第三代EGFR-TKIs在非小细胞肺癌中的耐药机制及应对策略

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［摘要］ 表皮生长因子受体酪氨酸激酶抑制剂(epidermal growth factor receptor tyrosine kinase inhibitors，EGFR-TKIs)靶向治疗相对于传统化疗具有很大的优势，已成为晚期非小细胞肺癌*EGFR*敏感突变患者的一线治疗方案。然而，耐药现象不可避免地发生。*EGFR*第20号外显子的*T*790*M*突变是第一、二代EGFR-TKIs的主要耐药机制。第三代EGFR-TKIs，如AZD9291、CO-1686等可克服T790M耐药，并在临床试验中显示出良好的治疗效果，然而，第三代EGFR-TKIs的耐药同样不可避免，该文就第三代EGFR-TKIs的耐药机制及目前的应对策略进行综述。

［关键词］ 表皮生长因子受体；非小细胞肺癌；第三代表皮生长因子受体酪氨酸激酶抑制剂；耐药机制
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The resistance mechanism and coping strategy of the third-generation EGFR-TKIs in NSCLC QIN Shanshan, CHANG Jianhua (Department of Medical Oncology, Fudan University Shanghai Cancer Center; Department of Oncology, Shanghai Medical College, Fudan University, Shanghai 200032, China)
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［**Abstract**］ Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) targeted therapy has great advantages compared to conventional chemotherapies and has become the first-line treatment of EGFR sensitive mutations in patients with advanced non-small cell lung cancer. However, the development of acquired drug resistance is inevitable. *EGFR T*790*M* mutation is the main mechanism of the first and second generation EGFR-TKIs. The third-generation EGFR-TKIs including AZD9291 and CO-1686 showed favorable treatment effect in clinical trials. However, resistance problems appeared soon. This review summarized the resistance mechanisms of the third-generation EGFR-TKIs and the potential coping strategy.

［**Key words**］ Epidermal growth factor receptor; Non-small cell lung cancer; The third-generation epidermal growth factor receptor tyrosine kinase inhibitors; Resistance mechanism

亚裔非小细胞肺癌(non-small cell lung cancer，NSCLC)患者表皮生长因子受体(epidermal growth factor receptor，*EGFR*)基因敏感突变比例为30%~50%[1]，其中女性、非吸烟者的突变比例更高。最常见的*EGFR*基因敏感突变类型为19号外显子的缺失(*Del*19)和21号外显子的点突变(*L*858*R*)[2]。对于*EGFR*基因突变的患者，表皮生长因子受体酪氨酸激酶抑制剂(epidermal growth factor receptor tyrosine kinase inhibitors，EGFR-TKIs)的疗效明显优于传统化疗药物，并且不良反应的发生率更低，给药更方便，患者依从性高，从而提高患者的生活质量[3-6]。美国NCCN指南推荐EGFR-TKIs用于*EGFR*基因敏感突变的NSCLC患者的一线治疗。然而EGFR-TKIs初始治疗有效的患者，大部分在用药10个月左右都会不可避免地出现耐药[7-8]。

1 第三代EGFR-TKI耐药机制及应对策略

第三代EGFR-TKIs主要针对携带T790M位点的*EGFR*突变患者而研发，这类药物能够与T790M EGFR的ATP结合位点不可逆结合，包括AZD9291(osimertinib)、CO-1686(rociletinib)、BI 1482694(HM61713)、EGF816和PF-06747775，所有

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这些药都已进入临床试验[9-14]。基于良好的试验结果，AZD9291已被美国食品药品管理局(Food and Drug Administration，FDA)批准用于*T*790*M*突变阳性的晚期NSCLC。第三代EGFR-TKIs在一线治疗中的表现同样优越，总体有效率高达73%，最长疗效持续时间在数据截止时长达13.8个月。但是经过9~13个月的治疗，患者都不同程度的出现了耐药。

目前针对第三代EGFR-TKIs，已报道的耐药机制如下。

1.1 获得*C*797*S*突变

Thress等[15]研究了AZD9291耐药的进展期肺癌患者的血浆DNA，对其中7份血浆游离DNA(cell-free DNA，cfDNA)进行了二代测序，发现1份出现*EGFR C*797*S*突变。随后用AZD9291处理了15份*T*790*M*阳性的cfDNA样本并进行了差异显示聚合酶链反应(differential display polymerase chain reaction，DD-PCR)分析，但是经过处理后出现了AZD9291耐药，结果显示，6例*C*797*S*突变阳性，5例*T*790*M*突变阳性、*C*797*S*突变阴性，4例*T*790*M*突变缺失但仍携带*EGFR*敏感突变，说明*C*797*S*获得性阳性及*T*790*M*突变缺失可能与AZD9291耐药相关。另有研究提示*C*797*S*突变阳性跟AZD9291[16]与HM61713[17]耐药相关。*EGFR*突变阳性的Ba/F3细胞系，经过第三代EGFR-TKIs、WZ4002、CO-1686和AZD9291处理后出现*L*718*Q*、*L*844*V*和*C*797*S*突变，所有这3种突变都对WZ4002和CO-1686耐药，只有*C*797*S*对AZD9291耐药[18]。MGH121 Res#1是第三代EGFR-TKIs耐药细胞系，其中*C*797*S*是获得性突变之一[19]。*L*858*R*/*T*790*M*/*C*797*S*突变阳性的细胞对所有的EGFR-TKIs均耐药，当*T*790*M*和*C*797*S*在同一个等位基因或同一细胞的不同等位基因上时，结果显示，有*T*790*M*突变阳性的对第二代EGFR-TKIs耐药，而有*C*797*S*突变的对第三代EGFR-TKIs耐药，两种突变都有的对所有的EGFR-TKIs都耐药。

1.2 *T*790*M*突变

Piotrowska等[20]的研究显示，13例*T*790*M*突变阳性NSCLC患者经过CO-1686治疗后耐药，对他们的病灶再次进行活检后发现，6例出现*T*790*M*突变缺失，其中有2例出现小细胞肺癌的转化，3例出现EGFR的扩增，7例保持*T*790*M*突变阳性。

1.3 *L*718*Q*突变

1例患者经过吉非替尼和化疗治疗后出现疾病进展，再活检发现*T*790*M*突变，换AZD9291治疗，治疗13个月后又出现疾病进展，同一组织的二代测序技术发现，*EGFR L*718*Q*突变，这一发现也为揭示AZD9291复杂耐药机制及后续新药的研发提供了新靶点[21]。

1.4 *BRAF V*600*E*获得性突变

1例经过第一、二线EGFR-TKIs治疗后耐药的*T*790*M*突变患者经过AZD9291治疗后出现*BRAF V*600*E*突变[22]。

1.5 *HER*-2、*MET*基因的扩增

一项病例研究显示，在经过AZD9291治疗10个月的该患者中发现*CMET*基因的扩增，而没有*T*790*M*或*C*797*S*的突变[23]。另有研究显示，在经过AZD9291治疗9个月的患者中出现*MET*基因的扩增[23]。最近的一项研究表明，7例患者当接受AZD9291(*n*=5)或CO-1686b(*n*=2)治疗而进展后，再次进行组织活检，发现2例有*HER*-2的扩增，3例有*MET*的扩增，1例有*C*797*S*突变，1例有*KRAS G*12*S*突变，并认为*MET*和*ERBB*2的突变，是通过EGFR非依赖的旁路途径而对第三代EGFR-TKIs耐药的[24]。在这些EGFR非依赖途径的耐药机制中，*MET*基因的扩增和蛋白的过表达是对第一及第三代EGFR-TKIs耐药最常见的机制。

1.6 *Del*19及*T*790*M*缺失突变

韩国报道了4例携带有*Del*19及*T*790*M*缺失突变的患者，经过AZD9291治疗后，1例*EGFR LREAT*747*del*/*T*790*M*缺失，1例转化为小细胞肺癌，1例出现成纤维细胞因子1扩增，另外1例*T*790*M*突变且伴有EGFR配体的扩增[25]。

1.7 *NRAS*突变

一项临床前试验指出，*NRAS*突变包括*E*63*K*的突变及野生型*NRAS*或*KRAS*的扩增跟AZD9291耐药相关[26]。它不仅对AZD9291耐药，也对吉非替尼和阿法替尼耐药。在体外AZD9291联合MEK抑制剂司美替尼阻止PC9(Ex19del)细胞系耐药的产生及延缓NCI-

H1975(L858R/T790M)细胞系耐药的产生。在体内，AZD9291联合司美替尼可以使*EGFR*/*T*790*M*的转基因模型的肿瘤退缩。

根据以上研究，第三代EGFR-TKIs耐药大致可分为4类：① 出现耐药突变，如*C*797*S*突变、*L*718*Q*突变；② 旁路激活，如*MET*扩增；③ 表型改变，如腺癌向小细胞肺癌转化；④ 下游信号通路的激活，如*MAPK*1扩增直接激活下游增殖信号通路产生EGFR-TKIs的获得性耐药。

2 第三代EGFR-TKIs耐药后治疗策略

2.1 基础研究及动物研究

在AZD9291耐药动物模型中，AZD9291联合司美替尼可使肿瘤缩小[26]。体外实验发现，针对MAPK1扩增引起对WZ4002耐药的患者，通过阻滞MEK或ERK可以恢复WZ4002的敏感性及阻止耐药的出现。因此，在未来的靶向治疗中应该考虑联合治疗[27]。近期Wang等[28]报道了一种能够克服AZD9291耐药的新一代靶向药EAI045，是一种针对特定*EGFR*耐药突变的变构抑制剂，对突变型的选择敏感性是野生型的1 000倍，研究证实EAI045对于具有二聚体缺陷的*EGFR*突变明显具有更强的活性，EAI045与西妥昔单抗的联合显著抑制了具有*L*858*R*/*T*790*M*突变的Ba/F3细胞系的增殖。以上体外研究证实，EAI045对于具有*T*790*M*突变的处于单体状态的EGFR具有明显活性。在*L*858*R*/*T*790*M*突变阳性的肺癌小鼠模型中，分别单独及与西妥昔单抗联合测试EAI045的效果，单用EAI045处理的小鼠未见有效，但在EAI045及西妥昔单抗联合处理的小鼠中观察到肿瘤显著消退。另外在*L*858*R*/*T*790*M*/*C*797*S*突变的Ba/F3细胞系及*L*858*R*/*T*790*M*/*C*797*S*突变的肿瘤移植小鼠中也观察到类似的现象。以上研究结果证实，EAI045是首个针对*EGFR T*790*M*及*C*797*S*突变的变构体抑制剂，并且其与西妥昔单抗联合时有效。但这些数据仅限于实验室，是否会转化成临床获益有待进一步研究。

2.2 临床研究

AZD9291联合司美替尼治疗*EGFR*突变肺癌的Ⅰ期试验正在进行。对MET高表达的患者，C-MET抑制剂ARQ197(tivantinib)联合AZD9291的缓解率达50%[29]。联合免疫治疗方面，Ⅰ期TATTON研究的初步结果显示，AZD9291联合MEDI4736(durvalumab)在*EGFR T*790*M*突变的NSCLC患者中获得57%的总有效率[30]。TATTON研究及Ⅲ期CAURAL研究因间质性肺病的不良反应而暂停。

第三代EGFR-TKIs耐药机制的发现将为后续药物的发展提供重要的线索及依据，针对*EGFR L*718*Q*耐药突变及*G*12*S*突变是否也可以研发出新的靶向药物值得大家思考。另外其他耐药通路的发现也为联合治疗提供了更多的依据。EGFR-TKIs联合其他药物将是未来克服多种耐药肿瘤未来的发展方向。除西妥昔单抗外，MET及MEK抑制剂也许对于联合治疗也有一定价值。免疫检查点抑制剂已被证实可用于多种晚期肿瘤的治疗，也被认为是克服TKI耐药的联合治疗方法。

3 结语

肺癌的发生、发展是一个多方向、多步骤的复杂网络系统，随着精准医疗的发展，靶向药物的研发如火如荼的进行中，虽然针对不同靶点的新的靶向药物不断问世，但耐药问题也不可避免，从而增加了靶向治疗的难度，所以必须关注及探索此类药物的耐药机制，针对不同耐药机制，可以研发出针对耐药靶点的新的靶向药物，制定出更合理的治疗策略，提高患者的生存期，改善患者的生活质量。

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