Interstitial Lung Disease, Combined Therapy, Drug Toxicity

1. 引言

非小细胞肺癌(non-small cell lung cancer, NSCLC)约占肺癌病例的 85%，是导致全球癌症相关死亡的主要原因之一[1]。随着分子靶向治疗的发展，表皮生长因子受体酪氨酸激酶抑制剂(EGFR-TKI)已成为 EGFR 突变阳性 NSCLC 患者的标准治疗选择，显著改善了患者的生存预后。然而，EGFR-TKI 相关间质性肺疾病(interstitial lung disease, ILD)作为其严重且可能致命的不良反应，日益受到临床关注。ILD 以肺部炎症和纤维化为核心特征，临床表现为呼吸困难、低氧血症及影像学上的弥漫性浸润性病变，其发生机制涉及 EGFR 信号通路抑制导致的上皮修复障碍、促纤维化因子释放异常等多重病理生理过程。尽管不同代际 EGFR-TKI 的 ILD 风险存在异质性，但随着联合治疗策略(如免疫检查点抑制剂、抗血管生成药物或放疗的联用)的广泛探索，ILD 风险的管理愈发复杂，亟需系统性总结与风险分层策略的优化。

目前，三代 EGFR-TKI (如吉非替尼、奥希替尼)因作用机制差异，其 ILD 风险特征显著不同。第一代药物通过可逆性抑制 EGFR 通路，在亚洲人群中 ILD 发生率较高，可能与遗传易感性相关[2]；而第三代药物因选择性靶向 T790M 耐药突变，其 ILD 风险呈现剂量依赖性和人群异质性[3]。然而，联合治疗的推广使 ILD 风险分析面临新挑战：例如，EGFR-TKI 与免疫检查点抑制剂(ICI)联用可能通过协同激活免疫反应，显著增加重度 ILD 的发生风险[4]；而与抗血管生成药物的联合则可能通过抑制纤维化通路减轻肺损伤[5]。此外，放疗与 EGFR-TKI 的时序安排和剂量参数亦被证实影响 ILD 的病理进程[6]。这些复杂交互作用提示，ILD 的风险不仅取决于药物本身的特性，更受联合治疗方案、患者基线特征(如吸烟史、肺功能状态)及治疗阶段的多重影响。尽管已有研究提出基于风险分层的监测策略和干预措施(如跨代换药、剂量调整)，但多数证据源于单药治疗或小型临床研究，联合治疗的 ILD 风险机制和长期管理仍存在

重大知识缺口。因此，系统梳理不同代际 EGFR-TKI 及联合疗法的 ILD 风险特征，阐明其分子机制与临床管理策略，对优化治疗决策、改善患者生存质量具有重要意义。

本综述围绕 EGFR-TKI 单药及联合治疗的 ILD 风险，从不同代际药物的毒性差异、联合治疗的机制交互、风险调控策略等维度整合最新研究进展，以期为临床实践提供循证依据，并为未来研究方向提出展望。

2. 不同代际 EGFR-TKI 的间质性肺病(ILD)风险特征

2.1. 第一代 EGFR-TKI 的 ILD 风险特征

第一代 EGFR-TKI (如吉非替尼、厄洛替尼)在 EGFR 突变阳性非小细胞肺癌的治疗中具有里程碑意义，但其引发的间质性肺病风险始终是临床关注的重点。研究表明，第一代药物通过抑制 EGFR 信号通路，可能干扰肺部上皮细胞的修复能力，导致炎症微环境中促纤维化因子的异常释放，从而诱发 ILD [7]。这一机制在高风险人群中尤为显著，例如长期吸烟者、男性患者及既往存在肺部纤维化病史的个体。值得注意的是，亚洲人群的 ILD 发生率普遍高于非亚洲人群，可能与遗传背景或环境暴露差异相关[8]。

在临床实践中，剂量调整被证实是降低 ILD 风险的有效策略。低剂量治疗方案在特定人群(如老年患者或合并基础肺病的患者)中显示出良好的安全性，且未显著影响药物疗效[9]。此外，对于因 ILD 中断治疗的患者，跨代换用其他 EGFR-TKI 可显著降低 ILD 复发风险，这一策略为临床提供了重要的管理思路[10]。

2.2. 第二代 EGFR-TKI 的 ILD 风险特征

第二代 EGFR-TKI (如阿法替尼、达克替尼)通过不可逆结合 EGFR 及抑制 ErbB 家族成员，显著延长了患者的无进展生存期，但其广谱激酶抑制特性可能增加 ILD 的潜在风险。临床试验数据显示，第二代药物的 ILD 发生率与第一代药物相近，但在真实世界应用中，通过剂量优化和严格的基线筛查，其风险可控性得到提升[11] [12]。

研究设计对风险评估的影响不容忽视。例如，在严格排除高风险人群(如基线存在脑转移或 ILD 病史)的临床试验中，第二代药物的 ILD 发生率显著降低，提示患者筛选在安全性管理中的重要性[12]。此外，跨代换药策略被证实可降低 ILD 复发风险[10]。

2.3. 第三代 EGFR-TKI 的 ILD 风险差异与管理

第三代 EGFR-TKI 因其对耐药突变的覆盖能力成为治疗晚期 NSCLC 的重要选择，但其 ILD 风险在不同药物间存在显著差异。部分新型第三代药物在早期临床试验中显示出更优的肺安全性，这可能与其选择性抑制特定 EGFR 突变亚型或减少对正常肺组织的毒性作用相关[3] [13]。

治疗阶段和患者基线特征对 ILD 风险的影响尤为突出。在术后辅助治疗中，患者的 ILD 发生率显著低于转移性治疗环境，这可能与辅助治疗人群的基线肺功能更优及合并症较少有关[14] [15]。此外，吸烟史和基线肺部异常(如无症状肺阴影)被明确为 ILD 的独立危险因素，提示在治疗前需完善影像学及肺功能评估[15]。

在联合治疗策略中，抗血管生成药物的引入可能通过抑制纤维化相关通路降低 ILD 风险。例如，EGFR-TKI 与贝伐珠单抗的联合方案显示出潜在的肺保护效应，其机制可能与调节血管通透性及减少炎症细胞浸润相关[16] [17]。对于 ILD 后的管理，临床需根据病理亚型制定个体化策略：低级别 ILD (如机化性肺炎)患者可在密切监测下谨慎续药，而严重类型(如弥漫性肺泡损伤)需永久停药以避免致命性结局[15] [18]。

3. EGFR-TKI 联合疗法的 ILD 风险机制与优化策略

3.1. EGFR-TKI 联合免疫检查点抑制剂的 ILD 风险

EGFR-TKI 与免疫检查点抑制剂的联合治疗在理论上可通过协同作用增强抗肿瘤疗效，但临床实践表明此类组合可能显著增加 ILD 风险，尤其是第三代药物与 PD-L1 抑制剂的联用。机制研究指出，EGFR-TKI 可能通过激活巨噬细胞相关通路(如 IL-6/JAK/STAT3)，加剧 ICI 诱导的免疫过度激活，从而引发细胞因子风暴和肺部炎症反应[19]。近年研究表明，表皮生长因子受体酪氨酸激酶抑制剂(EGFR-TKI)与免疫检查点抑制剂(ICI)联合治疗 EGFR 突变非小细胞肺癌(NSCLC)时，显著增加间质性肺病(ILD)风险(发生率高达 24%~29%)，涉及免疫通路协同激活与肺部微环境重塑的共同作用[20] [21]。核心机制聚焦于免疫调节失衡：奥希替尼通过抑制巨噬细胞 EGFR 磷酸化，上调 IL-6/JAK/STAT3 通路活性，与 ICI 诱导的 T 细胞过度活化协同，触发促炎因子(如 IL-6、TGF-β)大量释放，形成“细胞因子风暴”并加剧肺泡上皮损伤。这一机制在动物模型中进一步验证，联合治疗显著增强了肺部炎症浸润[19]。相比之下，第一/二代 EGFR-TKI 联合免疫检查点抑制剂的 ILD 风险较低，提示药物分子结构或靶点选择性的差异可能影响毒性特征[22] [23]。

真实世界数据进一步揭示了 ILD 风险的多因素叠加效应。例如，PD-1/PD-L1 抑制剂序贯 EGFR-TKI 治疗可能显著升高 ILD 风险，尤其是在免疫治疗停药后短期内转换至靶向治疗时[23]。此外，基线肺部异常(如间质性肺改变)和遗传易感性(如亚洲人群的高风险倾向)被证实为风险放大因素，凸显了治疗前全面评估的必要性[24] [25]。在临床决策中，需权衡联合治疗的潜在生存获益与 ILD 风险，例如在特定人群(如无基线肺部病变或快速进展高风险患者)中选择靶向治疗单药或低毒性联合方案[4]。

3.2. EGFR-TKI 联合抗血管生成药物的 ILD 风险调控

EGFR-TKI 与抗血管生成药物(如贝伐珠单抗)的联合方案在降低 ILD 风险方面展现出独特潜力。研究表明，抗血管生成药物可能通过抑制 VEGF 介导的血管渗漏和成纤维细胞活化，减轻肺纤维化进程[5]。部分临床试验证实，此类联合方案的 ILD 发生率显著低于单药治疗，提示其肺保护效应的临床价值[16]。

多中心 III 期 ARTEMIS-CTONG1509 试验显示，厄洛替尼联合贝伐珠单抗的一线治疗中，ILD 发生率极低(联合组与单药组各 1 例)且未显示额外毒性[26]，这一结果与 JO25567 研究的结论一致(联合组 ILD 发生率 2.7% vs 单药组 3.9%，无严重事件) [27]。值得注意的是，这些研究均在基线排除 ILD 患者，提示对于无肺纤维化病史的人群，联合方案的 ILD 风险可能与单药治疗相当。类似地，WJOG 8715L 与 ETOP BOOSTER 试验中奥希替尼联合贝伐珠单抗的 ILD 发生率仅 11% (均为 1~2 级)或未报告病例[28] [29]。然而，长期多线靶向治疗的累积毒性仍需警惕。例如，部分病例报告指出，多代 EGFR-TKI 序贯治疗可能导致不可逆的 ILD 恶化，提示临床需关注药物选择顺序及治疗间隔[30]。在优化联合治疗安全性方面，严格筛选低风险患者(如无吸烟史或 ILD 病史)并规范监测流程(如定期影像学随访)被证实为有效策略[27] [31]。未来研究需进一步探索生物标志物(如肺泡灌洗液中的特定炎症因子)在风险分层中的应用，以实现更精准的患者管理[27] [29]。

3.3. EGFR-TKI 联合放疗的 ILD 风险与干预策略

EGFR-TKI 与放疗(RT)的联合应用在局部晚期 NSCLC 治疗中具有重要地位，但其 ILD 风险因治疗时序和剂量参数的不同而显著差异。同步放疗通过协同效应显著提高局部控制率及总生存期，但治疗相关毒性反应发生率较高；序贯放疗采用分阶段治疗模式，虽可降低不良反应风险并提高治疗完成率，但其生存获益较同步方案降低。同步放靶治疗可能通过协同损伤肺泡上皮细胞和加剧炎症反应，显著增加

ILD 发生率[32] [33]。危险因素包括高剂量肺部照射、治疗重叠时间过长及特定 TKI 类型的使用[32] [34]。

相比之下，序贯策略显示出更优的安全性。吉非替尼诱导后放疗的临床试验中，ILD 事件多为低级别且可控，提示治疗时序的优化对风险管理的意义[35] [36]。机制层面，放疗诱导的 DNA 损伤与 EGFR-TKI 对信号通路的抑制可能协同促进促纤维化因子(如 TGF-β)的释放，进而驱动 ILD 进展[6] [32]。

在临床实践中，通过限制肺部照射剂量、缩短治疗重叠期及选择序贯治疗方案，可有效降低 ILD 风险[33] [34]。此外，新型治疗模式(如联合免疫调节剂或靶向纤维化通路药物)的探索为未来优化疗效与安全性提供了方向[6]。

4. 结论

EGFR-TKI 的治疗革新显著改善了 EGFR 突变型非小细胞肺癌患者的生存结局，但其伴发的间质性肺疾病(ILD)风险在联合治疗时代亟需系统性管理。现有研究已明确不同代际 EGFR-TKI 的 ILD 风险特征：第一代药物因遗传易感性及信号通路抑制效应在亚洲人群中风险较高，第三代药物则与剂量、治疗阶段及患者基线肺功能状态密切关联。联合治疗中，免疫检查抑制剂的协同免疫激活显著增加了重度 ILD 的发生率，而抗血管生成药物或序贯放疗可能通过调节纤维化或优化治疗时序降低风险。机制层面，研究揭示了 ILD 与 EGFR 通路抑制、免疫微环境紊乱及促纤维化因子释放的多通路交互作用。临床管理策略逐步完善，如通过风险分层(吸烟史、影像基线评估)、剂量调整及跨代换药实现个体化干预，早期识别与动态监测(如生物标志物 KL-6 联合影像随访)显著提升了 ILD 防控效率。

尽管成果显著，现有证据仍存在局限性：长期随访数据的缺乏限制了多线治疗累积毒性的评估。未来需开展大规模前瞻性研究，明确不同药物组合及治疗顺序对 ILD 风险的长期影响。在临床实践层面，跨学科协作(如肿瘤科与呼吸科联合管理)和患者教育(如早期症状识别)将进一步提升 ILD 的防控水平。

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