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埃克替尼对非小细胞肺癌*EGFR* 18外显子突变的临床疗效

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[摘　要] **目的：**探讨埃克替尼对非小细胞肺癌(non-small cell lung cancer，NSCLC)*EGFR* 18外显子G719X/E709X/G724S的临床疗效。**方法：**回顾性分析24例埃克替尼治疗*EGFR* 18外显子少见突变的NSCLC患者，服用至病情进展或出现不可耐受的毒副作用，比较疗效。**结果：**24例G719X/E709X/G724S突变患者中G719X突变19例，中位无进展生存时间2.8个月，E709X突变3例，中位无进展生存时间3.1个月，G724S突变2例，中位无进展生存时间3.5个月。G724S突变患者生存时间稍长。复合突变与单纯突变相比，复合突变中位无进展生存时间更长(G719X突变3.3个月vs. 2.6个月，*P*=0.029；E709X突变7.2个月vs. 2.7个月，*P*=0.225)。**结论：**埃克替尼在*EGFR*基因18外显子少见突变的疗效上比传统敏感突变未见明显优势，但复合突变比单纯突变临床获益更多。

[关键词] 非小细胞肺癌；埃克替尼；18外显子

Clinical efficacy of icotinib in patients with advanced non-small cell lung cancer harboring *EGFR* exon 18 mutations

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Abstract **Objective:** To investigate the efficacy of icotinib in patients with non-small cell lung cancer (NSCLC) that carrying G719X/E709X/G724S in *EGFR* exon 18. **Methods:** We retrospectively analysed 24 cases of *EGFR* 18 exon rare

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mutation NSCLC patients until the progress of the disease or the emergence of the side effects and clinical efficacy was observed after months followed-up. **Results:** Twenty-four patients with G719X/E709X/G724S mutations were enrolled. Mutations including G719X, E709X and G724S mutations were observed in 19, 3 and 2 patients, respectively. In total, the median progression-free survival (PFS) were 3.1 months, respectively. Patients with G724S mutation manifested the longest median PFS (3.5 months), followed by those with E709X (3.1 months) and G719X (2.8 months). Patients with complex mutations showed a better PFS than those with single mutations (G719X mutations 3.3 months vs. 2.6 months, *P*=0.029; E709X 7.2 months vs. 2.7 months, *P*=0.225). **Conclusion:** Icotinib is less effective in patients with exon 18 uncommon mutations than in those with common mutations. Patients with complex mutations benefited more from icotinib than those with single mutations.

Keywords non-small cell lung cancer; icotinib; exon 18

在世界范围内，肺癌是肿瘤相关性死亡的主要原因，其中非小细胞肺癌(non-small cell lung cancer，NSCLC)占80%~85%[1-3]。近年来随着精准医学的发展，*EGFR*基因突变改变了NSCLC治疗的临床实践[4]。在NSCLC患者中30%~60%的东亚人群和10%~20%的高加索人群存在*EGFR*基因突变[5-7]，*EGFR*基因突变的NSCLC优势人群主要在女性非吸烟的腺癌患者[8-9]，*EGFR*-TKIs抑制剂如吉非替尼，厄洛替尼或埃克替尼对*EGFR*基因突变的NSCLC高度敏感[10-11]，其中埃克替尼是浙江贝达药业有限公司自主研发。本研究回顾性分析埃克替尼对*EGFR*基因18外显子少见突变的临床疗效，并为后期大样本验证积累经验。

1 对象与方法

1.1 对象

1.1.1 纳入标准

1)经病理诊断确诊为NSCLC，经扩增受阻突变系统(amplification refractory mutation system，ARMS)方法或者二代测序(next-generation sequencing，NGS)方法检测为*EGFR* 18外显子少见突变；2)未接受过化疗或既往接受过化疗但已从任何一次化疗的毒性反应中恢复过来；3)根据实体瘤疗效评价标准(response evaluation criteria in solid tumors，RECIST)，至少含1个可测量病灶；4)年龄≥18岁，自愿签署知情同意书。

1.1.2 排除标准

1)本研究前曾确诊或者治疗过的其他恶性肿瘤；2)既往患有神经或精神病史；3)存在严重呼吸、心血管和肝肾疾病。

1.1.3 资料来源

本研究收集福建省肿瘤医院、浙江省肿瘤医院及武警浙江总队医院2013年7月至2016年11月间*EGFR* 18外显子G719X/E709X/G724S突变的晚期NSCLC患者24例，本研究经成员单位医院医学伦理委员会批准。

1.2 方法

给予埃克替尼125 mg，每天3次，直至出现任何疾病进展的客观证据，或发生不可耐受的不良事件。

1.3 研究因素与评价标准

研究因素包含年龄、性别、吸烟史、ECOG评分、TNM分期等。不吸烟定义是一生吸烟<100支。近期疗效评价：根据RECIST 1.1评价近期疗效，分为完全缓解(complete response，CR)、部分缓解(partial response，PR)、疾病稳定(stable disease，SD)和疾病进展(progressive disease，PD)。客观缓解率(objective response rate，ORR) =(CR+PR)/(CR+PR+SD+PD)×100%。疾病控制率(disease control rate，DCR)=(CR+PR+SD)/(CR+PR+SD+PD)×100%。每周复查血常规，每周期复查肝肾功能、心电图、B超及CT，每2个化疗周期评价疗效直至疾病进展。颅内病灶评估采用脑MRI，颅外病灶评估采用CT。

1.4 统计学处理

无进展生存期(progression-free survival，PFS)用Kaplan-Meier法进行分析，使用Log-rank法进行单因素预后分析，PFS指从埃克替尼治疗至第一次发生疾病进展或任何原因死亡的时间。所有统计使用SPSS 19.0统计软件进行分析。

2 结果

2.1 临床病理特征

总计3 279例NSCLC患者采用ARMS方法

或NGS方法进行*EGFR*基因检测，其中*EGFR*阳性患者1 347例(1 347/3 279，41.08%)，73例*EGFR*基因18外显子突变患者中24例服用埃克替尼，临床病理特征见表1，男性女比例接近1:1，年龄以65岁以下居多，有吸烟史患者略少于未吸烟患者，PS评分以0~1为主，组织亚型以腺癌为主，突变类型：G719X 19例(G719S+S768I 1例，G719A 1例，其余17例小试剂盒未分亚型)，E709X 3例(E709_T710>D 1例，E709A 1例，E709K+L858R 1例)，G724S 2例，埃克替尼治疗在三线以上占绝大多数，分期以IV期为主(表1~2)。

表1 24例埃克替尼治疗*EGFR*基因18外显子突变的非小细胞肺癌临床特征

Table 1 Clinicopathologic characteristics of 24 cases of patients with *EGFR* exon 18 mutations treated by icotinib

临床病理特征	例数
性别	
男	14
女	10
年龄/岁	
<65	16
≥65	8
吸烟史	
是	7
否	17
PS评分	
0~1	17
2~3	7
组织亚型	
腺癌	24
非腺癌	0
突变类型	
G719X	20
E709X	2
G724S	2
埃克替尼治疗	
一线	1
二线	2
三线及以上	21
分期	
IIIB	4
IV	20

表2 24例埃克替尼治疗的*EGFR*基因18外显子突变的非小细胞肺癌具体亚型

Table 2 Specific subtype of 24 cases of patients with *EGFR* exon 18 mutations whom were therapy by icotinib

突变类型	例数(%)
G719X	19 (79.17)
单纯型	10 (41.67)
G719X+S768I	8 (33.33)
L861Q+G719X	1 (4.17)
E709X	3 (12.50)
单纯型	2 (8.33)
E709X+L858R	1 (4.17)
G724S	2 (8.33)
G724S+S768I	1 (4.17)
G724S+S768I+V769M	1 (4.17)

2.2 疗效分析

埃克替尼对*EGFR*基因18外显子突变的NSCLC治疗效果数据显示：ORR和DCR分别为33.33%和75.99%，在这些患者中，未见CR患者，PR共计8例，SD共计10例，中位PFS为3.1个月。亚组分析中埃克替尼对*EGFR* 18外显子G719X单纯突变与复合突变的PFS(2.6个月vs. 3.3个月，P=0.029)，E709X单纯突变与复合突变的PFS(2.7个月vs. 7.2个月，P=0.225) (表3，图1~8)。

表3 埃克替尼对非小细胞肺癌*EGFR*基因18外显子的疗效分析

Table 3 Clinical efficacy of icotinib with advanced non-small-cell lung cancer harboring *EGFR* exon 18 mutations

突变类型	*n*	CR	PR	SD
G719X	19	0	6	8
E709X	3	0	2	0
G724S	2	0	0	2

突变类型	PD	ORR/%	DCR/%	PFS/月
G719X	5	31.58	73.68	2.8
E709X	1	66.66	66.66	3.1
G724S	0	0	100.00	3.5

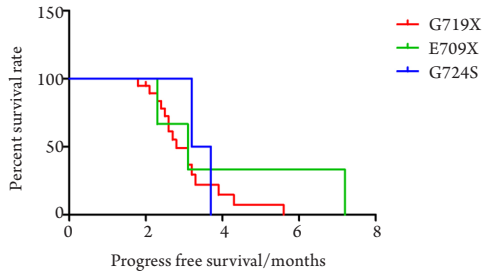

图1 埃克替尼对*EGFR* 18外显子的PFS(*P*=0.441)

Figure 1 PFS of *EGFR* 18 exon by icotinib (*P*=0.441)

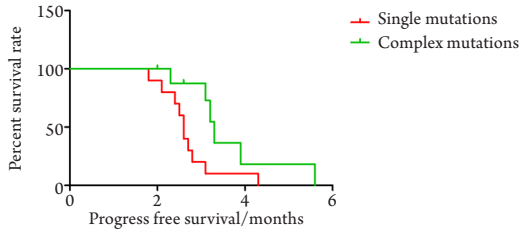

图2 埃克替尼对*EGFR* 18外显子G719X单纯突变与复合突变的PFS(*P*=0.029)

Figure 2 PFS comparison between patients harboring *EGFR* exon 18 G719X single mutations and complex mutations by icotinib (*P*=0.029)

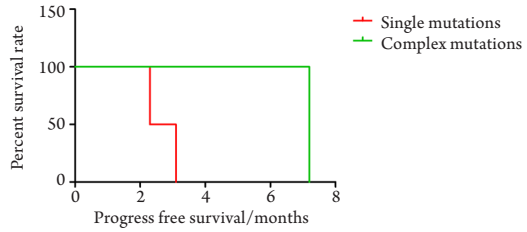

图3 埃克替尼对*EGFR* 18外显子E709X单纯突变与复合突变的PFS(*P*=0.225)

Figure 3 PFS comparison between patients harboring *EGFR* exon 18 E709X single mutations and complex mutations by icotinib (*P*=0.225)

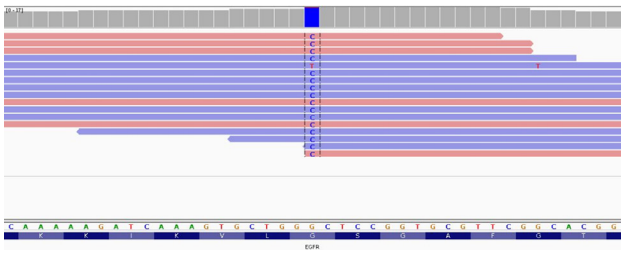

图4 *EGFR* G719A IGV图

Figure 4 IGV of *EGFR* G719A

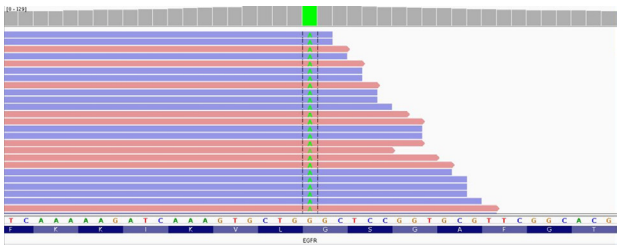

图5 *EGFR* G719S IGV图

Figure 5 IGV of *EGFR* G719S

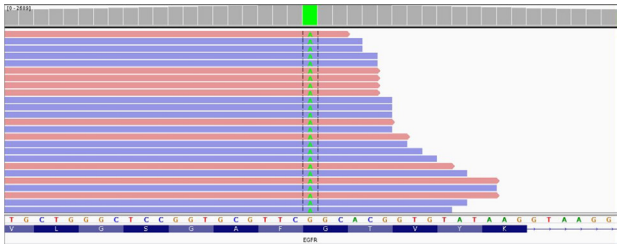

图6 *EGFR* G719C IGV图

Figure 6 IGV of *EGFR* G719C

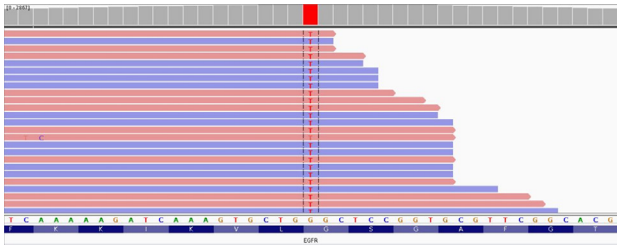

图7 *EGFR* E709A IGV图

Figure 7 IGV of *EGFR* E709A

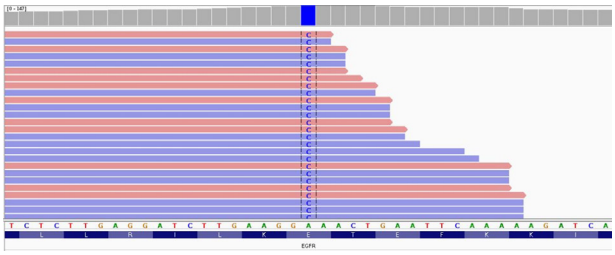

图8 *EGFR* G724S IGV图

Figure 8 IGV of *EGFR* G724S

3 讨论

*EGFR*基因突变最主要存在于18~21外显子的酪氨酸激酶区域，最主要类型是19外显子的缺失突变以及21外显子的L858R点突变[12-13]，其占*EGFR*基因突变的80%~90%[14-15]，少见突变中最常见的为18外显子G719X点突变，21外显子

L861Q点突变，它们对一代EGFR TKIs相对敏感，中位生存时间超过6个月以上。18外显子突变包括A671T，A702S，Q701L，I706T，L707X，E709X，G719X，S720F，G721C，G724S和T725T等，其中E709X，G719X和G724S最常见[16-21]。本研究中18外显子的突变占*EGFR*基因突变型5.42%(73/1 347)，与以往研究类似。

目前国际上均有一代或二代EGFR TKIs(吉非替尼，厄洛替尼或阿法替尼)治疗18外显子少见突变的报道，但未见埃克替尼的报道，Kobayashi等[18]报道阿法替尼或neratinib对G719X突变NSCLC的ORR(80%)优于一代EGFR TKIs(35%~56%)。Kuiper等[21]报道了10例G719X突变的NSCLC，7例患者服用阿法替尼，疗效分析PR 1例(PFS：24.6个月)，SD 3例(PFS：2.6，6.4，10.0个月)，PD 3例(0.2，0.8，2.3个月)。Chiu等[22]报道78例G719X，9例G719X+L861Q和10例G719X+S768I发现：ORR分别为36.8% vs. 88.9% vs. 50.0%，DCR分别为72.4% vs. 100.0% vs. 100.0%。本研究选择*EGFR*-TKIs埃克替尼治疗G719X突变发现：埃克替尼对*EGFR* 18外显子G719X单纯突变与复合突变的PFS(2.6个月vs. 3.3个月，*P*=0.029)。

Wu等[19]报道了18例E709X突变的ⅢB/Ⅳ期腺癌NSCLC，服用一代EGFR TKIs(吉非替尼，厄洛替尼)。Kuiper等[21]报道了5例E709X突变的NSCLC，4例患者服用阿法替尼，疗效分析PR 2例(PFS：12.2个月，16.7个月)，SD 2例(PFS：0.8个月，7.1个月)，PD 3例(0.2个月，0.8个月，2.3个月)。本研究中埃克替尼治疗E709X突变发现：*EGFR* 18外显子E709X单纯突变与复合突变的PFS(2.7个月vs. 7.2个月，*P*=0.225)。

目前国内外未见EGFR TKIs用于G724S突变NSCLC患者的治疗，临床前研究[23]发现西妥昔单抗对G724S突变结直肠癌敏感，本研究发现G724S突变2例且均为复合突变，疗效评价SD，中位PFS 3.5个月。

本研究局限性在于入选患者由于基因检测公司选择的不同，导致基因结果会有部分差异，可能影响用药决策而影响患者预后，我们会在后期前瞻性、单臂、开放性研究中统一公司，减少检测上的系统偏倚。

总之，本研究作为首个埃克替尼对*EGFR* 18外显子疗效分析，虽然我们发现埃克替尼在*EGFR*基因18外显子少见突变的疗效上比传统突变未见明显优势，但复合突变比单纯突变临床获益更多。

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