肺癌靶向耐药

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晚期非小细胞肺癌EGFR-TKIs获得性耐药后治疗策略研究进展★

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摘要：肺癌是癌症相关死亡的首要原因。非小细胞肺癌(NSCLC)约占肺癌的85%,且患者在诊断时大多为晚期。随着表皮生长因子受体(EGFR)在肺癌中被发现,针对特定基因突变的靶向治疗成为晚期NSCLC的重要治疗方式,并显著延长了患者生存期。尽管第一、二、三代EGFR-酪氨酸激酶抑制剂(TKI)蓬勃发展,但随着治疗时间的推移,患者都可能面临耐药和进展。为克服这一难题,基于耐药机制的相关治疗策略正在研究中。本文旨在对近年来EGFR-TKIs,特别是在疗效及安全性上作为指南更优推荐的第三代EGFR-TKIs的耐药机制和治疗策略的研究进展进行综述。

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；获得性耐药；耐药机制；治疗策略
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Research progress of treatment strategies after acquired resistance to EGFR-TKIs in advanced non-small cell lung cancer★

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Abstract: Lung cancer is the worldwide leading cause of cancer-related death. Non-small cell lung cancer (NSCLC) accounts for about 85% of all lung cancer. Many patients developed into advanced stage of the disease when first diagnosed. With the discovery of epidermal growth factor receptor (EGFR) mutation in lung cancer, targeted therapy become an important strategy for advanced NSCLC. It significantly prolonged the patients′ survival. Although first-, second- and third-generation of EGFR-tyrosine kinase inhibitors (TKI) have been successively developed and prescribed, patients eventually get drug resistance and disease progression as time goes on. In order to overcome this difficulty, relevant treatment strategies based on drug resistance mechanisms are under study. This review aims to summarize the research progress of EGFR-TKIs resistance mechanisms and treatment strategies in recent years, especially of the third-generation EGFR-TKIs, which are preferentially recommended in guidelines for its efficacy and safety.

Keywords: NSCLC; EGFR-TKI; Acquired drug resistance; Mechanism of drug resistance; Treatment strategies

前言

肺癌是全球发病率、病死率最高的恶性肿瘤[1]。据统计,2020年全球肺癌新发人数220万,死亡人数180万,5年生存率仅10%~20%[2]。其中,非小细胞肺癌(non-small cell lung cancer, NSCLC)占比约85%,且大部分患者诊断时已丧失手术机会[3]。化疗曾是治疗晚期肺癌的主要手段,Delbaldo等[4]进

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行的一项 Meta 分析奠定了铂类为基础的双药方案在 NSCLC 治疗中的重要地位。但一线含铂双药化疗疗效有限，客观缓解率（objective response rate，ORR）为 25%~35%，无进展生存期（progression-free survival，PFS）仅 4~6 个月，中位总生存期（overall survival，OS）不足 1 年[5-6]。表皮生长因子受体（epidermal growth factor receptor，EGFR）于 2004 年首次被发现，其酪氨酸激酶结构域的激活突变在东亚 NSCLC 患者中检出率高达 50%，且在从未吸烟或轻度吸烟女性患者中发生率较高[7-8]。与之对应的 EGFR-酪氨酸激酶抑制剂（tyrosine kinase inhibitor，TKI）的研发问世显著改善了患者预后，自此晚期肺癌的治疗步入了靶向时代。肺癌 EGFR 突变主要集中在 18~21 号外显子，其中，19 号外显子框内缺失（19 del）和 21 号外显子点突变（L858R）为经典的药物敏感突变[9]；而罕见的 20 号外显子插入突变、18 号外显子突变（G719X、L861Q、S768I 等）为非经典突变，对第一代 TKIs 并不敏感[10-11]。第三代 EGFR-TKIs 治疗非经典突变 NSCLC 的相关研究正在开展[11]。IPASS 研究采用第一代 EGFR-TKI 吉非替尼（gefitinib）一线治疗 EGFR 突变 NSCLC 患者，首次证明其疗效优于化疗（中位 PFS：9.5 个月 *vs*. 6.3 个月；*HR*=0.48，*P*<0.000 1）[12-13]，但由于其对比化疗 OS 获益并不显著（中位 OS：21.6 个月 *vs*. 21.9 个月；*HR*=1.00，*P*=0.990），且与 EGFR 结合松散而易产生耐药，第二代 TKIs 应运而生[11]。第二代 EGFR-TKIs 为不可逆性泛 ERBB 抑制剂，可同时结合 EGFR、ERBB2、ERBB3 及 ERBB4。LUX-Lung 3、LUX-Lung 6 两项研究表明，对于 EGFR 突变晚期 NSCLC 患者，一线使用阿法替尼（afatinib）的中位 OS 与化疗组相近，但在 19del 亚组患者中优于化疗；相比第一代 EGFR-TKIs，一线治疗中位 PFS（11.0 个月 *vs*. 10.9 个月；*HR*=0.73，*P*=0.017）有所改善，但也带来更高的毒副作用发生率[14-15]。遗憾的是，无论一代还是二代 EGFR-TKIs，耐药后均常见 EGFR T790M 耐药突变。因此，第三代 EGFR-TKIs 在设计上针对性地与 T790M 位点形成不可逆性结合，进而抑制下游通路，起到抗肿瘤作用[16]。目前，涉及晚期 NSCLC EGFR-TKIs 获得性耐药机制和治疗策略的相关研究方兴未艾，本文将对近年来 EGFR-TKIs（尤其是第三代 EGFR-TKIs）耐药机制和耐药后治疗策略的研究进展进行综述。

1 获得性耐药现况

肿瘤耐药性是因药物在时间和空间上对癌细胞不同克隆施加的进化压力而产生，由随机获得的基因突变所驱动[17-19]。TKIs 的选择性压力可能会消除 EGFR 突变肿瘤中的敏感性克隆细胞，进而促使缺乏靶点或治疗后获得耐药性的细胞无限增殖[20-21]。EGFR-TKIs 获得性耐药一般定义为：（1）先前接受过 EGFR-TKI 单药治疗。（2）符合以下标准中的任意一条：1）携带对药物敏感的 EGFR 突变。2）EGFR-TKIs 治疗有客观临床获益（满足以下任意一项）：（a）疗效评估为部分缓解（partial responses，PR）或完全缓解（complete responses，CR）；（b）疾病稳定（stable disease，SD）≥6 个月；（c）EGFR-TKIs 治疗至少 30 天后出现疾病进展（progression of disease，PD）；（d）在停用 EGFR-TKIs 之后至使用新疗法之前的时间段内未行其他干预性系统治疗[22]。随着二代测序（next generation sequencing，NGS）的应用，与 EGFR-TKIs 治疗失败相关的获得性耐药机制（图 1）得到了广泛研究，依据通路可将其分为：EGFR 依赖性（EGFR 突变及野生型 EGFR 扩增）、EGFR 非依赖性（包括旁路途径、下游信号通路异常激活、组织学转化等）及其他一些耐药尚不明确的机制。EGFR 依赖性耐药是 EGFR 基因/蛋白发生改变，致使 EGFR-TKIs 靶向结合 EGFR 能力减弱或失效的结果；而 EGFR 非依赖性耐药则是由于 EGFR 之外的致癌途径异常激活导致脱靶。现有研究显示，不同代 EGFR-TKIs 耐药机制有所差异，尽管存在相似机制，但其在各代药物耐药人群中占比也有差异，而奥希替尼在一线与二线用药后获得性耐药机制也呈现出不同类型和占比[23]。克服耐药的治疗策略主要基于疾病进展模式和耐药机制，个体化精准治疗应贯穿于整个基因驱动的肺癌治疗过程，耐药后治疗也应如此。

1.1 不同代 EGFR-TKIs 耐药机制

第一、二代 EGFR-TKIs 耐药机制：小分子 EGFR-TKIs 通过干扰三磷酸腺苷（adenosine triphosphate pocket，ATP）与酪氨酸激酶域结合发挥作用。包括吉非替尼、厄洛替尼（erlotinib）、埃克替尼（icotinib）在内的第一代 EGFR-TKIs 以可逆的竞争性抑制与 EGFR 结合；而阿法替尼、达可替尼（dacomtinib）等第二代 EGFR-TKIs 则以不可逆的竞争性抑制与 ERBB 家族多个成员共价结合[9]。尽管第一、二代 TKIs 相比化疗显著

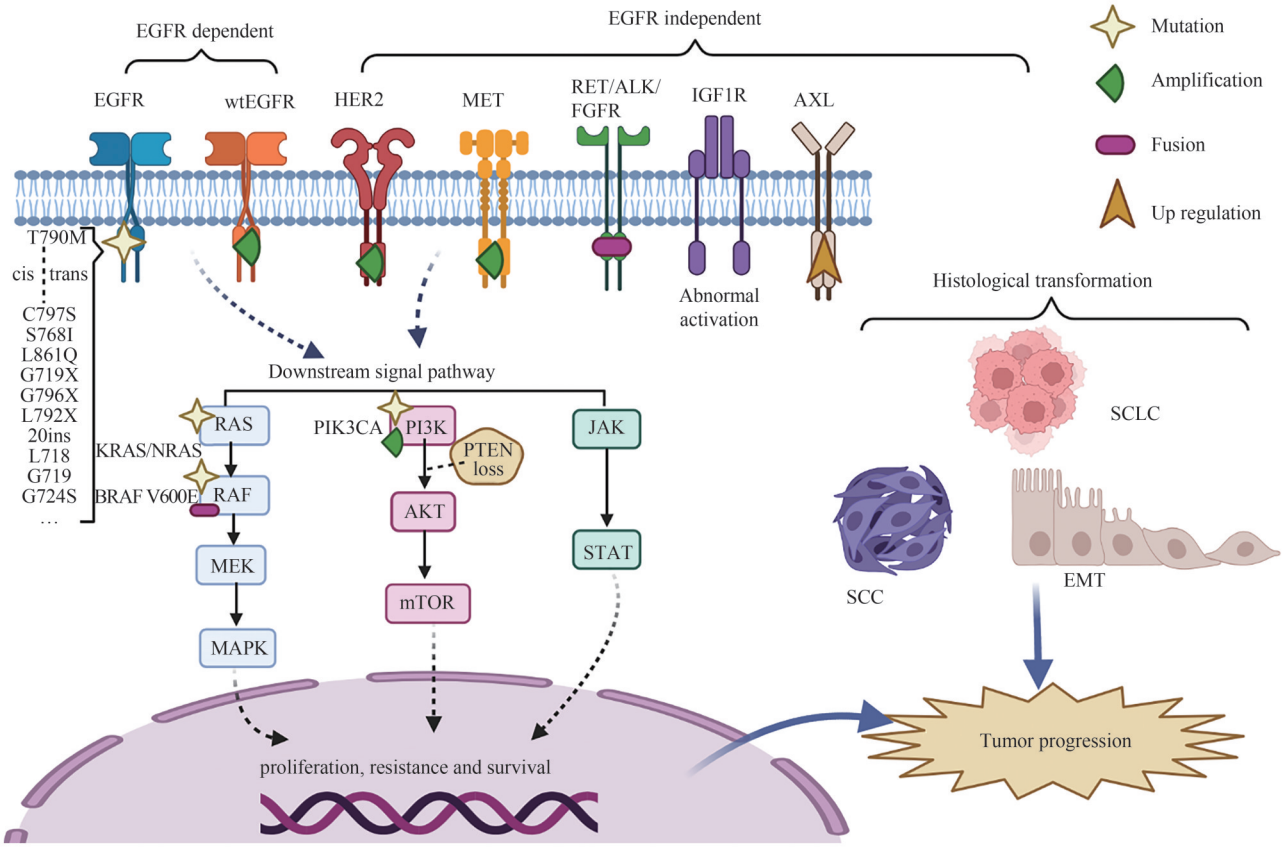

图 1　EGFR-TKIs 获得性耐药机制

Fig. 1　Mechanisms of acquired resistance to EGFR-TKIs

改善了 EGFR 突变晚期 NSCLC 患者的生存期，但 PFS 仍止步于 10~14 个月[12, 24-27]。研究发现，40%~55% 的获得性耐药是由于 T790M 突变[21, 28-30]；紧随其次的为 MET 扩增，占比约 20%；HER2 扩增占比 10%~15%；EGFR 扩增合并 T790M 突变约为 10%；小细胞肺癌（small cell lung cancer，SCLC）转化也占 10% 左右[31-32]；其他小概率耐药机制包括 KRAS、BRAF、PIK3CA 突变等[32]。

第三代 EGFR-TKIs 耐药机制：目前，国内外对第三代 EGFR-TKIs 耐药机制的研究主要集中于奥希替尼（osimertinib）。而国内上市的阿美替尼（almonertinib）、伏美替尼（alflutinib/furmonertinib），未上市的罗西替尼（rociletinib）、艾维替尼（abivertinib）、纳扎替尼（nazartinib）等第三代药物耐药机制虽有部分报道，但尚缺乏大型队列的数据分析[33]。奥希替尼通过与半胱氨酸（Cys）797 残基不可逆性共价结合来克服 EGFR T790M 突变介导的耐药，并保留对 EGFR 经典突变和野生型受体的抑制作用[16]。基于 AURA 研究，奥希替尼被美国食品药品监督管理局（Food and Drug Administration. FDA）批准用于 EGFR T790M 突变晚期 NSCLC 二线治疗[16]。FLAURA 研究进一步探索了奥希替尼对比吉非替尼/厄洛替尼用于初治 EGFR 敏感突变 NSCLC 一线治疗的有效性[28]。该研究确立了奥希替尼的一线治疗地位，但仍避免不了耐药进展。ELIOS 研究是首个对比治疗前和疾病进展后肿瘤组织活检样本分子特征的前瞻性研究，目的是探索奥希替尼一线治疗的耐药机制[34]。该研究纳入 154 例患者，数据截止时有 46 例患者的配对样本可供评估，其中 MET 扩增和过表达分别占 17% 和 50%，而 EGFR C797S 占 15%。值得注意的是，NKX2-1 扩增可能是潜在的新型耐药机制，有待后续研究。虽然奥希替尼耐药机制与第一、二代 EGFR-TKIs 具有相似性，但是比例不同，一线或二线使用奥希替尼后耐药情况也存在差异。有研究发现，一线使用奥希替尼后耐药情况整体上比二线使用更为复杂，主要体现在一线不明耐药机制较二线多（40%~50% *vs*. 30%~40%）且靶内耐药较二线少（16%~27% *vs*. 20%~35%）；但无论一线还是二线使用奥希替尼，耐药后野生型 EGFR 扩增（10%~15%）、MET 扩增（7%~15%）、HER2

扩增(一线 *vs*. 二线,2% *vs*. 5%)以及组织学转化(一线 *vs*. 二线,12%~15% *vs*. 5%~15%)发生率大致相等[23]。有研究报道4%~7%的患者耐药涉及致癌基因融合变异,且主要发生在二线使用奥希替尼后[35-36]。此外,一线耐药患者中有10%表现为细胞周期相关基因变异,这类基因变异在奥希替尼二线治疗后耐药中占12%[36-37]。

1.2 EGFR-TKIs耐药后治疗策略 EGFR-TKIs是EGFR阳性晚期NSCLC患者的一线治疗方案,现阶段耐药后治疗多参考中国临床肿瘤学会(Chinese Society of Clinical Oncology,CSCO)指南和美国国立综合癌症网络(National Comprehensive Cancer Network, NCCN)指南,两者在治疗策略和用药上稍有差异。此处根据CSCO指南2022版和NCCN指南2023.2版对EGFR敏感突变(19del/L858R)晚期NSCLC患者一线耐药后的治疗策略进行比较(表1)[38-39]。

表1 EGFR敏感突变(19del/L858R)NSCLC患者一线耐药后的治疗策略

Tab. 1 Treatment strategy for NSCLC patients with EGFR sensitive mutation (19del/L858R) after first-line drug resistance

CSCO指南2022版	NCCN指南2023.2版
二线治疗 (1)寡进展或CNS进展: Ⅰ级推荐:继续原EGFR-TKIs治疗+局部治疗 Ⅱ级推荐:再次活检明确耐药机制 (2)广泛进展: Ⅰ级推荐:再次活检 1) T790M+:奥希替尼/阿美替尼/伏美替尼 2) T790M-/三代TKIs治疗失败:含铂双药化疗±贝伐珠单抗(非鳞癌) Ⅱ级推荐:再次活检。T790M+:含铂双药化疗±贝伐珠单抗 Ⅲ级推荐:培美曲塞+顺铂+贝伐珠单抗+信迪利单抗	无症状/有限转移灶 (1)一线奥希替尼: 1)继续奥希替尼治疗 2)对局限性病灶可行根治性局部治疗(如SABR、SRS或手术) (2)一线非奥希替尼: 1) T790M+:奥希替尼 2) T790M-:继续[厄洛替尼±(雷莫芦单抗/贝伐单抗)]/阿法替尼/吉非替尼/达克替尼治疗 局限性病灶可行根治性局部治疗(如SABR、SRS或手术)
后线治疗 Ⅰ级推荐:单药化疗 Ⅱ级推荐:单药化疗+贝伐珠单抗(非鳞癌);安罗替尼	多发转移灶 首先视身体情况,可考虑初始全身治疗(参考Ⅳ期无驱动基因、NSCLC);如治疗后失败且继续进展,则考虑后续治疗(参考Ⅳ期无驱动基因、NSCLC)

注:CNS:中枢神经系统;SABR:立体定向消融放射治疗;SRS:立体定向放射外科。

Note: CNS: central nervous system; SABR: stereotactic ablative radiotherapy; SRS: stereotactic radiosurgery.

对于少见突变(S768I、L861Q、G719X),CSCO指南未单独列出,而NCCN指南可参考敏感突变耐药后治疗策略。对于其他基因驱动耐药的情况,如MET、HER2扩增等,治疗策略仍在研究中。治疗SCLC转化方面,CSCO指南提出,依据进展模式采取不同治疗方案:系统快速进展采用标准SCLC化疗方案;局部缓慢进展采用标准SCLC化疗方案/继续原EGFR-TKIs联合局部治疗;系统缓慢进展可行标准SCLC化疗或在此基础上联合原EGFR-TKIs治疗。但以上推荐尚缺乏高级别循证医学研究证据。

2 获得性耐药后治疗策略研究进展

近年来,由于基因检测技术的发展,越来越多的耐药机制浮出水面,耐药后治疗策略的探索也围绕不同机制展开。因此,本文对EGFR-TKIs获得性耐药后治疗策略的研究进展以耐药机制分类叙述(表2)。

2.1 EGFR依赖性

2.1.1 T790M突变 第一、二代EGFR-TKIs耐药中,近60%是由于EGFR T790M“守门人”突变。T790M突变导致EGFR基因20号外显子第790号位点的苏氨酸(T)被甲硫氨酸(M)所替换并形成空间位阻,使药物与ATP口袋结合受阻,而ATP与EGFR结合不受影响[40]。针对T790M突变,目前国内市场已有奥希替尼、阿美替尼和伏美替尼获批上市,韩国也上市了拉泽替尼(lazertinib)[41-42],但新款第三代药物的发展仍势如破竹。IBIO-102研究显示,贝福替尼(befotertinib)治疗经EGFR-TKIs治疗失败后

表 2　基于 EGFR-TKIs 获得性耐药机制的耐药后治疗策略

Tab. 2　Post-resistance treatment strategies based on the acquired resistance mechanism of EGFR-TKIs

EGFR 依赖性	EGFR 非依赖性	其他治疗策略
1. T790M 突变： 新三代 EGFR-TKIs：贝福替尼[43]、瑞泽替尼、艾维替尼、奥瑞替尼等 2. C797S 突变： （1）与 T790M 呈顺式突变：布加替尼+西妥昔单抗[48] （2）与 T790M 呈反式突变：第一代 EGFR-TKIs+奥希替尼[49] （3）仅 C797S 突变：新四代 EGFR-TKIs 如 BLU-945、EAI045、BLU-701、BBT-176 等[51] 3. 其他 EGFR 依赖性耐药机制： （1）20ins：CLN-081、波奇替尼、莫博赛替尼、埃万妥单抗[57] （2）其他少见突变不伴有 T790M：第一、二代 EGFR-TKIs[53, 59-60]	1. MET 扩增： （1）EGFR-TKIs 联合 MET-TKIs：吉非替尼+特泊替尼/卡马替尼、奥希替尼+赛沃替尼/特泊替尼[51, 70-71] （2）EGFR-TKIs 联合双特异性抗体：拉泽替尼+埃万妥单抗[51] （3）ADC 联合模式：Teliso-V+奥希替尼/厄洛替尼/纳武利尤单抗[72-73] 2. HER2 扩增： （1）抗 HER2 单抗：曲妥珠单抗+紫杉醇[80] （2）ADC 药物：T-DM1 单药或联合奥希替尼/奈拉替尼、T-DXd、RC-48[81-84] （3）HER2 靶向药物：吡咯替尼[85] 3. 下游信号通路异常： BRAF V600E 突变：奥希替尼+维莫非尼、曲美替尼联合达拉非尼[89] 4. 组织学转化： （1）SCLC 转化：EP 方案+EGFR-TKIs、度伐利尤联合奥拉帕利[100, 103] （2）EMT 转化：TWIST-1 抑制剂、SOX 抑制剂、AXL 抑制剂、SAC 抑制剂[108-111] 5. 其他 EGFR 非依赖性耐药机制： 奥希替尼+对应驱动基因相关抑制剂	1. 以化疗为基础的联合治疗： 拉泽替尼+埃万妥单抗+化疗、AK112+化疗、信迪利单抗+IBI305+化疗[128-129, 134] 2. 其他靶向治疗： （1）抗血管联合 ICIs/EGFR-TKIs：安罗替尼+TQ-B2450/第一、三代 EGFR-TKIs[142-144] （2）ADC：HER3-DXd、DS-1062、IMMU-132[51] （3）PROTAC：MS154、DDC-01-163、SIAIS125/126、Compound 3/4、MS39、CP17 等[148-149]

携带 T790M 突变的 NSCLC 患者，中位 PFS 达 16.6 个月（75 mg 组 15.1 个月 *vs*. 100 mg 组 17.9 个月），不良反应多为 1~2 级[43]。另外，瑞泽替尼（rezetinib）、艾维替尼、奥瑞替尼（oritinib）等也有望挤入赛道。

2.1.2　C797S 突变　C797S 突变是 EGFR 基因 20 号外显子第 797 位点上丝氨酸（S）取代半胱氨酸（C）的错义突变。该突变使奥希替尼无法在 ATP 结合域内形成共价键，进而不能抑制 EGFR 激活。C797S 可单独存在或合并 T790M 突变，两者共存时可依据是否位于同一条染色体上分为顺式突变（cis-mutation）和反式突变（trans-mutation）。cis 突变即 C797S 和 T790M 位于同一条 DNA 链上。cis 突变较 trans 突变常见，但治疗是其难点[44-47]。一项小样本（*n*=15）单臂研究发现，布加替尼（brigatinib）联合西妥昔单抗（cetuximab）治疗 C797S/T790M cis 突变患者（5 例）的疗效明显优于化疗（10 例），两组 ORR、DCR、中位 PFS 分别为 60% *vs*. 10%、100% *vs*. 60%、14 个月 *vs*. 3 个月[48]。trans 突变则是 C797S 和 T790M 位于不同 DNA 链上。欧洲肿瘤医学会议（European Society for Medical Oncology，ESMO）专家共识认为，第一代 EGFR-TKIs 联合奥希替尼治疗对 C797S/T790M trans 突变有一定疗效[49]。值得一提的是，该联合方案治疗 trans 突变要警惕后续“转顺”可能[47, 50]。小部分患者仅有 C797S 突变，虽对奥希替尼耐药，却保留了对第一、二代 TKIs 的敏感性。包括 EAI045、BLU-945、BLU-701、BBT-176 在内的第四代 EGFR-TKIs 正在研究中，旨在克服 C797S 和 T790M 突变[51]。SYMPHONY 研究在剂量递增阶段共纳入 33 例 EGFR 突变 NSCLC 患者，采用 BLU-945 治疗后 2 周检测患者的循环肿瘤 DNA（circulating tumor DNA，ctDNA），结果显示，400 mg 药物剂量下，T790M 和 C797S ctDNA 水平均下降，其中有 3 例患者达到清除标准[52]。

2.1.3　其他 EGFR 依赖性耐药机制　部分少见突变也被认为是 EGFR 依赖性耐药机制，如 20 号外显子 G796R/S/D 突变可通过空间位阻效应引起奥希替尼耐药[53-55]，而 L792X 突变可对 EGFR 激酶域结合区产生空间干扰[53, 56]。通常认为，20 号外显子插入

突变（20ins）与原发性耐药有关，目前也有获得性20ins介导奥希替尼耐药的报道。由于20ins结构的特殊性，其对EGFR-TKIs并不敏感。对于20ins突变，目前在研药物有CLN-081、波奇替尼（poziotinib）、莫博赛替尼（mobocertinib，TAK-788）、埃万妥单抗（Amivantamab）等[57]。另有累及18号外显子的L718和G719残基、G724S突变被认为可介导耐药，但需进一步研究证实[53, 58]。有体外研究报道，这些少见突变在不伴T790M突变时仍保留对第一、二代EGFR-TKIs的敏感性[53, 59-60]。

EGFR扩增可见于多个癌种，NSCLC约占其中的9%[61]。有研究报道，第一、二代EGFR-TKIs耐药后的EGFR扩增常与其他EGFR突变共存，但不能确定其是否介导耐药；而目前认为野生型EGFR扩增可能与奥希替尼耐药有关，这可能是由于针对EGFR突变具有选择性的奥希替尼对野生型EGFR亲和力有限[61-63]。有研究表明，野生型EGFR可借助外泌体转移至EGFR突变的敏感细胞来介导奥希替尼耐药[64]。细分野生型和突变型EGFR扩增的方法以及对应治疗手段目前尚无定论。

2.2 EGFR非依赖性

2.2.1 MET扩增 原癌基因中，间质-上皮细胞转化因子（mesenchymal-epithelial transition factor，MET）基因所编码的c-MET蛋白是一种酪氨酸激酶受体，可通过与肝细胞生长因子（hepatocyte growth factor，HGF）结合激活下游信号通路（PI3K、MAPK、STAT等），进而发挥促细胞增殖、生长、迁移、侵袭和血管生成等效应[65]。包括MET14号外显子跳跃突变、MET融合、MET扩增及c-MET过表达等在内的MET变异可导致MET信号通路异常激活，并促进肿瘤的发生发展[66-67]。MET扩增作为常见的EGFR-TKIs耐药机制，能绕过EGFR激活和信号转导，并通过持续激活EGFR下游信号通路介导耐药。通过荧光原位杂交（fluorescence in situ hybridization，FISH）可测量MET基因拷贝数（gene copy number，GCN）与7号染色体着丝粒（CEP7）拷贝数的比值，进一步区分局部扩增与多倍体。目前，MET扩增的定义多采用GCN≥5或GCN/CEP7≥2[66, 68-69]。此外，NGS也是可以获得基因变异信息的检测方法[66]。

对于EGFR-TKIs耐药后MET扩增，TKIs联合方案有望成为一种治疗策略。Ⅰb/Ⅱ期INSIGHT研究[70]评估了强效高选择性MET抑制剂特泊替尼（tepotinib）联合吉非替尼对比化疗在对第一、二代EGFR-TKIs获得性耐药且含有MET过表达（IHC3$^+$）或MET扩增的EGFR突变NSCLC患者中的疗效和安全性，分析结果表明，特泊替尼联合吉非替尼耐受性良好。在MET扩增组中，TKIs联合对比化疗的中位PFS（16.6个月 *vs.* 4.2个月，*HR*=0.13）、中位OS（37.3个月 *vs.* 13.1个月，*HR*=0.10）、ORR（66.7% *vs.* 42.9%）、中位DOR（19.9个月 *vs.* 2.8个月）均有获益。此外，与化疗相比，该联合方案在MET过表达患者中的PFS、OS也显著获益。由此衍生的INSIGHT-2研究[71]正在进行，欲评估晚期EGFR突变对奥希替尼耐药后MET扩增的NSCLC患者对特泊替尼联合奥希替尼治疗的反应。TATTON研究结果表明，在EGFR突变治疗耐药且伴有MET扩增的NSCLC患者中，无论既往是否接受过第三代EGFR-TKIs治疗，采用MET抑制剂赛沃替尼（sevatinib）联合奥希替尼治疗能获得48%的PR。另一项Ⅰb/Ⅱ期研究则将MET-TKI卡马替尼（camatinib）联合吉非替尼用于耐药后伴MET过表达/扩增的NSCLC患者，结果显示，ORR在总人群中达27%，在GCN≥6的患者中达47%[51]。MET-TKIs与EGFR-TKIs联合治疗的注册临床研究如SAFFRON、SACHI等也在进行中。近年来，双特异性抗体进入了抗肿瘤药库，CHRYSALIS队列研究探索了埃万妥单抗作为一种可靶向EGFR和MET的新药的临床应用指征。该Ⅰ期研究对奥希替尼耐药的EGFR突变阳性NSCLC患者行埃万妥单抗和拉泽替尼联合治疗，ORR为36%[51]。号称生物导弹的抗体药物偶联物（antibody-drug conjugates，ADC）自2019年以来也研发火热。Telisotuzumab Vedotin（Teliso-V）是抗c-MET人源化单抗与细胞毒素微管蛋白抑制剂结合的ADC[72]。一项Ⅰ/Ⅰb期研究使用Teliso-V联合奥希替尼治疗EGFR突变晚期NSCLC奥希替尼耐药后c-Met过表达患者，ORR达58%，毒性可控；该研究还将Teliso-V分别与厄洛替尼、纳武利尤单抗联合，旨在探索这些联合模式的可行性，其结果拭目以待[73]。

2.2.2 HER2扩增 人表皮生长因子受体2（human epidermal growth factor receptor 2，HER2）基因编码ERBB2受体酪氨酸激酶，其变异类型类似MET，可见突变、扩增和过表达。HER2扩增通过绕开EGFR并交替激活MAPK、PI3K通路来介导耐药。对HER2的检测可采用FISH和NGS，但其在NSCLC中的检测和定义标准尚未完全确立[74-75]。ESMO专家共识推荐的FISH检测HER2扩增参考标准为：1）

GCN/CEP17≥2.0，HER2扩增阳性。2）GCN/CEP17<2.0时：（a）GCN≥6.0，HER2扩增阳性；（b）GCN<4.0，HER2扩增阴性；（c）4.0<GCN<6.0，无法确定扩增状态。3）众多HER2信号串连成簇时即为HER2扩增阳性。而NGS检测依据不同平台报告、验证队列和取材类型制定了可变标准[76-79]。

针对耐药后携带HER2扩增的患者，抗HER2单抗、ADCs、HER2靶向药物或许能成为可选的治疗策略。一项单臂Ⅱ期研究在EGFR-TKIs治疗进展后表达HER2（肿瘤活检组织IHC肿瘤细胞膜表达HER2≥1$^+$）的24例NSCLC患者中使用曲妥珠单抗（trastuzumab）联合紫杉醇治疗，结果发现4例HER2扩增（采用原位杂交技术，GCN≥10）的患者达到了100%缓解[80]。临床前研究表明，奥希替尼耐药HER2扩增的细胞株对奥希替尼和HER2 ADC恩美曲妥珠单抗（trastuzumab emtansine，T-DM1）联合方案具有药物敏感性[81]。一项研究发现，EGFR-TKIs治疗后进展并发HER2扩增和/或EGFR突变的肺癌患者接受T-DM1单药治疗，ORR可达51%，并在肺癌细胞系和患者来源异种移植瘤模型中测试了T-DM1和泛ERBB抑制剂奈拉替尼（neratinib）组合对HER2扩增的疗效，结果显示肿瘤显著消退[82]。德曲妥珠单抗（trastuzumab deruxtecan，T-DXd；DS-8201）也是一种HER2 ADC，Ⅱ期DESTINY-Lung01研究显示了其在HER2突变/过表达NSCLC患者中的应用潜力[83]。另有国产ADC维迪西妥单抗（disitamab vedotin，RC-48）在HER2表达阳性胃癌、乳腺癌和尿路上皮癌相关研究中取得了显著疗效[84]，其在HER2突变或过表达NSCLC患者中应用的临床研究（CXSL2200559、CTR20190939）也在进行中。吡咯替尼（pyrotinib）为国产泛ERBB抑制剂，在一项前瞻性、多中心、单臂研究中展现了其治疗HER2扩增晚期NSCLC患者的有效性和可控的安全性。该研究纳入HER2扩增患者27例，其中13例（30.8%）患者EGFR-TKIs耐药；总人群达主要终点6个月PFS的占51.9%（95% *CI*：34.0~69.3%），ORR为22%（95% *CI*：10.6%~40.8%），中位PFS达6.3个月，（95% *CI*：3.0~9.6个月），中位OS超过1年[85]。这些研究结果均支持抗HER2单抗、ADCs、HER2靶向药物在HER2介导的EGFR-TKIs耐药背景下进行后续研究。

2.2.3 下游信号通路异常 EGFR发挥生物学效应所涉及的下游信号通路的改变也会导致获得性耐药产生。PI3K/AKT通路中PIK3CA突变或扩增会导致该通路持续活化，促使肿瘤进展并对治疗耐药[21, 37]。体外实验表明，PI3K抑制剂联合EGFR-TKIs具有克服此类耐药的潜力[86]。PTEN缺失也会促进PI3K信号活化，被认为是第三代EGFR-TKIs的获得性耐药机制[87]。MAPK信号转导的上游基因RAS（KRAS、NRAS）和RAF（BRAF V600E）突变同样赋予了晚期NSCLC对奥希替尼的耐药性[35-37, 53, 88]。临床前研究表明，NRAS突变对MEK抑制剂与奥希替尼联用敏感，但需要更多证据来验证。一项前瞻性研究对5例奥希替尼治疗失败后获得BRAF V600E突变的患者进行EGFR、BRAF联合抑制，其中4例患者从奥希替尼联合维莫非尼（BRAF-TKI；vemurafenib）治疗中获益、1例患者经曲美替尼（MEK-TKI；trametinib）联合达拉非尼（BRAF-TKI；dabrafenib）治疗有效，中位PFS为7.8个月，但需后续扩大样本量进一步研究证实该方案的安全性及有效性[89]。

2.2.4 组织学转化 组织学转化通过肿瘤病理类型变化来介导耐药，不同于EGFR相关信号通路途径。SCLC转化、鳞癌（squamous cell carcinoma，SCC）转化及上皮-间充质转化（epithelial-mesenchymal transition，EMT）被认为与EGFR-TKIs耐药有关。

SCLC是一种恶性程度高、易较早发生广泛转移的神经内分泌肿瘤[90]，对化疗敏感，但总体预后极差，OS往往不超过1年[91-92]。SCLC转化常预示着肿瘤侵袭性强且预后不良。有数据显示，NSCLC向SCLC转化的中位转化时间为17.8个月，总人群OS为31.5个月，自诊断SCLC转化起，患者中位OS仅为6~10个月[90, 93]。转化型SCLC发生机制目前有肿瘤细胞异质性假说、肿瘤干细胞假说和分子机制假说[94]。George等[95]对110个经典SCLC组织进行基因组测序，发现可分析的肿瘤组织中几乎都含有TP53和RB1双等位基因失活。Lee等[96]研究发现，NSCLC患者初诊时如同时携带RB1及TP53失活突变，发生SCLC转化的风险与未转化组相比显著提高（82% *vs.* 3%，*OR*=131，95% *CI*：19.9~859）。结合上述研究，转化型SCLC与经典SCLC具有相似的基因组分子特征，RB1和TP53的基因状态或许可用来预测经EGFR-TKIs治疗的NSCLC患者发生SCLC转化的风险。此外，两者在病理类型、临床表现及药物敏感性等方面也具有相似性[97]。广泛期SCLC标准治疗采用含铂双药化疗或在此基础上联用免

疫治疗[98]。依托泊苷+铂类(EP)方案对转化型SCLC有效已有报道,但疗效有限,中位PFS仅为3.4个月,而接受免疫治疗的患者似乎未显示疗效[90, 93, 99]。有个案报道EP方案联合EGFR-TKIs能为SCLC转化患者带来获益,PFS延长至7.7个月[100],这或许能成为SCLC转化且携带EGFR敏感突变肺癌患者的治疗希望。最近一项研究通过多组学分析发现,与经典SCLC相比,转化型SCLC的肿瘤微环境近似"冷肿瘤",会抑制包括细胞因子信号转导、T细胞免疫和中性粒细胞介导免疫在内的肿瘤免疫激活,这可能解释了免疫治疗对转化型SCLC疗效不佳的原因[101]。联合治疗或许能通过改变肿瘤免疫微环境提高肿瘤对免疫治疗的敏感性。多腺苷二磷酸核糖聚合酶1[poly(ADP-ribose) polymerase 1, PARP1]在SCLC中呈高表达,而单药免疫治疗对SCLC疗效欠佳[102]。基于此,有研究将程序性死亡受体配体1(programmed death-ligand 1, PD-L1)抑制剂度伐利尤单抗(durvalumab)联合PARP抑制剂奥拉帕利(olaparib)用于治疗复发型SCLC患者,并意外发现该方案在EGFR突变转化型SCLC患者中显示出持久反应,研究者认为该联合方案可能诱导肿瘤浸润淋巴细胞(tumor infiltrating lymphocyte, TIL)[102]。因此,一项度伐利尤联合奥拉帕利治疗EGFR突变、转化型SCLC患者的Ⅱ期临床研究正在开展[103]。

约15%一线和二线接受奥希替尼治疗的患者可发生SCC转化[104]。与SCLC转化类似,SCC转化中也保留了原始的EGFR突变[105-106]。EMT转化则通过上调波形蛋白表达、下调E-钙黏蛋白表达、增加间质细胞表型并赋予细胞迁移能力来介导EGFR-TKIs耐药,其转录因子TWIST-1过表达是介导EMT转化对奥希替尼耐药的驱动因素[107-108]。一项临床前研究提示了TWIST-1抑制剂克服EMT转化耐药的可能[108]。另有研究表明,SOX抑制剂、AXL抑制剂、SAC抑制剂也是治疗EMT转化的潜在策略[109-111]。然而,无论上述何种病理类型变化目前都缺乏有效治疗手段,仍以全身化疗为主。因此,在缺乏其他耐药机制的情况下,应尽可能再次进行组织活检以获得组织学转化证据,进一步探究病理类型转化的耐药机制、治疗策略、预后及影响因素。

2.2.5 其他EGFR非依赖性耐药机制 诸如RET、ALK、BRAF、FGFR等基因融合/染色体重排均属于EGFR-TKIs耐药的罕见事件[35, 112-115]。一项纳入12例EGFR-TKIs耐药RET融合NSCLC患者的系列分析表明,奥希替尼联合RET抑制剂塞普替尼(selpercatinib)能带来50%的ORR和7.4个月的中位DOR[116],类似的组合还有奥希替尼+普拉替尼(pralsetinib)[113]。也有报道称,奥希替尼与ALK抑制剂阿来替尼(alectinib)、克唑替尼(crizotinib),MEK抑制剂曲美替尼,FGFR抑制剂厄达替尼(erdatinib)等分别联合使用对相应融合基因驱动获得性耐药有效[117-118]。这种双通路联合抑制的模式可能克服基因融合介导的耐药,但需警惕TKIs联合带来的不良反应。

细胞周期蛋白基因(D1、D2、E1)、细胞周期蛋白依赖性激酶基因(CDK4、CDK6)和CDK抑制剂2A基因(CDKN2A)扩增或突变也与奥希替尼获得性耐药有关[36-37]。在体外实验中,CDK4/6抑制剂帕博西尼(palbociclib)与奥希替尼联合克服了奥希替尼耐药[119]。临床前证据也表明,阿贝西利(abemaciclib)单药对一线奥希替尼耐药有效,将两者联合作为一线治疗具有预防或延缓奥希替尼耐药的潜力[120]。据报道,奥希替尼和多靶点(MET、VEGFR1/2/3、ROSE1、RET、AXL、NTRK、KIT)抑制剂卡博替尼(cabozantinib)组合可能克服AXL表达上调所介导的奥希替尼耐药[121]。一些临床前研究也表明,AXL可能是一个有潜力的药理学靶点[122-123]。胰岛素样生长因子1受体(insulin-like growth factor 1 receptor, IGF1R)异常激活被认为是一个非遗传获得性耐药原因[124],IGFR1抑制剂联用奥希替尼有望解决IGF1R激活引起的耐药问题[125]。

2.3 耐药后其他治疗策略

2.3.1 以化疗为基础的联合治疗 对于缺乏特异性耐药机制的情况,以铂类为基础的化疗是常用方案,但获益有限,而化疗联合EGFR-TKIs的疗效尚存在争议[126-127]。CHRYSALIS-2研究中的一个队列评估了第三代EGFR-TKI(lazertinib)、EGFR/MET双特异性抗体(amivantamab)联合化疗(卡铂+培美曲塞)治疗20例经EGFR-TKIs治疗后复发且携带EGFR突变NSCLC患者的疗效,结果显示,中位随访7.1个月,ORR达50%,75%的患者无进展[128]。AK112是一种新型PD-1/VEGF双抗药物。NCT04736823试验中的一个队列探究了AK112联合化疗二线治疗EGFR-TKIs耐药晚期非鳞NSCLC患者的疗效,ORR和DCR分别取得了68.4%和94.7%的成绩,后续研究正在进行[129]。一项回顾性研究显示,患者经

EGFR-TKIs治疗后PD-L1高表达的比例明显增加，这可能为使用免疫检查点抑制剂（immune checkpoint inhibitor，ICI）提供了环境基础[130]。然而，ICI单药或双免疫治疗效果欠佳[131-132]。IMPower150亚组分析显示，ICIs联合抗血管药物和化疗可改善EGFR突变晚期转移性非鳞NSCLC患者的PFS[133]；基于此，ORIENT-31研究设计了信迪利单抗（sindilimab）联合贝伐珠单抗类似物（IBI305）和化疗对比单用化疗在EGFR-TKIs治疗失败的EGFR突变局部晚期非鳞NSCLC患者中的疗效[134]。第二次期中分析表明，相比化疗组，三联方案可显著改善患者的中位PFS（7.2个月 *vs.* 4.3个月），OS结果尚未公布，≥3级治疗相关不良事件（treatment-related adverse event，TRAE）发生率相近（59.5% *vs.* 56.9%）[135]。该研究中，信迪利单抗联合化疗对比单用化疗也显示了具有临床意义的生存获益，中位PFS明显延长（5.5个月 *vs.* 4.3个月，*HR*=0.72，95% *CI*：0.55~0.95，*P*=0.018 1）[135]。相反，一项随机、开放标签Ⅲ期研究CheckMate722旨在探索EGFR突变晚期NSCLC经TKIs治疗进展的患者接受纳武利尤单抗（nivolumab）联合化疗对比单用化疗的疗效，结果显示，联合治疗组与化疗组中位PFS的差异无统计学意义，中位OS分别为19.4个月和15.9个月（*HR*=0.82，95% *CI*：0.61~1.10），3~4级TRAE发生率分别为45%和29%[136]。此外，该研究并未设计添加抗血管生成药物的分组。两项研究结果不同可能是样本量不足及入组人群基线水平差异所致，ORIENT-31研究中敏感突变患者、T790M突变患者及使用奥希替尼患者的占比均较CheckMate722研究高。因此，需在基线水平、既往EGFR-TKIs治疗情况等方面进一步评估，以明确ICIs联合化疗模式的敏感人群。

2.3.2 其他靶向治疗 新型国产抗血管药物安罗替尼（anlotinib）是一种小分子多靶点TKI，能通过抑制肿瘤血管生成和肿瘤细胞生长来发挥抗肿瘤作用，在多种晚期恶性实体瘤的治疗中展现了良好的安全性和疗效[137]。ALTER-0303研究确立了安罗替尼在晚期NSCLC三线及以上治疗中的应用基础[138]。该研究亚组（*n*=138）分析显示，对于伴有EGFR突变、既往二线治疗失败的患者，安罗替尼对比安慰剂的OS为10.7个月 *vs.* 6.3个月（*HR*=0.59，*P*=0.025），PFS为5.6个月 *vs.* 0.8个月（*HR*=0.21，*P*<0.000 1）[139]。除单药和后线应用外，安罗替尼在先用和联用上的探索也正在进行[137, 140]。对于EGFR-TKIs耐药后晚期NSCLC患者的治疗，可参考安罗替尼联合ICIs或安罗替尼联合EGFR-TKIs策略。既往研究表明，抗血管药物可下调血管因子水平、减少免疫抑制因子，从而对免疫微环境进行调节[141]，因此，抗血管联合免疫治疗可能具有协同增效作用。ALTER-L038是一项多中心、单臂临床研究，采用安罗替尼联合TQ-B2450（PD-L1抑制剂）治疗EGFR TKIs耐药患者。初步探索阶段确定安罗替尼12 mg联合TQ-B2450 1 200 mg为推荐剂量；在扩展研究中，截至2021年1月，入组且可评估患者18例，中位PFS为8.0个月，DCR达77.8%，3级TRAE发生率为16.7%，未见4~5级TRAE[142-143]。2021年ESMO大会也有安罗替尼联合第一、三代EGFR-TKIs一线治疗EGFR突变晚期NSCLC相关研究的壁报展示，后续结果值得期待。机制上，有研究证实，安罗替尼联合奥希替尼可通过使c-MET/MYC/AXL轴失活来逆转NSCLC对奥希替尼的耐药，以增强抗肿瘤作用[144]。也有研究显示，安罗替尼联合奥希替尼可通过抑制EGFR和FGFR信号通路克服EGFR过表达患者奥希替尼耐药[145]。安罗替尼在晚期NSCLC中极具广阔的应用前景，在克服EGFR-TKIs耐药上也具有不凡的潜力。

HER3在EGFR突变肿瘤中常呈过表达[23]。HER3变异能通过激活包括PI3K、MAPK在内的致癌信号通路间接介导肿瘤对EGFR-TKIs的抗性。Patritumab deruxtecan（HER3-DXd；U3-1402）是靶向HER3的新型ADC。一项Ⅱ期研究表明，采用HER3-DXd治疗EGFR-TKIs耐药患者，ORR为25%，DCR为70%，且对多种耐药机制（C797S、MET扩增、HER2突变、BRAF融合及PIK3CA突变）具有疗效[146]。另一项旨在评估HER3-DXd+奥希替尼组合克服耐药可能性的Ⅰ期研究也正在进行中[51]。

TROP2在NSCLC中也呈过表达。Datopotamab deruxtecan（Dato-DXd；DS-1062）是一种靶向TROP2的ADC，在Ⅰ期TROPION-PanTumor01研究中的初步结果显示出令人鼓舞的活性[51]。Sacituzumab govitecan（SG；IMMU-132）是另一款新型TROP2 ADC，拟评估SG治疗转移性实体瘤疗效的Ⅱ期TROPiCS-03研究也值得期待[51]。

目前，EGFR蛋白靶向降解嵌合体（proteolysis targeting chimera，PROTAC）的研究仍处于起步阶段。PROTAC是一种通过利用细胞中天然的泛素-

蛋白酶体系统诱导靶向蛋白降解从而发挥抗肿瘤作用的新兴技术[147]。PROTAC由靶蛋白配体、连接子和E3泛素连接酶配体（如CRBN、VHL）组成，一端通过靶蛋白配体特异性识别并结合靶点，另一端则依靠E3泛素连接酶配体特异性识别并结合E3配体，靶蛋白经泛素化修饰被蛋白酶体识别降解，进而丧失蛋白功能[147]。与传统小分子抑制剂占位驱动不同，PROTAC以事件驱动为基础，既能在低剂量下发挥作用，又能在降解靶向蛋白后游离出来参与下一个催化循环[147]。因此，PROTAC治疗具有高效、可克服耐药、突破不可成药靶点的优势和潜力。在肺癌领域，靶向EGFR的PROTAC也正在研究中[148]。如基于EGFR-TKIs与CRBN配体结合的MS154、DDC-01-163、SIAIS125/126等，基于EGFR-TKIs与VHL配体的Compound 3/4、MS39、CP17等药物在临床前研究中均显示了较好的抗肿瘤活性。有研究报道，双靶点PROTAC可同时靶向EGFR和PARP，但改善药物吸收和药代动力学仍有一段路要走[148-149]。

3 讨论及展望

探索晚期NSCLC EGFR-TKIs获得性耐药后的治疗策略是临床刚需，其关键点之一就是依据耐药机制进行精准治疗。因此，耐药后再次活检、基因检测技术选择和药物研发设计无疑是解决问题的关键密钥。

虽然再次组织活检有利于耐药机制的探索，但临床实践困难重重，即便如此，在耐药进展时取病理组织活检仍具有重要的临床意义。液体活检技术（如ctDNA、循环肿瘤细胞、外泌体等）相比于传统组织活检，具有无创、可重复性高的特点，能定量、动态地探究耐药患者基因组学背景，以指导临床分型和治疗选择，同时能早期监测耐药发生[150-151]。相关专家共识推荐，当患者组织活检不可及时，液体活检可作为补充，有条件时两者同时进行，以排除组织学转化可能[152]。

基因检测技术上，相比于一代测序，NGS更具检测深度和广度，能同时检测已知突变和未知突变，从DNA水平发现新靶点及潜在可治疗靶点并指导临床。一项研究利用NGS对1 015例晚期泛癌患者进行DNA、RNA测序（肿瘤活组织与血液样本配对），结果表明，80.5%的患者检测出潜在可操作性基因组变异不少于1个，其中接受以NGS为导向测序指导治疗（这些治疗可能不被标准指南所推荐）的患者中，37%实现了临床获益[153]。晚期NSCLC患者EGFR-TKIs耐药后行NGS检测也日渐运用于临床，以指导后续治疗。有专家共识强烈推荐使用1种及以上广谱检测手段明确广泛进展患者的耐药机制，为后续治疗策略提供依据[152]。有研究认为，即使肿瘤的异质性和复杂性会带来疗效差异，除联合NGS、数字微滴聚合酶链式反应（digital droplet polymerase chain reaction，ddPCR）外，通过比较肿瘤初始原发灶、个体内转移灶、相同病变纵向活检结果来探索肿瘤遗传演化对NSCLC患者的治疗决策也具有重大价值[154]。此类研究往往需通过不易获得的尸检才能实现，因此任重而道远。此外，单细胞测序能很好地解析驱动因子改变所致肿瘤异质性的克隆演化，也有望探究耐药持久性（drug-tolerant persistence，DTP）在癌细胞亚群中的发生发展，以推动耐药相关研究[155-156]。通过单细胞测序，研究发现CD74在药物耐受状态中起到关键作用，其表达上调可能是导致奥希替尼耐药的新机制，或许能为克服耐药或预防耐药提供新见解[157]。

对于耐药后治疗策略，目前的研究方向主要集中于靶向驱动基因和药物联合，药物研发设计方面也有所突破。除了靶向药物、ICIs外，ADCs也进入了战场，这些药物排兵布阵的差异会带来不同战果，但无论如何，都是为了寻求更好的方法来实现晚期NSCLC患者更多获益。未来治疗策略不只局限于药物间的排列组合，耐药机制的探究也有助于发散临床研究设计思路。除了利用泛素-蛋白酶体系统降解靶向蛋白的PROTAC，S-棕榈酰化、S-亚硝基化、甲基化等各种蛋白翻译后修饰（post-translational modification，PTM）也可通过调节多个EGFR位点来影响EGFR激酶活性，这可能为克服EGFR-TKIs耐药提供潜在研究方向[158]。技术进步、科研创造将是改善EGFR突变NSCLC患者结局的关键。

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