

• 综述 •

非小细胞肺癌 EGFR-TK 非经典突变临床研究进展*

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[摘要] 目前已发现 594 种表皮生长因子受体(epidermal growth factor receptor, EGFR)突变类型, 其中 95% 以上的突变存在于编码酪氨酸激酶结构域的基因的 18~21 号外显子中。在总突变中, Del19(19 号外显子缺失突变)与 L858R(21 号外显子点突变)突变约占 84.60%, 被确认为 EGFR-TK 敏感突变。其余突变包括: G719X(18 号外显子点突变), E709X(18 号外显子点突变), Del18(18 号外显子缺失突变), Ins19(19 号外显子插入突变), Ins20(20 号外显子插入突变), L861Q(21 号外显子点突变)等为非经典突变, 约占总突变形式的 12.10%。非小细胞肺癌(non-small cell lung cancer, NSCLC) EGFR 各类型非经典突变对不同 EGFR-TKIs 治疗的反应差别很大, 因此, 了解 EGFR 非经典突变对靶向治疗的反应, 对存在非经典突变的 NSCLC 患者的治疗具有重大意义。本文对 NSCLC 各个 EGFR 非经典突变的类型及针对此类突变的靶向治疗进展进行综述, 以为临床治疗提供参考。

[关键词] 表皮生长因子受体; 表皮生长因子受体酪氨酸激酶抑制剂; 非小细胞肺癌; 非经典突变

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Clinical Research Advances in Uncommon EGFR-TK Mutation in Non-Small Cell Lung Cancer

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[Abstract] At present, there are 594 types of epidermal growth factor receptor (EGFR) mutations, of which more than 95% exist in exon 18-21 of the gene encoding tyrosine kinase (TK) domain. The mutations of Del19 and L858R account for 84.60% of the total mutations and are considered to be EGFR-TK sensitive mutations. Other mutations include G719X, E709X, Del18, Ins19, Ins20, L861Q, etc. which are uncommon mutations, accounting for 12.10% of the total mutations. The response of uncommon EGFR mutations in non-small cell lung cancer (NSCLC) to EGFR-TKIs treatment varies greatly. Therefore, it is of great significance to understand the response of uncommon EGFR mutations to targeted therapies for NSCLC patients with uncommon mutations. In order to provide experience for clinical treatment, the types of uncommon EGFR mutations and targeted therapies aiming to those mutations were reviewed in this paper.

[Key words] Epidermal growth factor receptor; Epidermal growth factor receptor tyrosine kinase inhibitors; Non-small cell lung cancer; Uncommon mutation

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肺癌是目前对全人类生命健康威胁最大的恶性肿瘤之一^[1-2]。肺癌按照组织学类型分为小细胞肺癌及非小细胞肺癌(non-small cell lung cancer,

NSCLC), 其中 80% ~ 85% 肺癌为 NSCLC^[3]。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) Gefitinib 于 2003 年被美国食品药品监督管理局批准用于治疗晚期 NSCLC^[4], 该类药物通过抑制酪氨酸酶磷酸化达到抑制肿瘤生长及延长晚期 NSCLC 患者无进展生存期 (progress-free survival, PFS) 的效果^[5-6]。EGFR 敏感突变患者可接受 EGFR-TKIs 治疗^[7-8]。在亚洲, 此类患者约占 NSCLC 患者总人数的 50%^[9]。19 号外显子的缺失突变 (Del19) 和 21 号外显子点突变 (L858R) 约占 EGFR 总突变的 84.60%, 此二类突变类型已被确定为 TK 敏感突变。除敏感突变外, 发生在 18 ~ 21 号外显子中的其他突变被称为非经典突变, 约占总 EGFR 突变的 12.10%^[10]。EGFR-TKIs 在晚期 EGFR 敏感突变类型的 NSCLC 患者中的疗效显著在多项临床实验中被证实^[11-12]。由于 EGFR 非经典突变的 NSCLC 患者突变率低, 其靶向药物治疗方案缺乏高级别循证医学数据支持, 而各类 EGFR 非经典突变对各类 EGFR-TKIs 治疗结局差别巨大^[13]。因此针对 EGFR 非经典突变的相关研究具有重要的医学价值。

1 EGFR 突现状

EGFR 基因突变约 95% 以上发生在 18 ~ 21 号外显子中, 约 3.30% 发生在其他外显子中。在 18 ~ 21 号外显子突变中, 敏感突变约占 84.60%, 18 号外显子非经典突变约占 3.70%, 19 号外显子非经典突变约占 0.60%, 20 号外显子非经典突变约占 6.90%, 21 号外显子非经典突变约占 0.90%^[10,14-15] (图 1)。

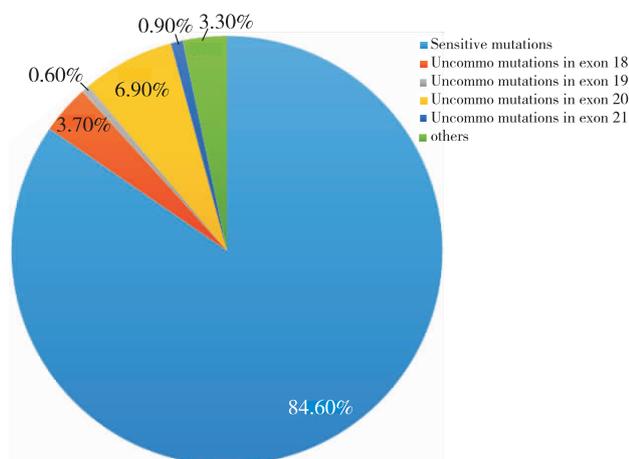


图 1 EGFR 基因突变形式构成比
Figure 1. Constituent Ratio of EGFR Gene Mutation

Forms

2 EGFR 非经典突变基因相关研究

2.1 18 号外显子相关研究

18 号外显子非经典突变主要表现为密码子 G719X、E709X 点突变与密码子 709 处缺失突变^[13]。

2.1.1 G719X 突变 EGFR 中的 G719X (X 表示 A, S, C 等) 突变是指点突变, 导致 719 位的甘氨酸被其他残基取代, 分别为丙氨酸 (G719A), 丝氨酸 (G719S), 半胱氨酸 (G719C)。G719X 突变约占总 EGFR 突变的 3.10%^[10]。Choi 等^[16-18]发现 G719S 突变致瘤性较敏感突变弱, 并在体外实验中进一步发现 Gefitinib 能以增加剂量的方式抑制 G719S 的自身磷酸化。与敏感突变 L858R 相比, Gefitinib 需要以更高的浓度抑制 G719S 突变^[19]。在临床实验中, Chiu 等^[20]发现在 G719X 突变患者中, 口服一代 TKIs (包括 Gefitinib 与 Erlotinib) 的客观缓解率 (objective remission rate, ORR) 和疾病控制率 (disease control rate, DCR) 分别为 36.8% 和 72.4%, 证实了 G719X 突变较敏感突变相比更低的中位生存时间 (6.3 月 vs 11.1 月)。Otsuka 等^[21]报道在接受一代 TKIs 治疗的 G719X 突变患者中, 接受 Erlotinib 治疗较接受 Gefitinib 治疗的患者拥有更长的 PFS。二代 TKIs 中 Neratinib 在 G719X 突变类型的患者中表现出显著的疗效, 3/4 的 G719X 突变患者表现出部分缓解, 肿瘤直径缩小超过 50%, ORR 为 75%, DCR 为 100%, 但由于其对 EGFR 敏感突变患者无效, 因此, Neratinib 在肺癌治疗中的地位仍不确定^[22-23]。此外, Yang 等^[24]在 LUX-Lung 试验系列中发现, 接受 Afatinib 治疗的 G719X 突变患者, ORR 为 77.8% (14/18)。表明二代 TKIs 在 G719X 突变患者中较一代 TKIs 拥有更加显著的疗效。

2.1.2 E709X 突变 E709X 点突变为 18 号外显子的另一非经典突变, E709X 突变约占总 EGFR 突变的 0.30%^[10]。其对一代 TKIs 疗效反应较敏感突变低, Wu 等^[25]学者研究发现: 在接受一代 TKIs 治疗的 25 例 E709X 突变患者中对 EGFR-TKIs 的 DCR 为 72.2% (13/18), 中位 PFS 为 6.2 月 (范围 0.6 ~ 77.4 月), 中位总生存期为 29.3 月 (范围 5.4 ~ 104.6 月)。在体外实验中, 与一代或三代 TKIs 相比, E709X 点突变患者对 Afatinib 或 Neratinib 具有高度敏感性^[13]。

2.1.3 DelE709-T710insD Del E709-T710insD 是

密码子 709 处最常见的缺失突变^[13], 约占总 EGFR 突变的 0.30%^[10]。目前缺乏临床研究数据。Kobayashi 等^[13]的体外基础研究表明二代 EGFR-TKIs 较一代 TKIs 对 DelE709-T710insD 转染的 Ba/F3 细胞抑制作用更强。

2.2 19 号外显子相关研究

19 号外显子非经典突变表现为插入突变和点突变。

2.2.1 19 号外显子插入突变 19 号外显子插入突变约占 EGFR 突变的 0.60%^[10], 包括: I744-K745ins-KIPVAI、K745-E746insIPVAIK、K745-E746insVPVAIK、K745-E746insTPVAIK。目前缺乏临床试验数据。体外试验均显示 19 号外显子插入突变对 Afatinib 敏感^[10]。

2.2.2 19 号外显子点突变 D761Y 19 号外显子点突变主要表现为 D761Y, 有研究认为它的出现可能与 EGFR-TK 耐药相关, 但耐药程度弱于 20 号外显子点突变 T790M^[26-27]。目前缺乏临床试验数据。

2.3 20 号外显子相关研究

20 号外显子非经典突变主要表现为插入突变与点突变。

2.3.1 20 号外显子插入突变 20 号外显子插入突变包括: V769-D770insASV、D770-N771insSVD、H773-V774insH、A763-Y764insFQEA、H773-V774insPH、H773-V774insNPH、N771-P772insH、H771-P772insN、H773-V774insAH、D770delinsGY、V774-C775insHV。以上突变约占总 EGFR 突变的 5.80%^[10, 28-29]。除 A763-Y764insFQEA 外, EGFR20 号外显子插入突变对一、二代 TKIs 靶向治疗不敏感^[30-31]。研究发现 A763-Y764insFQEA 突变在体外实验中可被亚微摩尔浓度的一代 TKIs 抑制。3 例携带 A763-Y764insFQEA 突变的 NSCLC 患者经每日 150 毫克 Erlotinib 治疗后, 影像学表现病灶缩小或稳定。因此, 有研究者认为 A763-Y764insFQEA 是 EGFR-TK 敏感突变^[32]。

在最新体外实验中发现, Pozitotinib 有效抑制了具有 EGFR20 号外显子插入突变的 Ba / F3 细胞系的生长。Pozitotinib 在具有 EGFR20 号外显子插入突变的 Ba / F3 细胞系中平均 IC50 值(50% 的抑制浓度)为 1.0nM, 使得 Pozitotinib 较 Osimertinib 疗效增强约 100 倍, 并且在体外比 Afatinib 强 40 倍。在 Pozitotinib 的 II 期临床试验中, 起始剂量为每日口服 16mg, 超过半数(55%) 患者接受剂量减少, 最常见的不良事件为: 皮疹和腹泻。根据实体瘤反应评估

标准(Response Evaluation Criteria in Solid Tumors, RECIST)1.1, 11 名患者 ORR 为 64%。虽然临床数据尚未成熟, 但截至 2018 年 1 月, 11 例患者中 5 例有疾病进展, 尚未达到中位 PFS^[33]。针对 EGFR20 号外显子插入突变的氨基甲酸酯类药物正在研发中, 其在携带 EGFR20 号外显子插入突变的 Ba/F3 细胞和 EGFR P772-H773insPNP 患者衍生的肺癌细胞系 DFCH127 中表现出优异的抑制信号传导作用^[34]。体外研究报道, EGFR20 号外显子插入突变对 Osimertinib 敏感^[35], 但仍缺乏临床试验数据。

2.3.2 20 号外显子点突变 20 号外显子点突变主要为: S768I, 约占总 EGFR 突变的 1.10%^[10]。在体外实验中, S768I 突变对 Afatinib 较 Osimertinib 更敏感^[36]。在 LUX-Lung 2、3 和 6 试验的联合分析中, 接受 Afatinib 治疗的 S768I 突变患者, ORR 为 100%, 中位 PFS 为 14.7 个月^[24]。

2.3.3 20 号外显子耐药突变 T790M 20 号外显子中 T790M 点突变的发生率可高达 50%^[37], 但在新诊断的患者中很少发现突变^[38]。T790M 为 EGFR-TKIs 治疗的耐药突变已经被证实, 排除非经典突变范围^[32]。

2.4 21 号外显子相关研究

21 号外显子非经典突变主要表现为点突变 L861Q, 约占总 EGFR 突变的 0.90%^[10, 39-40]。L861Q 突变是由 21 号外显子第 2828 位点的 T 被 A 取代所致, 具有类似于 L858R 突变的致癌活性^[35]。日本的一项多中心回顾性研究显示 L861Q 突变患者接受一代 EGFR-TKIs 的 ORR 为 37.5%、DCR 为 87.5%^[21]。Yang 等^[24]的 LUX-Lung 试验系列研究中, 16 例 L861Q 突变患者使用 Afatinib 的 ORR 为 56.3%、PFS 为 8.2 个月、OS 为 17.1 个月, 显示与一代 EGFR-TKIs 比较, 二代 Afatinib 疗效更佳, 可以获得更长的 PFS 和更高的 ORR。对于第 3 代的 EGFR-TKIs, Banno 等^[36]体外研究发现 L861Q 突变对于 Osimertinib 敏感, 但目前缺少临床试验数据。

3 小结

总之, NSCLC 中, 由于非经典突变发生率低, 针对非经典突变的研究缺乏高等级循证医学数据支持, 但目前研究表明其客观有效率及无进展生存期较敏感突变对 EGFR-TKIs 反应低且对各种 EGFR-TKIs 反应差别较大。根据 EGFR 非经典突变靶向治疗的疗效制定治疗方案, 对这类 NSCLC 患者的治疗尤为重要。目前, 针对 Ins20 非经典突变的新药

研究有重大进展,为非经典突变患者带来了更多的生存希望。当前,精准治疗已经是肿瘤的治疗模式之一,非经典突变的治疗对不同 EGFR-TKIs 治疗反应差别较大且当 TKIs 治疗失败后,不同非经典突变类型患者的后续治疗方案是否有所差异,仍需我们继续探索。但随着检测手段的多样化及简易化,可实现动态监测患者基因状态,为临床靶向治疗提供了坚实的精准治疗证据及后续治疗选择。随着更多检测方法的应用,例如高通量测序,越来越多的非经典突变及复合突变被发现,这对临床医生提出了更大挑战,如何给予患者更加适合的靶向治疗选择仍需我们进一步深入研究。

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