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晚期肺腺癌患者获得性EGFR-TKI耐药后治疗的研究进展

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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 inhibitor, EGFR-TKI)的出现给肺腺癌患者带来福音，但EGFR-TKI的耐药问题亟需解决。为了进一步改善患者的生存，本文就晚期肺腺癌患者获得性EGFR-TKI耐药后治疗的研究现状进行综述，探讨EGFR-TKI耐药后治疗策略的临床意义及如何选择个体化治疗方案。

关键词

肺腺癌，表皮生长因子受体，酪氨酸激酶抑制剂，获得性耐药

Research Progress of Acquired EGFR-TKI Resistance in Patients with Advanced Lung Adenocarcinoma

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Abstract

The emergence of epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) brings

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good news to patients with lung adenocarcinoma, but the problem of drug resistance of EGFR-TKI needs to be solved urgently. In order to further improve the survival of patients, this paper reviewed the research status of acquired EGFR-TKI post-drug resistance treatment in patients with advanced lung adenocarcinoma, and discussed the clinical significance of EGFR-TKI post-drug resistance treatment strategy and how to select individual treatment plan.

Keywords

Adenocarcinoma of Lung, Epidermal Growth Factor Receptor, Tyrosine Kinase Inhibitors, Acquired Drug-Resistance

1. 引言

肺癌在全球的发病率和死亡率居高不下，造成严重的社会和经济负担。虽然从 2020 新发癌统计来看肺癌发生率已被乳腺癌超过，但肺癌的致死率依然是最高的。肺腺癌是肺癌的主要组织类型，约占 40%以上。对于不可切除的晚期肺腺癌来说放化疗曾是经典的治疗策略。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)是一种小分子酪氨酸激酶抑制剂，以吉非替尼、厄洛替尼、阿法替尼、达克替尼、奥西替尼等为主的 EGFR-TKI 已普遍应用于 EGFR 阳性的肺腺癌患者的治疗。相对于放化疗，EGFR-TKI 不仅能使患者有更好的生存获益，而且毒副作用小，大大提高了患者的生存质量。然而尽管 EGFR-TKI 具有低毒高效的特点，但最终都难免出现耐药的结局。一、二代 EGFR-TKI 在经过中位 8~13 个月的疾病控制后，最终会出现耐药。如果三代 EGFR-TKI 也已经耐药，则无更新的 EGFR-TKI 可以选用，后续该如何处理？现将晚期肺腺癌患者获得性 EGFR-TKI 耐药的后续治疗策略作以综述。

2. EGFR-TKI 获得性耐药的定义

EGFR-TKI 的出现给 EGFR 突变阳性的这一部分患者带来了福音，但与此同时获得性耐药也成了严峻的挑战。Jackman 等[1]对 EGFR-TKI 获得性耐药的定义做了精确描述，即 EGFR 突变阳性的非小细胞肺癌(Non-Small Cell Lung Cancer, NSCLC)患者在接受 EGFR-TKI 治疗后，根据实体瘤疗效评价标准(Response Evaluation Criteria In Solid Tumors, RECIST)达到疾病稳定或缓解持续 6 个月以上，在继续使用 EGFR-TKI 的时候，出现 RECIST 评价的疾病进展。

3. EGFR-TKI 获得性耐药的临床亚型及一般机制

根据 EGFR-TKI 获得性耐药后的临床情况的不同，可将其分为三种临床亚型：中枢神经系统(central nervous system, CNS)豁免型、微进展型、全身进展型[2]。CNS 豁免型一般是由于一些 TKI 对血脑屏障的穿透性很弱，中枢神经系统虽出现病灶，但其他部位对 TKI 的反应良好[3]；微进展型一般是指除神经系统以外少于 4 个局部病灶位点的进展[4] [5]；全身进展指全身多处多系统的进展；临床上一般根据进展的类型来决定下一步如何对耐药进行处理。

EGFR-TKI 获得性耐药的机制也是多种多样的，根据目前的研究结果来看，耐药的机制大致分为三种情况：EGFR 靶基因修饰、其他旁路激活及组织表型转变。EGFR 靶基因修饰最常见的就是 T790M 突

变(EGFR 20 号外显子第 790 位点上的苏氨酸被蛋氨酸所取代)，大约占第一、二代 EGFR-TKI 获得性耐药的 50%以上[6]。C797S 突变(EGFR 20 号外显子第 797 位点上的半胱氨酸被丝氨酸所取代)是第三代 EGFR-TKI 奥西替尼获得性耐药的较常见突变之一[7]，奥西替尼耐药后的部分患者同时携带 T790M 突变和 C797S 突变，当两种突变位于同一条 DNA 链上时，则称为 T790M/C797S 顺式突变，当两种突变位于不同 DNA 链上时，称为 T790M/C797S 反式突变[8]。还有部分奥西替尼耐药的患者在发生了 C797S 突变以后，原有的 T790M 突变丢失[9]。另外的 EGFR 靶基因修饰还有 L747S 突变、D761Y 突变、L792F/H 突变、L718Q 突变、G796S/R 突变等[10] [11] [12] [13] [14]。其他旁路激活主要有 MET 扩增、HER2 扩增、AXL 激活、PIK3CA 激活、IGF1R 激活、BRAF 激活、RAS 突变、FGFR 扩增、MAPK 激活等[15]-[22]。MET 扩增是较常见旁路激活通道，约占 EGFR-TKI 获得性耐药的 5%~10%，可见于吉非替尼、厄洛替尼、阿法替尼、奥西替尼的耐药。扩增的 MET 基因可以通过 ERBB3/PI3K/Akt 信号通路来介导 EGFR-TKI 的耐药[23]。组织表型转变主要包括肺腺癌转变成小细胞肺癌(Small cell lung cancer, SCLC)或肺鳞癌和上皮间质转化(Epithelial-mesenchymal transition, EMT)。SCLC 转化见于大约 5%的耐药患者[24]。Niederst 等[25]通过研究 EGFR-TKI 耐药患者的肿瘤和细胞样本发现，所有转换成 SCLC 的样本都没有 RB 的表达。RB 基因又叫成视网膜细胞瘤基因，它是世界上第一个被克隆和完成全序列测定的抑癌基因。由于原发性 SCLC 中存在 RB 基因的缺乏，所以 RB 的丢失可能是肺腺癌患者在 EGFR-TKI 获得性耐药后转变为 SCLC 的原因之一。AXL 激酶、TGF-IL6 等的激活可能是 EMT 形成的原因[18] [26]。

4. 第一、二代 EGFR-TKI 耐药后的治疗

第一代 EGFR-TKI 主要包括吉非替尼、厄洛替尼、埃克替尼，第二代 EGFR-TKI 主要包括阿法替尼、达克替尼。一代 EGFR-TKI 主要针对 19 外显子缺失、21 外显子 L858R 点突变等。二代 EGFR-TKI 对 EGFR 的 G719X、S768I 和 L861Q 等罕见突变位点有较好的效果。在临床上二代 TKI 并没有明显优于一代 TKI 且副作用更大，况且一代 TKI 出现耐药后，二代 TKI 也不能克服耐药，因此二代 TKI 临床运用范围比较有限。

4.1. 局部进展

局部进展包括非 CNS 的微进展和只有 CNS 进展的豁免进展。CNS 豁免进展的目前的主要治疗方案包括：手术切除、手术切除 + 全脑放射治疗(Whole brainradiation therapy, WBRT)、立体放射外科治疗(Stereotactic Radiosurgery, SRS)、WBRT 辅助治疗(手术切除或 SRS 以后)、继续 TKI 单药治疗、TKI + WBRT、TKI + 鞘内化疗等[27] [28] [29] [30] [31]。非 CNS 的微进展一般指原发灶进展或者非 CNS 有限位点进展。微进展后一般采用局部病灶手术切除、立体定向放疗或者继续使用 EGFR-TKI [32] [33]。ASPIRATION 研究[34]纳入的 207 例肺腺癌患者中 171 例出现了无进展生存期(Progression free survival, PFS)终点，其中 93 例在厄洛替尼进展后继续使用厄洛替尼治疗，这些患者的中位 PFS1 和 PFS2 分别为 11.0 个月(95% CI, 9.2~11.1)和 14.1 个月(95% CI, 12.2~15.9)；客观缓解率(Overall response rate, ORR)为 66.2%；中位总生存期(Overall survival, OS)为 31.0 个月(95% CI, 27.3-未达到)。对于局部进展后的患者，继续 TKI 治疗也是可行的策略。有研究表明在使用 TKI 达到局部进展以后继续 TKI 联合局部治疗可以使 PFS 延长 6 个月以上[4]。

4.2. T790M 突变

对于全身性进展的患者，局部治疗难以奏效，此时就需要寻求靶向治疗、免疫治疗或者全身放化疗。研究显示未经治疗的 NSCLC 患者标本中出现 T790M 阳性突变的概率大约为 3.6%，而经过吉非替尼、厄洛替尼或阿法替尼治疗耐药以后的 NSCLC 患者，其阳性率达到 50%以上。由此可见 T790M 突变与 TKI 耐药有很大的相关性[35] [36]。第三代 EGFR-TKI 奥西替尼在 T790M 突变阳性的耐药患者中发挥了显著

的效果。AURA2 期扩展研究[37]纳入 201 例经一、二代 TKI 治疗后进展并携带 T790M 突变的患者，对其中的 198 例进行了疗效评估，ORR 为 62% (95% CI, 54%~68%)，疾病控制率 (Disease control rate, DCR)为 90% (95% CI, 85~94)，中位 PFS 为 12.3 个月(95% CI, 9.5~13.8)，122 位患者的中位缓解持续时间(Duration of response, DOR)为 15.2 个月(95% CI, 11.3-未达到)。

4.3. MET 扩增

MET 扩增是引起 EGFR-TKI 获得性耐药比较常见的旁路激活突变，MET 的抑制剂主要有卡马替尼(capmatinib, INC280)、卡博替尼(cabozantinib, xl184)等。Wu 等[38]的一项 Ib/II 临床研究表明：在 TKI 耐药以后携带 MET 扩增的患者后续吉非替尼联合卡马替尼治疗的 ORR 达 27%，在 MET 基因拷贝数 ≥6 的这一批患者中 ORR 达到 47%，中位 PFS 为 5.45 个月(95% CI, 3.71~7.10)。另一项关于卡博替尼的临床研究显示 EGFR-TKI 获得性耐药后 TKI 联合卡博替尼的中位 PFS 达到了 4.7 个月[39]。因此对于 TKI 获得性耐药以后携带 MET 扩增的患者 TKI 联合 MET 抑制剂是可行的选择。另外对于同时携带 MET 扩增和 T790 突变的患者可以用奥西替尼联合 MET 抑制剂来治疗。

4.4. HER2 扩增

人表皮生长因子受体-2 (Human Epidermal GrowthFactor Receptor 2, HER2)是一种原癌基因。阿法替尼是多靶点蛋白激酶不可逆抑制剂，属于第二代 EGFR-TKI，同时它还是 HER2 的抑制剂之一[40]。Landi 等[41]的一项临床研究指出吉非替尼、厄洛替尼治疗进展后出现 HER2 突变的这部分患者接受阿法替尼治疗的中位 PFS 为 3.9 个月。

4.5. PIK3CA 激活突变

PIK3CA 基因编码的蛋白是 PI3Ks 的催化亚单位，PI3Ks 是一种脂激酶。PIK3CA 基因的突变可以导致 PI3Ks 的催化活性异常增强，促使细胞发生癌变。PIK3CA 激活突变主要通过 PI3K/PTEN/AKT 信号通路来产生 TKI 的获得性耐药[42]。Buparlisib (BKM120)是 PIK3 的抑制剂，有关研究表明在 TKI 获得性耐药后 BKM120 联合吉非替尼的 PFS 为 2.8 个月，但研究只纳入 10 例进行研究，因此 BKM120 的临床价值还有待进一步研究[43]。

4.6. AXL 激活突变

AXL 是一种调控多个下游信号通路的受体酪氨酸激酶，它在肿瘤的增殖、入侵、迁移、上皮间质细胞转化(EMT)、肿瘤血管生成以及肿瘤微环境中的免疫调节等过程中发挥重要的作用。有研究表明 AXL 激酶的激活可以引起 TKI 获得性耐药[18]。Bemcentinib (R428, BGB324)是一种 AXL 抑制剂，关于 AXL 激活突变所致的 TKI 耐药的临床研究正在进行中[44]。

4.7. 无相应靶点

当 TKI 获得性耐药后检测不到新增靶点时，化疗、抗血管生成治疗、三代 TKI、免疫治疗等都是可用的选择。有研究认为 TKI 耐药后化疗联合 TKI 不仅不能使患者生存获益，而且还会增加毒副作用[45]。Johnson 等[46]认为在不考虑突变靶点的情况下，热休克蛋白 90 (HSP90)的抑制剂 AUY922 联合吉非替尼可以使 TKI 耐药的患者缓解获益。

4.8. 转变为小细胞肺癌或肺鳞癌

TKI 获得性耐药部分肺腺癌的患者转变为 SCLC 或肺鳞癌，后续的治疗一般为化疗或者放疗。SCLC

一般采用 EP 方案(依托泊苷 + 顺铂)，肺鳞癌为 GP 方案(吉西他滨 + 顺铂)。另外抗血管生成治疗、免疫治疗或与化疗联合治疗都是可选方案。

5. 第三代 EGFR-TKI 耐药后的治疗

第三代 EGFR-TKI 是不可逆的酪氨酸激酶抑制剂，主要代表是奥西替尼(osimertinib)，又称泰瑞沙或 AZD9291。AURA 的一系列临床研究已经证明了奥西替尼的卓越效果，FLAURA 研究[47]也证实了奥西替尼作为一线治疗的优势。第三代 EGFR-TKI 局部进展后的治疗方案与第一、二代相似，在此不再赘述。

5.1. C797S 突变

C797S 突变是奥西替尼耐药后较常见的突变，有 T790M/C797S 顺式突变及反式突变之分，有些患者在耐药后出现 T790M 丢失的情况。Wang 等[48]的研究指出布加替尼联合西妥昔单抗可以使奥西替尼耐药后出现 T790M/C797S 顺式突变这一部分患者获益。西妥昔单抗(Cetuximab)属于嵌合型 IgG1 单克隆抗体，分子靶点为 EGFR，布加替尼(Brigatinib)是间变性淋巴瘤激酶(anaplastic lymphoma kinase, ALK)的抑制剂。二者联合治疗后的 ORR 为 60%，中位 PFS 为 14 个月。本研究虽然病例数较少，但也给 T790M/C797S 顺式突变的这部分患者带来希望。部分个案研究表明对于 T790M/C797S 反式突变，联合一代 EGFR-TKI 和三代 EGFR-TKI 有不错的效果[49] [50]。对于奥西替尼耐药后出现 T790M 丢失的这部分患者也有使用一代 EGFR-TKI 进行治疗的案例，大型的临床研究也处于入组阶段。

5.2. MET 扩增

MET 介导的 TKI 突变大多是由于扩增引起的，三代 TKI 耐药发生后也可以发生 MET 扩增。沃利替尼(Savolitinib)是 MET 的抑制剂之一，Sequist 等[51]的一项多中心临床研究中携带 MET 突变的 69 例奥西替尼耐药患者经 Savolitinib 联合奥西替尼治疗后的 ORR 为 30%，中位 PFS 为 5.4 个月。Amivantamab (JNJ-372)是 EGFR-MET 双抗，在一项临床研究中 Amivantamab 联合三代 TKI 效果显著，58 例 EGFR 三代药耐药患者总有效率为 28%，27 例 EGFR 20 外显子插入突变患者的总有效率为 30% [52]。

5.3. HER2 扩增或突变

HER2 是奥西替尼耐药后出现的突变之一，其中大部分为 HER2 扩增，目前有几项关于克服 TKI 耐药后 HER2 突变的临床研究正在进行中。恩美曲妥珠单抗(T-DM1)是 HER2 的靶向药，Peters 等[53]的一项研究中，部分患者为 TKI 耐药并 HER2 过表达的患者，T-DM1 能够使这部分患者获益。HER2 的 16 外显子跳跃突变是新发现的奥西替尼耐药的机制之一，阿法替尼在显示对这类患者有效[54]。

5.4. Kras 突变

Kras 是一种鼠类肉瘤病毒癌基因，正常的 Kras 基因可抑制肿瘤细胞生长和发展。一旦发生突变，就会持续刺激细胞生长从而导致肿瘤的发生。奥西替尼耐药的部分患者也检测到了 Kras 突变，它主要通过 RAS-MAPK 通路来促进耐药。这个突变尚无明显有效靶向药物，不过丝裂原活化蛋白激酶激酶(MEK)抑制剂可以抑制这个通路[55]。TATTON 研究中，司美替尼(Selumetinib)联合奥西替尼对于 TKI 耐药的患者有效，Selumetinib 是 MEK 抑制剂，纳入的 36 例患者的 ORR 为 42% [56]。

5.5. BRAF 突变

BRAF 基因是一种原癌基因，编码 RAF 家族丝氨酸/苏氨酸蛋白激酶，该蛋白在调节 MAPK/ERK 信号通路中起作用，参与细胞分裂，分化等，一旦发生了突变，身体就易于患癌。V600E 是 BRAF 基因最

容易癌变的一个位点。Ho 等[15]指出 BRAF V600E 是奥西替尼获得性耐药的机制之一，从他们的一项体外细胞试验来看 BRAF V600E 的抑制剂康奈非尼(Encorafenib)联合奥西替尼能够很好地抑制奥西替尼耐药后体外肿瘤组织细胞的生长，为临床研究奠定细胞学基础。

5.6. RET 融合

RET 是一种原癌基因，它可以编码一种称为 RET 的跨膜蛋白，该蛋白属于一种受体酪氨酸激酶。RET 蛋白发挥生物学作用的信号通路包括 PI3K-AKT-mTOR 途径以及 RAS-RAF-MEK-ERK 途径。RET 基因发生突变可造成细胞过度增殖，进而导致肿瘤的发生发展。Xu 等[57]的一项研究回顾性分析了 3873 例 EGFR 突变的肺癌患者的基因检测资料，发现 6 例患者出现 RET 融合，而这六例患者都是使用奥西替尼耐药以后出现的 RET 融合。卡博替尼(Cabozantinib)是 VEGFR2、MET、RET 的强效抑制剂，一项二期临床研究[58]纳入 26 例 RET 重排(其中 16 例 RET 融合)的肺腺癌患者，使用 Cabozantinib 后 25 例产生反应，ORR 为 28%。因此对于奥西替尼耐药后出现 RET 融合的患者 Cabozantinib 有一定的应用前景。普雷西替尼(Pralsetinib, BLU-667)也是对 RET 融合有靶向作用的新药，Piotrowska 等[59]分析了 41 例奥西替尼耐药患者标本，其中包括 2 例 RET 融合。在体外用 BLU-667 处理以后细胞以后，携带 RET 融合的细胞再次对奥西替尼产生反应。后续又用 BLU-667 联合奥西替尼治疗这两例患者，最终都产生了影像学反应且不良反应可耐受。

5.7. 无相应靶点

奥西替尼治疗后无明确靶点或者出现无特定抑制剂的罕见靶点时，可以选择化疗、抗血管生成(单药或者联合化疗)、免疫单药或者免疫联合化疗与抗血管生成等。雷莫芦单抗(Ramucirumab)是抗血管生成药物，它是血管内皮细胞生长因子受体 2 (Vascular Endothelial Growth Factor Receptor 2, VEGFR2)的拮抗剂，它联合奥西替尼的一项 I 期临床研究结果显示二者联合有广阔应用前景[60]。Patritumab Deruxtecan (U3-1402)是 HER3 的抗体药物偶联物(antibody-drug conjugate, ADC)，一项体外研究表明 U3-1402 能够明显抑制奥西替尼耐药细胞系[61]。2019 年世界肺癌大会上的一项研究数据显示，I 期临床的 30 名 EGFR 突变的晚期 NSCLC 患者中既有第一、二代治疗后耐药的，也有第三代耐药的，而且部分患者耐药后无相应的靶点。U3-1402 对 TKI 耐药患者的疾病控制率达 95.7% (23 例可评估的患者中 22 例患者的病灶缩小)。目前一项评估 U3-1402 与奥希替尼联合治疗 EGFR 突变的晚期或转移性 NSCLC 患者的临床试验已经展开。

5.8. 转变为小细胞肺癌或肺鳞癌

第三代 TKI 奥西替尼耐药后也会转变为小细胞肺癌或肺鳞癌，只是几率比第一、二代要低[62] [63]。奥西替尼耐药转变为 SCLC 或鳞癌的患者在选择标准放化疗的同时还可以行组织表本的基因检测，如果患者依然保留 EGFR 突变，尤其是有脑转移的患者，化疗联合奥西替尼可能会使这部分患者获益。

6. 小结与展望

EGFR-TKI 是目前携带 EGFR 突变的晚期肺腺癌患者的一线治疗方法，一线治疗耐药后对其耐药原因进行研究有重要意义。肺腺癌患者的驱动基因突变率比较高，靶向治疗不仅延长了肺腺癌患者的生命，而且也大大提高了他们的生活质量。用于克服奥西替尼耐药的第四代 EGFR-TKI 也已处于临床试验阶段，随着对驱动基因及其耐药机制的不断研究以及各大临床实验的不断推广，针对晚期肺腺癌治疗的策略也会越来越多。将肺癌患者个体化治疗与综合治疗相结合，相信在不久的将来，肺癌一定能成为像高血压、糖尿病一样的慢性病。

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