综 述

晚期经治非小细胞肺癌EGFR-TKIs获得性RET融合突变耐药的研究进展

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[摘要] 随着分子生物学研究的深入，非小细胞肺癌(NSCLC)开启了基于突变分子靶向治疗的精准医疗时代。表皮生长因子受体(EGFR)驱动突变与NSCLC的发生发展密切相关，基于此研发的EGFR-酪氨酸激酶抑制剂(TKIs)取得了显著的治疗效果，但获得性耐药仍是限制其长期应用的主要因素之一。EGFR-TKIs获得性耐药除包括*EGFR*再突变、*MET*扩增、*HER2*扩增、组织转化等外，受体酪氨酸激酶(RTK)融合突变被证实是一种罕见但可靶向的重要获得性耐药机制。在获得性*RTK*融合突变中，转染重排(RET)融合突变是研究者关注的可及靶点，随着对RET分子的不断探索，针对RET融合突变的药物相继获批上市，对于获得性RET融合突变介导EGFR-TKIs治疗的获得性耐药，目前临床上有不同的处理策略。本文就RET的结构和功能及其与EGFR-TKIs获得性耐药的关系及治疗策略进行综述，以期进一步改善患者生存结局。

[关键词] 非小细胞肺癌；靶向治疗；EGFR-TKIs耐药；转染重排

Research progress on acquired RET fusion induces secondary resistance to EGFR therapy in advanced EGFR-mutated non-small cell lung cancer

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[**Abstract**] With the in-depth study of molecular biology, non-small cell lung cancer (NSCLC) has opened the era of precision medicine based on mutation-based molecular targeting therapy. Epidermal growth factor receptor (EGFR) driver mutations are closely related to the progression of NSCLC, and EGFR-tyrosine kinase inhibitors (TKIs) developed based on this have achieved significant therapeutic effects, but acquired drug resistance is still one of the major factors limiting their long-term use. As resistance mechanisms are further investigated, in addition to secondary *EGFR* mutation, *MET* amplification, *HER2* amplification, histologic transformation, etc., receptor tyrosine kinase (RTK) fusion mutation have been shown to be a targetable mechanism of acquired resistance. Among the acquired *RTK* fusion mutations, rearranged during transfection (RET) fusion mutations are the accessible targets of our concern. As the RET molecule continues to be explored, drugs targeting *RET* fusions have been approved and marketed. There are different clinical strategies to deal with acquired *RET* fusion mutation mediating resistance to EGFR-TKIs treatment. In this review, the structure and function of RET, its relationship with EGFR-TKIs resistance, and treatment strategies are reviewed to further improve patient survival outcomes.

[**Key words**] non-small cell lung cancer; targeted therapy; EGFR-TKIs resistance; rearranged during transfection

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统计数据显示，2020年全球范围内癌症新发病例1930万，癌症死亡病例近1000万，其中肺癌新发220万例(11.4%)，成为第二常见的癌症，死亡180万例(18.0%)，居癌症死亡首位[1]。约50%的肺癌全球新发及死亡病例发生在亚洲[2]，在我国，肺癌仍是癌症相关发病和死亡的首要原因，且呈增高趋势[3-4]。非小细胞肺癌(non-small cell lung cancer，NSCLC)占所有肺癌的80%以上，大多数早期肺癌患者常无症状，确诊时已是晚期，5年生存率低于15%[5-6]。随着精准医学的发展，分子靶向治疗在肺癌领域得到广泛应用[7]。表皮生长因子受体(epidermal growth factor receptor，EGFR)是一种受体酪氨酸激酶(receptor tyrosine kinase，RTK)，也是公认的NSCLC的有效治疗靶点[8-9]。EGFR-酪氨酸激酶抑制剂(tyrosine kinase inhibitors，TKIs)在晚期*EGFR*敏感突变的NSCLC(EGFR mutation NSCLC，*EGFRm* NSCLC)患者中显著获益，相较化疗成为更佳的治疗选择[10-12]，但不可避免存在耐药问题。在EGFR-TKIs获得性耐药机制中，RTK融合突变占4%~7%[13]。RTK融合包括间变性淋巴瘤激酶(anaplastic lymphoma kinas，ALK)、原癌基因1受体酪氨酸激酶(c-ros oncogene 1 receptor tyrosine kinase，ROS1)、转染重排(rearranged during transfection，RET)等，研究发现，EGFR-TKIs获得性耐药NSCLC患者中，RET是最常见的获得性耐药RTK融合突变，占43%，其次是ALK(26%)[14-15]。本文就RET的结构和功能及其与EGFR-TKIs获得性耐药的关系及治疗策略进展进行综述，以期对EGFR-TKIs耐药的晚期*EGFR*m NSCLC进行临床个性化、精准诊疗。

1 EGFR、EGFR-TKIs及EGFR-TKIs获得性耐药

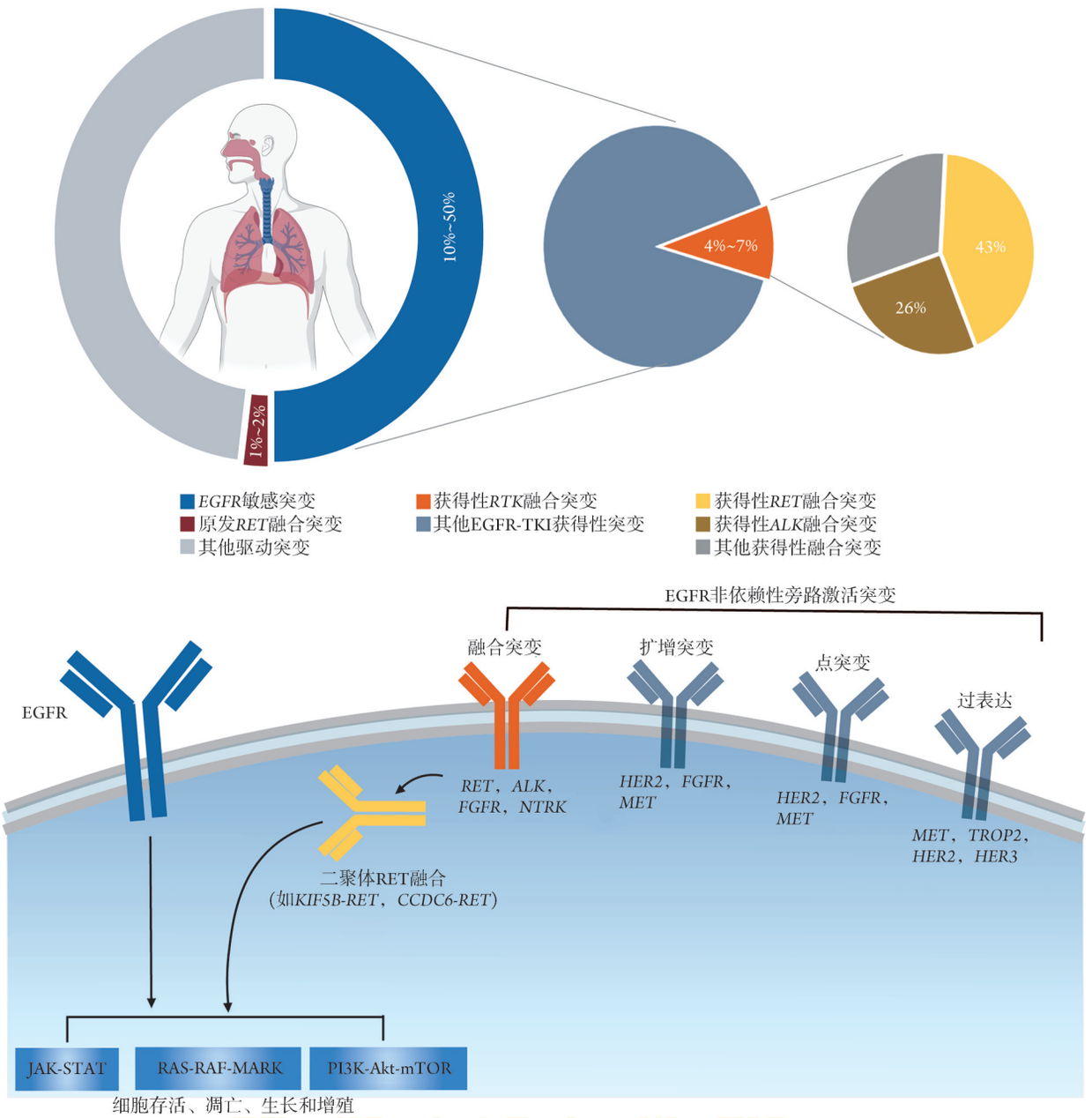
Cohen[16]于1958年首次发现一种新的生长因子，后续通过实验证实其与表皮生长相关，将其命名为表皮生长因子(epidermal growth factor，EGF)[17-18]。进一步研究发现，与EGF相结合的EGFR是一种RTK[19-20]。1984年，Downward等[21]发现，红白血病病毒癌基因同源物(erythroblastic leukemia viral oncogene homolog，ErbB)原癌基因与*EGFR*基因同源，首次将*EGFR*与癌症相关联，并通过实验进行了验证[22]。Passaro等[23]在10%~15%欧洲NSCLC患者及高达50%亚裔NSCLC患者中观察到*EGFR*激活突变。

*EGFR*激活突变作为NSCLC的治疗靶点之一，目前临床有3代药物相继应用于晚期*EGFR*敏感突变(外显子19缺失和*21 L858R*点突变)NSCLC的治疗中，吉非替尼和厄洛替尼等第1代EGFR-TKIs是ATP的可逆性竞争抑制剂[24]，也是靶向治疗的里程碑，尽管初始反应良好，但对第1代EGFR-TKIs的耐药通常在1年内出现[25]，最主要的耐药机制是*T790M*突变(60%)[26]；为克服这一耐药机制后续相继研发了第2、3代EGFR-TKIs，以阿法替尼为代表的第2代EGFR-TKIs是不可逆泛EGFR抑制剂，但未解决*T790M*突变的耐药问题[27]；第3代奥希替尼是对典型*EGFR*敏感突变和*T790M*耐药突变具有更高效力和选择性的不可逆抑制剂。FLAURA试验比较了奥希替尼与吉非替尼/厄洛替尼治疗晚期*EGFR*敏感突变NSCLC患者的疗效，结果显示，中位无进展生存期(progression-free survival，PFS)显著获益(18.9个月*vs.* 10.2个月)，但面临获得性耐药问题[28]。

靶向药物的获得性耐药机制包括“靶向(on-target)”耐药(主要由EGFR激酶结构域中的获得性耐药突变介导)和“脱靶(off-target)”耐药(由非靶向激酶改变介导，如旁路信号通路激活、表型转化、组织学转化、药代动力学变化等)(图1)。其中，*RET*融合突变作为旁路信号通路激活机制，参与晚期NSCLC患者对EGFR-TKIs的获得性耐药，并在第3代EGFR-TKIs耐药后显著富集[29-31]。EGFR-TKIs耐药源于空间和时间的克隆选择对癌症细胞所施加的进化压力或基因突变的随机获取[32-33]，而*RET*融合突变是通过选择预先存在的低水平亚克隆还是通过后期药物压力下基因突变而出现目前仍存在争议[34]；研究发现，获得性耐药较选择预先存在的耐药亚克隆更为被临床接受[35-36]。近期的TRACERx研究发现，*RTK*突变是通过旁路基因再激活而非亚克隆选择[37]，并在前期临床前研究中得到验证[38]；*RET*的原发及获得性融合伴侣的检出差异也佐证了这一观点，原发性*RET*融合突变NSCLC患者的主要融合伴侣类型是*KIF5B-RET*，而*CCDC6-RET*是最常见的*EGFR*m NSCLC患者EGFR-TKIs获得性耐药的融合伴侣。

2 *RET*基因的结构和功能、原发性RET融合及RET-TKIs

1985年，*RET*基因于人淋巴瘤DNA转染的NIH/3T3细胞中被发现并命名为转染重排基因，其位于10号染色体长臂的10q11.2区域，包含21个外显子，大小为60 kb，编码由1100个氨基酸构成的单次跨膜RET蛋白[39-40]。RET蛋白包含酪氨酸激酶羧基末端的胞内区、跨膜区和富含半胱氨酸的钙黏素样细胞膜外区3个相对独立功能的结构区域[40-41]。RET蛋白细胞外结构域与配体结合可诱导其构象发生变化，促使酪氨酸受体磷酸化和下游信号通路RAS-RAF-MARK、PI3K-Akt-mTOR、JAK-STAT激活，从而参与肾脏形态发生、神经和神经内分泌组织发育以及精原干细胞维持等过程[39,42-43]。



NSCLC. 非小细胞肺癌；EGFR. 表皮生长因子受体；TKIs. 酪氨酸激酶抑制剂；RET. 转染重排；RTK. 受体酪氨酸激酶；ALK. 间变性淋巴瘤激酶；FGFR. 成纤维细胞生长因子受体；NTRK. 神经营养因子受体酪氨酸激酶；HER. 人表皮生长因子受体；MET. 间质表皮转化因子；TROP2. 人滋养层细胞表面抗原2；JAK. 非受体型蛋白酪氨酸激酶；STAT. 信号传导及转录激活蛋白；RAS. 大鼠肉瘤蛋白；MARK. 丝裂原活化蛋白激酶；PIK3K. 磷脂酰肌激酶；Akt. 蛋白激酶B；mTOR. 哺乳动物雷帕霉素靶蛋白

图1 晚期NSCLC EGFR-TKIs获得性耐药

Fig.1 Acquired resistance to EGFR-TKIs in advanced NSCLC

目前研究发现，*RET*基因是一种新型原癌驱动基因，其异常激活与多种癌症的发生和发展密切相关[42]。*RET*基因突变形式包括缺失、点突变、扩增和融合等，在NSCLC中主要是染色体重排引起原发性*RET*融合突变，阳性率为1%~2%，多见于女性和青年人，融合伴侣基因主要形式为*KIF5B-RET*(约占68.3%)、*CCDC6-RET*(16.8%)、*NCOA4-RET*(1.2%)[44]，*RET*基因与伴侣基因融合后致使配体非依赖性RET激酶活化，从而维持肿瘤细胞的增殖和存活[45-47]。因此，*RET*基因融合突变编码的RTK成为癌症治疗的新兴靶标[14,48]。

塞普替尼(Selpercatinib)[49]、普拉替尼(Pralsetinib)[50]作为治疗RET的选择性TKIs相继于2020年5月和2020年9月获得美国FDA批准上市。LIBRETTO-001研究发现，塞普替尼初治患者(n=39)的客观缓解率(objective response rate，ORR)为85%，中位PFS为18.4个月，并且展现出了良好的颅内转移灶控制能力[颅内ORR为82%，颅内疾病控制率(disease control

rate，DCR)为100%][51]。LIBRETTO-321研究发现，塞普替尼治疗国内晚期*RET*融合突变阳性NSCLC患者，可获得与LIBRETTO-001全球数据相一致的疗效和安全性[52]，且该药于2022年10月在国内获批上市。与此同时，基于ARROW的临床研究发现，普拉替尼在*RET*融合突变阳性NSCLC中具有广泛和持久的抗癌活性，国内人群的数据基本与全球试验数据一致[53]，且该药于2021年3月在国内获批上市。基于特异性RET抑制剂的精准研发，使*RET*融合突变成为有药可及的治疗靶点，并且目前这些RET抑制剂已纳入指南并改变了临床实践。

3 获得性RET融合突变

精准治疗，检测先行。在临床初诊和疾病进展时进行分子病理检测拓展了人们对NSCLC患者TKI耐药机制的理解。2015年，2例晚期*EGFR*m NSCLC患者采用厄洛替尼治疗后PFS分别为9、10个月，随后进行耐药前后全景变异分析(comprehensive genomic profiling，CGP)，结果显示，患者出现获得性*CCDC6-RET*融合突变，首次报道了EGFR-TKIs治疗进展的*EGFR*突变患者中，*RET*融合与*EGFR*突变共存[54]，表明在晚期*EGFR*m NSCLC中，*RET*融合突变可能是EGFR-TKIs获得性耐药的潜在机制。

早期研究认为，*RTK*融合是原发驱动突变而不是作为获得性耐药机制而发挥作用[55-57]。2017年，Daly等[38]发现，*FGFR3-TACC3*融合在EGFR途径的信号被EGFR-TKIs抑制时出现并为肿瘤发生进展提供了旁路途径信号，该研究提供了明确的临床前证据，让人们认识到*RTK*融合在获得性耐药中的作用。一项纳入3505例晚期*EGFR*m NSCLC患者的研究中，组织学检测到6例在EGFR-TKIs治疗期间获得*RET*融合突变[58]；另一项多中心研究通过细胞游离循环肿瘤DNA(cell-free circulating tumor DNA，cfDNA)测序证实，15例晚期NSCLC患者在EGFR-TKIs治疗耐药时获得*RET*融合突变[59]，在cfDNA检测到*RET*融合之前，其中6例EGFR-TKIs治疗耐药患者(具有详细治疗病史；3例接受厄洛替尼，3例接受奥希替尼和第1/2代TKIs)的中位PFS为17.5(6~46)个月。

此外有研究发现，非*KIF5B-RET*融合突变更有可能导致EGFR-TKIs治疗耐药[15,59]。近期研究发现，*CCDC6*是最常见的*RET*基因伴侣(38.7%)，其次是*KIF5B*(19.4%)和*NCOA4*(16.1%)[60]。在动物模型中，与*CCDC6-RET*或*NCOA4-RET*融合突变相比，*KIF5B-RET*融合突变高度依赖EGFR信号通路来促进细胞生长[61]。在晚期*EGFR*m NSCLC获得性耐药*RET*融合中，主要是非*KIF5B-RET*融合(特别是*CCDC6*或*NCOA4*作为融合伴侣)，而当*RET*融合作为原发性致癌驱动突变时，更常见的基因伴侣是*KIF5B*，因此，需要进一步探索不同*RET*融合基因伴侣可能存在的生物学差异并在临床检测中加以区分。

不同*EGFR*突变也显示出耐药差异，*EGFR19*缺失突变晚期NSCLC患者的*RET*融合发生率高于*L858R*点突变患者[59]，与既往研究一致，近期研究表明，与*L858R*点突变相比，*EGFR19*缺失突变更有可能产生获得性*RET*融合突变(64.5% *vs.* 29.0%)[15,60]。此外，伴*T790M*和(或)*C797S*突变患者的*RET*融合发生率高于没有这两种驱动突变的患者(分别为1.1% *vs.* 4.6% *vs.* 0.6%)[59]。

晚期NSCLC EGFR-TKIs获得性*RET*融合突变耐药的发生率为0.15%~4.9%(表1[15,29-31,59,62-64])，且在第3代EGFR-TKIs治疗耐药后明显富集。有研究报道，*RET*融合突变与奥希替尼耐药有关[59,63-65]，相较第1/2代EGFR-TKIs，使用奥希替尼的*EGFR*m NSCLC患者发生*RET*融合突变的频率更高[66-67]。这可能涉及多个因素，包括但不限于测序方法的局限、进展时取样率的影响以及不同EGFR-TKIs的特异性作用等。液体活检(liquid biopsy)和二代测序技术(next generation sequencing，NGS)的广泛使用可有助于阐明第3代EGFR-TKIs耐药，而早期研究由于检测局限未能关注到*RET*融合突变，以及组织和cfDNA基因组之间的差异，突出了重新评估晚期癌症患者肿瘤基因的价值，特别是在使用靶向药物治疗后[68-69]。此外，第1/2代EGFR-TKIs中获得性*RET*融合发生率较低可能与耐药时*T790M*突变的高发生率有关[26,29]，第3代EGFR-TKIs在全球范围内被用于治疗*EGFR-T790M*突变介导的*EGFR*m NSCLC患者，而与第1/2代EGFR-TKIs相比，其耐药谱更为广泛[70]；这表明第3代EGFR-TKIs可能会促进分子多样化，其中获得性*RET*融合突变可能与NSCLC对第3代EGFR-TKIs获得性耐药后预后不良有关[15]。

4 EGFR-TKIs获得性耐药伴有RET融合的治疗对策

4.1 化疗和免疫治疗　在特异性RET抑制剂出现前，针对NSCLC患者RET融合突变的治疗手段较为有限且缺乏特异性，主要一线治疗方案为含铂类联合培美曲塞化疗，几乎与驱动基因阴性的NSCLC患者一致。一项多中心回顾性研究显示，以化疗为基础的综合一线治疗PFS为5.2~9.2个月，二线治疗PFS为2.8~4.9个月[71]。将*RET*融合突变的NSCLC患者纳入免疫治疗仍处于探索阶段，研究发现，*RET*融合突变患者采用程序性细胞死亡蛋白-1(PD-1)及其配体(PD-L1)抑制剂治疗的中位PFS为2.1~4.2个月，ORR仅为6.3%~37.5%，对于PD-1/PD-L1药物治疗的应答率较低[72-73]，这可能是由于PD-L1的表达率差异很大

表1 晚期NSCLC EGFR-TKIs获得性RET融合突变耐药发生率

Tab.1 The incidence rate of acquired RET fusion mutation resistance to EGFR-TKIs in advanced NSCLC

EGFR-TKIs代数	发生率(%)	EGFR-TKIs治疗后进展(例)	获得性RET融合突变(例)	参考文献
第3代	2.6	78	2	Chmielecki等[26]
第3代	3.7	27	1	Schoenfeld等[28]
第3代	2.4	41	1	Oxnard等[59]
第3代	2.4	42	1	Le等[60]
第3代	4.9	41	2	Piotrowska等[27]
第3代	4.9	184	9	Rich等[56]
第3代	1.5	3919	58	Wang等[12]
第1/2代	0.15	8732	13	Wang等[12]
第1/2代	0.8	1627	13	Rich等[56]
第1代	0.68	145	1	Chmielecki等[61]

EGFR.表皮生长因子受体；TKI.酪氨酸激酶抑制剂；RET.转染重排

(为0~70%)[74]。近期研究发现，*RET*融合突变阳性NSCLC患者的PD-L1表达明显高于阴性患者[75]。因此，后续需要加大样本量进一步探索免疫治疗的获益人群。

4.2 多靶点药物治疗 过去10年中，*RET*融合突变阳性NSCLC患者的治疗已经从单纯化疗发展到多激酶抑制剂(multi-kinase inhibitors，MKIs)再到选择性RET-TKIs。多种市售的MKIs如卡博替尼(Cabozantinib)、阿来替尼(Alectinib)、凡德他尼(Vandetanib)、舒尼替尼(Sunitinib)、索拉非尼(Sorafenib)、仑伐替尼(Lenvatinib)等显示出对*RET*融合突变靶点的良好活性。在1例发生获得性*CCDC6-RET*融合突变的*EGFR*m NSCLC患者中检测到*CCDC6-RET*的循环肿瘤DNA(circulating tumor DNA，ctDNA)水平降低，采用卡博替尼单药治疗获得显著临床获益[76]。但1例厄洛替尼治疗后获得*CCDC6-RET*融合突变耐药的患者，采用阿来替尼单药治疗并没有临床获益[58]，分析原因可能是剂量不足以抑制异常激活的RET激酶。此外，多靶点抑制剂并未起到理想的高效、低毒精准靶向治疗作用而限制了其临床应用。一项*RET*融合阳性NSCLC应用MKIs的Ⅱ期临床研究显示，患者不良反应发生率高达96.2%，且73%的患者由于治疗相关不良事件(treatment-related adverse events，TRAEs)需药物减量[77]。2017年*Journal of Clinical Oncology*归纳了多靶点抑制剂的疗效，发现其中位持续缓解时间仅为1.8个月，中位PFS仅为2.3个月，中位总生存期(overall survival，OS)仅为6.8个月[78]。而选择性RET-TKIs的临床试验展现出持久的疗效且安全可控[51,53]，但对*EGFR*m NSCLC发生获得性*RET*融合突变的患者，需要进一步探索选择性RET-TKIs的临床获益情况。

4.3 RET-TKI联合EGFR-TKI *RET*与另一个基因融合发生于异常的DNA修复过程中[79]。由此产生的融合产物可激活在细胞增殖和存活中发挥重要作用的各种下游信号通路[80]。临床前研究表明，*CCDC6-RET*融合突变表达在存在EGFR-TKIs作用的情况下可导致持续的MAPK和PI3K信号传导，并足以引起EGFR-TKIs耐药[30]。获得性*RET*融合突变除可在*EGFR*突变的细胞中诱导对奥希替尼耐药外，当与卡博替尼联合使用时，还可恢复奥希替尼的治疗反应[66]。有研究探索了同时抑制RET和EGFR的作用，发现联合治疗在减少肿瘤细胞增殖或抑制肿瘤生长方面相较单独使用RET抑制剂更有效[81-82]。综上，*RET*基因融合是一种可靶向治疗的EGFR-TKIs获得性耐药机制，靶向、联合治疗将给EGFR-TKIs获得性耐药患者带来更多希望。

*RET*融合突变被认为是EGFR-TKIs靶向治疗获得性耐药的机制，旁路信号通路激活引起耐药的关键治疗策略是同时对驱动癌基因和旁路通路进行抑制。研究发现，采用奥希替尼的NSCLC患者在获得性*RET*融合突变时，使用EGFR-TKIs联合RET-TKIs(如塞普替尼或普拉替尼)的组合可克服由获得性*RET*融合突变介导的耐药[28]。临床研究证实，与单药靶向治疗相比，联合治疗可改善临床结局[82]。一例对阿法替尼耐药后检测出*NCOA4-RET*融合突变的患者，采用阿法替尼联合卡博替尼治疗后获得疾病稳定(stable disease，SD)，并维持7个月[58]。一例*EGFR19*缺失突变在接受阿法替尼治疗耐药后检测出*NCOA4-RET*融合突变的患者，采用奥希替尼联合普拉替尼治疗后获得部分缓解(partial response，PR)，并维持超过12个月[30]。近期研究显示，14例*EGFR*突变和*RET*融合突变阳性NSCLC患者接受奥希替尼联合塞普替尼治疗后，ORR和DCR分别为50%和83%[83]。以上临床前研究及临床探索实践为同时靶

向保留的原发*EGFR*驱动突变和获得性耐药的融合突变提供了基础，联合应用EGFR-TKIs和RET-TKIs可能是一种合理的治疗选择，具有潜在的应用前景。

5 总结与展望

肺癌严重危害人类生命健康，随着医学的进步和发展，伴有驱动基因的晚期NSCLC的诊疗模式结合了病理分型和分子分型，开启了精准医学的靶向治疗时代。TKIs广泛应用于NSCLC治疗，但其耐药现象不可避免。目前，第3代EGFR-TKIs的耐药机制十分复杂，并且没有特定的耐药治疗对策。RTK融合突变是EGFR-TKIs耐药中的一种情况，尽管其只存在少数肺癌患者中，但基于庞大的肺癌群体，仍不能忽视。唯有利用现有的技术手段，不断探索EGFR-TKIs可能的耐药机制和应对策略，才能制定更加精确的个体化治疗方案，进一步优化靶向治疗在NSCLC中的应用，真正为患者的个体化和精准化靶向治疗指明方向。

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