·论著·

EGFR-TKI靶向治疗IV期非小细胞肺癌患者疗效观察及对肺功能的影响

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【摘要】**目的** 探讨表皮生长因子受体酪氨酸激酶抑制剂(epidermal growth factor receptor -tyrosine kinase inhibitors，EGFR-TKI)靶向治疗IV期非小细胞肺癌患者疗效观察及对肺功能的影响。**方法** 选取2018年10月~2020年10月在本院就诊的IV期非小细胞肺癌患者92例，均接受一线EGFR-TKI靶向治疗联合化疗，即EGFR-TKI靶向治疗联合培美曲塞(培美曲塞二钠)和含铂类(顺铂、卡铂或者奈达铂)方案进行治疗，统计92例IV期非小细胞肺癌患者疗效、肺功能、生活质量、不良反应。**结果** 92例IV期非小细胞肺癌患者，其中男性38例，女性54例，年龄25~74岁，中位年龄53岁；CR 0例，PR 64例，SD 18例，PD 10例，ORR 69.57%(64/92)，DCR 89.13%(82/92)；92例IV期非小细胞肺癌患者中位PFS为20.32个月(95%CI：18.1~22.3个月)；治疗后肺功能指标FEV1/FVC、MVV、FEV1% pred均治疗前提高(*P*<0.05)；生活质量改善66例，改善率为71.74%(66/92)，稳定16例，稳定率为17.39%(16/92)，降低10例，降低为10.87%(10/92)；92例患者治疗后不良反应主要集中Ⅰ度、Ⅱ度、Ⅲ度，Ⅰ度肝功能受损45.65%，皮肤反应26.09%，其次分别为骨髓抑制、胃肠道反应、疲乏；Ⅱ度骨髓抑制20.65%，其次为肝功能受损、胃肠道反应；Ⅲ度不良反应骨髓抑制7.61%，其次为肝功能受损、胃肠道反应。**结论** EGFR-TKI靶向治疗IV期非小细胞肺癌患者，疗效理想，可显著促进患者肺功能恢复，安全性较好。

【关键词】表皮生长因子受体酪氨酸激酶抑制剂；靶向治疗；非小细胞肺癌；肺功能；安全性
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Effect of EGFR-TKI Targeting Therapy on Patients with Stage IV Non-small Cell Lung Cancer and Its Effect on Lung Function

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Abstract: ***Objective*** To explore the therapeutic effect of Epidermal Growth Factor Receptor -tyrosine Kinase Inhibitors (EGFR-TKI) in the treatment of patients with stage IV non-small cell lung cancer and its influence on lung function. How: Ninety-two patients with stage IV non-small cell lung cancer admitted to our hospital from October 2018 to October 2020 received first-line EGFR-TKI targeted therapy combined with chemotherapy, that is, EGFR-TKI targeted therapy combined with pemetrexed (pemetrexed disodium) and platinum-containing (cisplatin, carboplatin or nedaplatin) regimen. The efficacy, lung function, quality of life and adverse reactions of 92 patients with stage IV non-small cell lung cancer were analyzed. ***Results*** 92 patients with stage IV non-small cell lung cancer (NSCLC), including 38 males and 54 females, aged 25-74 years, median age 53 years; There were 0 CR cases, 64 PR cases, 18 SD cases, 10 PD cases, 69.57% ORR (64/92), 89.13% DCR (82/92) cases. The median PFS of 92 patients with stage IV NSCLC was 20.32 months (95%CI: 18.1-22.3 months). After treatment, FEV1/FVC, MVV and FEV1% pred were all increased (*P*<0.05). The quality of life in 66 cases was improved, the improvement rate was 71.74% (66/92), the stability rate was 17.39% (16/92) in 16 cases, and the reduction rate was 10.87% (10/92) in 10 cases. After treatment, the adverse reactions of 92 patients mainly concentrated in Ⅰ, Ⅱ and Ⅲ degrees, liver function was impaired in Ⅰ degree 45.65%, skin reaction was 26.09%, followed by bone marrow suppression, gastrointestinal reaction and fatigue. Second degree myelosuppression 20.65%, followed by liver function impairment, gastrointestinal reaction; Myelosuppression was 7.61% of grade III adverse reactions, followed by liver function impairment and gastrointestinal reactions. ***Conclusion*** EGFR-TKI targeted therapy in patients with stage IV non-small cell lung cancer has ideal efficacy, and can significantly promote the recovery of lung function in patients with good safety.

Keywords: Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor; Targeted Therapy; Non-small Cell Lung Cancer; Lung Function; Security

2020年全球癌症数据显示，肺癌死亡率最高，发病率第2[1]。其中非小细胞肺癌占据肺癌85%左右[2]。RGFR突变为非小细胞肺癌是一种在肺部组织中促进细胞生长和分裂的受体，是非小细胞肺癌中最常见的突变之一[3]，研究报道，白种人群中EGFR突变率为15%[4]，亚裔人群更高，可达到40%~65%[5]。常规化疗选择性差，在杀死肿瘤细胞同时，也对正常细胞产生影响，患者预后不理想[6-7]。EGFR酪氨酸激酶抑制剂是一种针对EGFR突变的靶向治疗药物，能够阻断EGFR蛋白的酪氨酸激酶活性，从而控制肺癌的生长和扩散[8-9]。EGFR-TKI包括第一代、第二代及第三代药，吉非替尼、厄洛替尼、埃克替尼，第二代主要是阿法替尼，第三代药主要是奥希替尼，无论选用哪种EGFR-TKI，均可有效提高EGFR突变晚期肺癌患者ORR，还可以有效延长患者PFS[10-11]。但是靶向治疗药物易出现耐药现象，治疗方案经优化后，可有效延长患者总生存期(overall survival，OS)，联合治疗属于目前用于延迟耐药的一种治疗策略，目前临床上常采用以EGFR-TKI为基础的联合治疗方案，均已取得理想效果[12-14]。本次研究主要探讨EGFR-TKI靶向治疗IV期非小细胞肺癌患者疗效，现报告如下。

1 资料与方法

1.1 研究对象 选取2018年10月~2020年10月在本院就诊的IV期非小细胞肺癌患者92例。

纳入标准：符合肺腺癌诊断标准；TNM分期符合第8版国际抗癌联盟(UICC)标准[15]；EGFR基因突变阳性；ECOG评分≤2分；OS≥3个月；至少具有一个可评价的肿瘤病灶组织。排除标准：肝肾功能障碍；合并血液系统、免疫系统、精神系统等疾病；脑转移；心肺功能障碍；入院资料不完整。

1.2 研究方法

1.2.1 治疗方法 92例患者均接受一线EGFR-TKI靶向治疗联合化疗，即EGFR-TKI靶向治疗联合培美曲塞和含铂类方案进行治疗，3周为一个周期，依据情况连续治疗约4~6个周期后，再采用序贯EGFR-TKI与培美曲塞或靶向单药治疗，直到不耐受或病情进展。EGFR-TKI：吉非替尼、盐酸埃克替尼或阿法替尼；化疗药物：培

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美曲塞二钠，铂类：顺铂、卡铂或奈达铂。

1.2.2 随访 电话、门诊随访，随访截至2023年4月30日。中位随访时间为18.5个月，均获得随访。

1.3 观察指标 统计92例IV期非小细胞肺癌患者疗效、肺功能、生活质量、不良反应。①疗效：依据RECIST标准[16]，客观有效率(ORR)=(CR例数+PR例数)/总例数×100%，疾病控制率=(CR例数+PR例数+SD例数)/总例数×100%；②肺功能，分别于治疗前1d和治疗周期结束后1d采用肺功能检测仪检测肺功能指标第一秒用力呼气量/用力肺活量(forced expiratory volume in 1 second/forced vital capacity，FEV1/FVC)、最大通气量(maximal voluntary ventilation，MVV)、第一秒用力呼气的容积占预计值的百分比(forced expiratory volume in 1 second percent predicted，FEV1% pred)；③生活质量[17]，采用生活质量评分(quality of life，QOL)，KPS评分增加≥10分表示QOL改善，KPS评分变化<10分表示QOL稳定，KPS评分减少≥10分表示QOL下降；④不良反应：不良反应评价参照美国国立癌症研究所(NCI)术语标准CTCAE 5.0版[18]，分为1~4级。

1.4 统计学方法 采用SPSS 26.0统计软件对数据进行分析，计量资料用($\bar{x}\pm s$)表示，比较用t检验；计数资料用[n(%)]表示，比较用χ^2检验；以*P*<0.05为差异有统计学意义。

表1 92例患者的临床特征

临床特征		例数	占比
性别	男性	38	41.30%
	女性	54	58.70%
年龄(岁)	≥53	47	51.09%
	<53	45	48.91%
吸烟史	有	26	28.26%
	无	66	71.74%
ECOG体能状态评分(分)	0	64	69.57%
	1	26	28.26%
	2	2	2.17%
临床分期	IVA	40	43.48%
	IVB	52	56.52%
EGFR突变类型	Exon-19 19-del	49	53.26%
	Exon-21 L858R	33	35.87%
	非经典突变	10	10.87%
TP53伴随情况	有	14	15.22%
	无	78	84.78%
EGFR-TKIs	埃克替尼	76	82.61%
	吉非替尼	12	13.04%
	阿法替尼	4	4.35%

2 结 果

2.1 92例患者的临床特征 92例IV期非小细胞肺癌患者，其中男性38例，女性54例，年龄25~74岁，中位年龄53岁，其他临床特征见表1。

2.2 两组疗效比较 CR 0例，PR 64例，SD 18例，PD 10例，ORR 69.57%(64/92)，DCR 89.13%(82/92)。

2.3 治疗前后肺功能指标FEV1/FVC、MVV、FEV1% pred变化 治疗后肺功能指标FEV1/FVC、MVV、FEV1% pred均治疗前提高(*P*<0.05)，见表2。

2.4 生存分析 92例IV期非小细胞肺癌患者中位PFS为20.32个月(95%CI：18.1~22.3个月)，见图1。

2.5 治疗后生活质量改善情况 生活质量改善66例，改善率为71.74%(66/92)，稳定16例，稳定率为17.39%(16/92)，降低10例，降低为10.87%(10/92)。

2.6 治疗后不良反应发生情况 92例患者治疗后不良反应主要集中Ⅰ度、Ⅱ度、Ⅲ度，Ⅰ度肝功能受损45.65%，皮肤反应26.09%，其次分别为骨髓抑制、胃肠道反应、疲乏；Ⅱ度骨髓抑制20.65%，其次为肝功能受损、胃肠道反应；Ⅲ度不良反应骨髓抑制7.61%，其次为肝功能受损、胃肠道反应，见表3。

表2 治疗前后肺功能指标FEV1/FVC、MVV、FEV1% pred变化

时间	例数	FEV1/FVC(%)	MVV(L/min)	FEV1% pred(%)
治疗前	92	65.32±6.41	80.31±13.46	49.36±7.81
治疗后	92	78.46±8.14	98.27±12.18	63.14±9.44
t		8.602	6.710	7.628
P		<0.001	<0.001	<0.001

表3 治疗后不良反应发生情况[n(%)]

CTCAE	骨髓抑制	肝功能受损	肾功能损伤	胃肠道反应	疲乏	皮肤反应
Ⅰ	14(15.22)	42(45.65)	5(5.43)	12(13.04)	12(13.04)	24(26.09)
Ⅱ	19(20.65)	9(9.78)	0	2(2.17)	0	0
Ⅲ	7(7.61)	2(2.17)	0	2(2.17)	0	0
Ⅳ	0	0	0	0	0	0

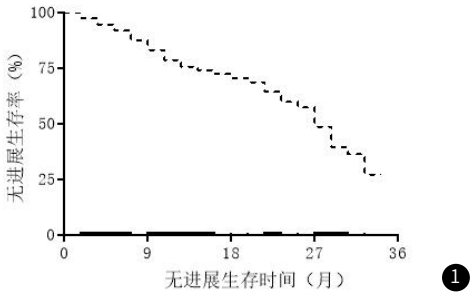

图1 92例IV期非小细胞肺癌患者无进展生存时间曲线

3 讨 论

EGFR-TKI靶向治疗晚期非小细胞肺癌属于一线治疗方案[19-20]。且多项研究均报道[21-23]，EGFR-TKI靶向治疗单药较常规化疗方案更有利于延长患者中位无进展生存时间。但是研究称，大部分患者在接受EGFR-TKI靶向治疗后易出现耐药，只能进行化疗或经基因检测是否存在其他靶点。由此，如何合理应用EGFR-TKI靶向治疗方案延迟患者耐药时间，最大可能延长患者的生存时间是目前主要研究方向。多项研究均报道[24-25]，对于EGFR突变晚期肺癌患者，采用EGFR-TKIs联合化疗进行治疗效果更理想。我国一名研究学者比较了EGFR-TKI靶向药物、常规化疗药物分别单用及联用治疗EGFR敏感突变的晚期肺癌患者，研究结果显示，与常规化疗单用、EGFR-TKI靶向药物单用进行比较，EGFR-TKI靶向药物联合常规化疗更有利于延长患者的生存时间，且不会增加患者不良反应发生率[26]。这一研究结果为EGFR-TKI靶向药物决策方案的制定提供了科学依据。

本次研究92例IV期非小细胞肺癌患者，接受一线EGFR-TKI靶向治疗联合化疗，依据患者耐受情况，采用序贯EGFR-TKI与培美曲塞或靶向单药治疗，ORR为69.57%，DCR为89.13%，与目前研究报道结果具有相似性。92例IV期非小细胞肺癌患者中位PFS为20.32个月，显著优于NEJ005研究中序贯或交替治疗模式的15.3个月[27-28]，又明显优于NEJ009研究[29]。且患者治疗后肺功能指标FEV1/FVC、MVV、FEV1% pred均治疗前提高。安全性方面，本研究EGFR-TKI靶向治疗联合化疗患者不良反应主要集中在肝功能受损、骨髓抑制，其次为皮肤反应、胃肠道反应和疲乏，

主要集中在Ⅰ度、Ⅱ度，Ⅲ度不良反应较少，Ⅳ度不良反应尚未发现，出现不良反应症状的患者经过对症治疗后均明显得到缓解。因此，在应用EGFR-TKI联合化疗治疗前，需要评估患者血常规、肝功能情况，对于血常规、肝功能异常的患者谨慎应用。

综上所述，EGFR-TKI靶向治疗Ⅳ期非小细胞肺癌患者，疗效理想，可显著促进患者肺功能恢复，安全性较好。但是在应用EGFR-TKI靶向治疗前，需要充分评估患者耐受情况、体能状况、依从性情况以及方案的成本金额可行性等。另外本次研究也存在一些局限性，尚未进一步观察不同突变类型患者生存情况，且随访时间较短，样本量偏少。因肿瘤的异质性，可以进一步通过观察动态基因变化，有利于制定更佳的联合治疗方案，延长患者出现耐药时间，尽可能让患者获益最大化。

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