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埃克替尼对非小细胞肺癌*EGFR* 21外显子少见突变的临床疗效

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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* 21外显子L861Q/L833F突变的临床疗效。**方法：**回顾性分析17例埃克替尼治疗*EGFR* 21外显子少见突变的NSCLC，服用至病情进展或出现不可耐受的毒副作用，并观察疗效。**结果：**17例L861Q/L833F突变患者中L861Q突变17例，中位生存时间2.2个月，L833F突变1例，中位生存时间4.2个月。L833F突变患者生存时间稍长。复合突变与单纯突变相比，复合突变中位生存时间更长(L861Q突变2.1个月vs. 5.6个月，*P*=0.065)。**结论：**埃克替尼在*EGFR*基因21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；21外显子

Clinical efficacy of icotinib in patients with advanced non-small cell lung cancer harboring *EGFR* exon 21 rare mutations

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Abstract　**Objective:** To investigate the efficacy of icotinib in patients with non-small cell lung cancer (NSCLC) that carrying L861Q/L833F in *EGFR* exon 21. **Methods:** We retrospectively analysed 17 cases of *EGFR* 21 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:** Seventeen patients with L861Q/L833F mutations were enrolled. Mutations including L861Q and L833F mutations were observed in 17 and 1 patients, respectively. In total, the median progression-free survival (PFS) were 2.2 months, respectively. Patients with L833F mutation manifested the longest median PFS (4.2 months), followed by those with L861Q (2.2 months). Patients with complex mutations show a better PFS than those with single mutations (L861Q mutations 2.1 months vs. 5.6 months, *P*=0.065). **Conclusion:** Icotinib is less effective in patients with exon 21 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 21

在世界范围内，肺癌的发病率和病死率逐年升高，已成为恶性肿瘤之首，其中非小细胞肺癌(non-small cell lung cancer，NSCLC)占80%~85%[1-3]。近年来随着个体化治疗时代的到来，*EGFR*基因突变改变了NSCLC治疗的临床实践[4]。*EGFR*基因最常见的两种突变形式：19外显子的缺失突变和21外显子L858R突变对表皮生长因子受体酪氨酸酶抑制剂(epidermal growth factor receptor tyrosine kinase inhibitor，EGFR-TKIs)高度敏感[5-9]，目前一代EGFR-TKIs吉非替尼和厄洛替尼对*EGFR*基因少见突变研究比较成熟，而具有中国特色的埃克替尼对*EGFR*基因少见突变疗效分析目前尚未报道[10-11]。本研究回顾性分析埃克替尼对*EGFR*基因21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

选取福建省肿瘤医院、浙江省肿瘤医院和武警浙江总队医院2013年7月至2016年11月间*EGFR* 21外显子L861Q突变的NSCLC患者17例，纳入标准：1)经组织学或细胞学检查诊断确诊为NSCLC，经ARMS方法或者次世代定序(next generation sequencing，NGS)方法检测为阳性；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；5)年龄≥18岁，自愿签署知情同意书。排除标准：1)本研究前曾确诊或者治疗过其他恶性肿瘤；2)既往神经或精神病史；3)存在严重呼吸、心血管和肝肾疾病。本研究经成员单位医院学伦理委员会批准，所有患者均知情同意。

1.2 方法

17例患者获取血或肿瘤组织标本经ARMS方法或NGS方法确诊为*EGFR* 21外显子少见突变的NSCLC后给予埃克替尼125 mg，每天3次，直至不能耐受而终止治疗。治疗期间定期检测患者血常规、肝肾功能、肿瘤标志物、心电图及影像学，评估疗效及研究其耐药机制。

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评分和TNM分期等。不吸烟定义是一生吸烟<100支。疗效评价标准使用WHO RECIST，包括完全缓解(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)。疾病控制率(disease control rate，DCR)为CR+PR+SD。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，*P*<0.05为差异有统计学意义。

2 结果

2.1 临床病理特征

总计3 279例NSCLC通过ARMS方法或NGS方法进行*EGFR*基因检测，其中*EGFR*阳性患者1 347例(41.08%)，其中47例患者为*EGFR*基因21外显子少见突变，其中17例服用埃克替尼，临床病理特征见表1，其中男性女比例13∶4，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：L861Q 17例，L833F 1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 17例埃克替尼治疗、*EGFR*基因21外显子少见突变的非小细胞肺癌临床特征

Table 1 Clinicopathologic characteristics of 17 cases of patients with *EGFR* exon 21 rare mutations whom were therapy by icotinib

临床病理特征	例数
性别	
男	13
女	4
年龄/岁	
<65	9
≥65	8
吸烟史	
是	8
否	9
PS	
0~1	13
2~3	4
组织亚型	
腺癌	12
非腺癌	5
突变类型	
L861Q	17
L833F	1
埃克替尼治疗	
一线	1
二线	2
三线及以上	14
分期	
ⅢB	3
Ⅳ	14

表2 17例埃克替尼治疗*EGFR*基因21外显子少见突变的非小细胞肺癌具体亚型

Table 2 Specific subtype of 17 cases of patients with *EGFR* exon 21 rare mutations treated by icotinib

突变类型	例数
L861Q	17
单纯型	14
L861Q+G719X	1
L861Q+L858R	1
L861Q+L833F	1
L833F	1
L833F+L861Q	1

2.2 21外显子疗效分析

埃克替尼对*EGFR*基因21外显子数据显示：ORR和DCR分别为23.53%和64.71%，在这些患者中，未见CR患者，PR共计4例，SD共计7例，中位PFS为2.2个月。亚组分析中埃克替尼对*EGFR* 21外显子L861Q单纯突变与复合突变的PFS(2.1个月vs. 5.6个月，P=0.065，表3，图1~3)。

表3 埃克替尼对非小细胞肺癌*EGFR*基因21外显子的临床疗效

Table 3 Clinical efficacy of icotinib on advanced non-small cell lung cancer harboring *EGFR* exon 21 rare mutations

突变类型	*n*	CR	PR	SD
L861Q	17	0	4	7
L833F	1	0	0	1
突变类型	**PD**	**ORR/%**	**DCR/%**	**PFS/月**
L861Q	6	23.53	64.71	2.2
L833F	0	0	100.00	4.2

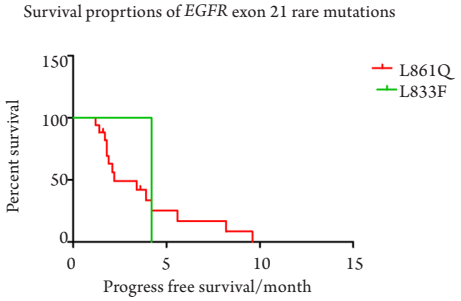

图1 埃克替尼对*EGFR* 21外显子少见突变的PFS(P=0.762)

Figure 1 PFS of *EGFR* 21 exon rare mutations by icotinib (P=0.762)

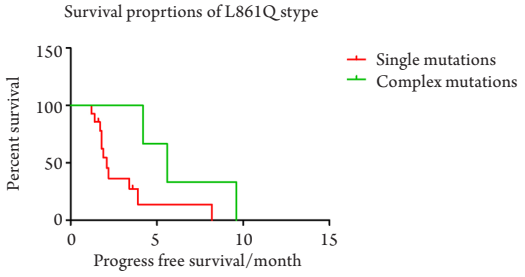

图2 埃克替尼对*EGFR* 21外显子L861Q单纯突变与复合突变的PFS(P=0.065)

Figure 2 PFS of patients harboring *EGFR* exon 21 L861Q single mutations and complex mutations (P=0.065)

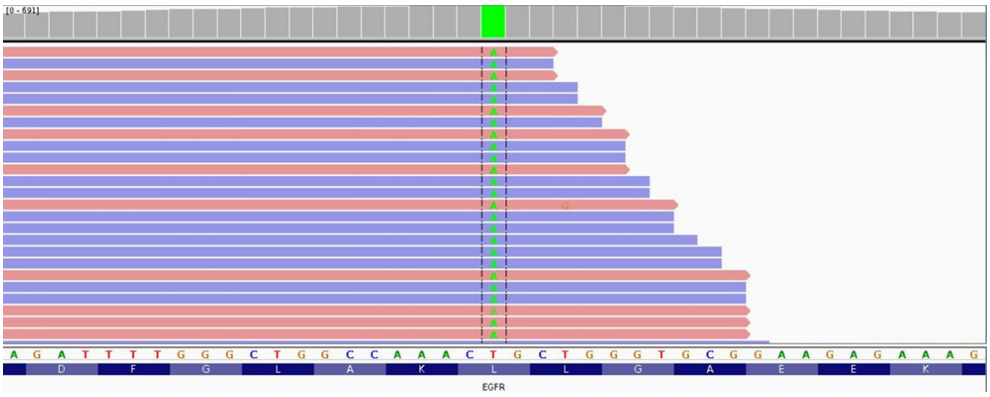

图3 *EGFR* L861Q IGV图

Figure 3 IGV of *EGFR* L861Q

3 讨论

少见突变中最常见的为18外显子G719X点突变，20外显子S768I以及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[12]。21外显子少见突变包括R832H，L833V，V834X，L835L，R836S，L838P，G857E，L858M，L861X，A864E，E866V，E868K，A871E，G873E等[13-17]，本研究中21外显子的突变占*EGFR*基因突变型3.49%(47/1347)，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21外显子少见突变的报道，但未见埃克替尼的报道。Kuiper等[17]报道了4例L861Q突变的NSCLC，3例患者服用EGFR TKIs，疗效分析PR 1例(PFS：1.8个月)，SD 1例(PFS：2.1个月)，NA 1例(6.4个月)，Chiu等[18]报道57例L861Q，9例L861Q+G719X，10例G719X+S768I发现，ORR分别为39.6% vs. 88.9%，DCR分别为75.5% vs. 100%。本研究选择具有中国特色的EGFR-TKIs——埃克替尼治疗L861Q发现：17例埃克替尼对*EGFR* 21外显子L861Q的PFS为2.2个月，其中单纯突变与复合突变的PFS(2.1个月vs. 5.6个月，*P*=0.065)。

EGFR-TKIs对其他*EGFR* 21外显子的疗效分析发现：1例L838P突变，PFS为2.2个月(SD)，1例L833V+L835H突变，PFS为11.7个月(PR)，1例L838V+L861Q突变，PFS为6.4个月(NA)，1例del L747_T751+D837T突变，PFS为15.0个月(CR)[17]。本研究中1例L833F+L861Q突变，PFS为4.2个月(SD)。

综上所述，本研究作为首个埃克替尼对*EGFR* 21外显子疗效分析，虽然我们发现埃克替尼在*EGFR* 基因21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，而且某些亚型如L833F等复合突变能从埃克替尼中获益，值得重视。

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