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EGFR 突变晚期非小细胞肺癌患者 1 例

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[摘　要] 浙江省衢州市柯城区人民医院收治1例晚期非小细胞肺癌(non-small cell lung cancer，NSCLC)。患者，女，65岁，无吸烟史，无肿瘤家族史。因“右下肺癌术后13年余，来院复查”入院。胸部增强CT示：两肺多发恶性肿瘤，左肺上叶最大层面约3.6 cm ×3.2 cm，右肺最大层面约5.9 cm ×3.5 cm，左侧第12肋膨胀性骨质破坏。头颅增强MRI示：双侧颞叶异常强化灶，大小约0.5 cm ×0.5 cm，考虑转移。左肺穿刺病理：(左)肺非小细胞癌，倾向腺癌。免疫组织化学：CK7(+)，napsin-A(+)，TTF-1(+)，p40(−)，p63(−)，Ki-67(5%+)。基因检测：*EGFR E19del*突变。一线予“吉非替尼片(易瑞沙)”靶向治疗，治疗后肺部病灶明显缩小，颅内病灶消失。16个月左右后疾病进展，进展后血液*EGFR T790M*突变检测阳性，使用“甲磺酸奥西替尼片(泰瑞沙)”治疗，疾病持续缓解中。

[关键词] 晚期非小细胞肺癌；表皮生长因子受体激酶抑制剂；*EGFR*突变；*EGFR T790M*突变

A case of advanced non-small cell lung cancer with EGFR mutation

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Abstract A 65-year-old female, never smoker, with advanced non-small cell lung cancer (NSCLC) was admitted to the Kecheng District People's Hospital of Quzhou, Zhejiang Province. The patient denied a family history of cancer. Due to a 13-year surgery history of the right lower lung cancer, the patient wanted to conduct a review. Enhanced chest CT showed multiple malignant tumors in both lungs, the largest layer of the left upper lobe was about 3.6 cm ×3.2 cm, the largest part of the right lung was about 5.9 cm ×3.5 cm, and the left flank was expansive bone destruction. Enhanced cranial MRI showed abnormal enhancement of bilateral temporal lobe (about 0.5 cm ×0.5 cm), indicating metastasis. The pathology of left lung puncture was NSCLC and prone to adenocarcinoma. In the further immunohistochemistry study, the results demonstrated CK7 (+), napsin-A (+), TTF-1 (+), p40 (−), p63 (−), Ki-67 (5%+). The genetic testing of tissue identified a common EGFR mutation (E19del). Based on the above results, “gefitinib (Iressa)” was initiated as the first-line treatment. The lung lesions were significantly reduced and the intracranial lesions disappeared during gefitinib therapy. However, the disease

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progressed after 16 months and a novel EGFR mutation (T790M) was detected. Hence, the patient acquired another targeted therapy with "oxitinib mesylate (Terisha)", and the disease continues to be relieved.

Keywords advanced non-small cell lung cancer; EGFR kinase inhibitor; EGFR mutation; EGFR T790M mutation

肺癌是世界范围内发病率和病死率最高的肿瘤，确诊时多数患者分期较晚是影响肺癌预后的重要因素。非小细胞肺癌(non-small lung cancer cell，NSCLC)占所有肺癌病例的80%以上。随着肺癌系列致癌驱动基因的相继确定，国内外多项研究[1-4]表明靶向治疗药物大大改善和延长携带相应驱动基因的NSCLC患者的预后和生存。浙江省衢州市柯城区人民医院(以下简称我院)收治1例晚期NSCLC患者，现汇报如下。

1 临床资料

患者，女，65岁，农民。2004年3月28日因“体检发现右下肺结节1个月”在当地医院就诊，于2004年4月19日行“右下肺切除术”，术后病理：(右下肺)细支气管肺泡癌。术后行化疗2次，具体不详。2017年6月13日来我院复查。PS 0分，无不适主诉。既往体健，无吸烟史，无肿瘤家族史。入院后2017年6月14日胸部增强CT示：两肺多发恶性肿瘤，左肺上叶最大层面约3.6 cm ×3.2 cm(图1A)，右肺最大层面约5.9 cm ×3.5 cm(图1B)，左侧第12肋膨胀性骨质破坏。

2017年6月16日头颅增强MRI示：双侧颞叶异常强化灶，大小约0.5 cm ×0.5 cm，考虑转移(图2)。

全腹部增强CT未提示转移。彩超扫查双侧颈部、锁骨上、腋窝未见明显肿大淋巴结。肺肿瘤标志物未见异常。2017年6月19日行CT引导下左肺穿刺活检。2017年6月23日病理：(左)肺非小细胞癌，倾向腺癌。免疫组织化学：CK7(+)，napsin-A(+)，TTF-1(+)，p40(−)，p63(−)，Ki-67(5%+)。2017年6月30日基因检测：*EGFR E19del*突变。诊断：肺恶性肿瘤(肺内、脑、骨，T4N0M1c，IV B期，腺癌，*EGFR E19del*突变)。2017年7月7日开始予“吉非替尼片(易瑞沙)0.25 g每日1次”靶向治疗。患者肿瘤骨转移，予破骨细胞抑制剂“唑来膦酸针4 mg静滴，每4周1次”抑制骨破坏。2017年8月5日复查胸部CT平扫：两肺多发恶性肿瘤，对照2017年6月14日CT两肺病灶均较前明显缩小，左肺上叶最大层面约3.1 cm ×2.5 cm(图3A)，右肺最大层面约1.9 cm ×2.0 cm(图3B)，部分小结节灶目前显示不清。左侧第12肋膨胀性骨质破坏。头颅MRI增强：对照2017年6月16日MRI片，颅内未见异常。

定期复查，2018年11月3日胸部CT平扫：两肺多发恶性肿瘤；对照2018年7月28日CT片右肺下叶其中一枚结节较前增大，余病灶同前大致相仿；新见L2右侧横突骨转移伴软组织肿块形成，左侧第12肋膨胀性骨质破坏。患者无临床症状，拒绝行再次活检及基因检测，要求继续“吉非替尼片(易瑞沙)”治疗。

2019年2月20日患者因“腰部、臀部及双下肢酸胀痛伴麻木不适”来院就诊。2019年2月20日腰椎MRI平扫：L_1附件、L_2椎体及附件骨转移伴L_2椎体病理性骨折，局部软组织肿块形成，突入椎管内压迫脊髓圆锥、马尾终丝及硬膜囊，相应平面椎管狭窄；T_{12}，L_3，L_4附件斑片状T2WI稍高信号(T12转移可能，余待排；图4)。

2019年2月21日胸部CT平扫：两肺多发恶性肿瘤；对照2018年11月3日CT片，两肺新见多发粟粒结节及结节灶，考虑肺内转移(图5)；L_1，L_2右侧横突骨转移伴软组织肿块较前增大；左侧第12肋膨胀性骨质破坏。

患者拒绝再次活检，2019年2月27日行血液*EGFR T790M*突变检测阳性，突变率4.9%。经MDT讨论，2019年3月1日开始予“甲磺酸奥西替尼片(泰瑞沙)80 mg，每日1次”靶向治疗，继续予破骨细胞抑制剂“唑来膦酸针4 mg静滴，每4周1次”抑制骨破坏，并建议腰椎转移部位行手术治疗，术后行局部放疗，但患者拒绝手术与放疗。服药5 d后患者疼痛、麻木等症状消失，至当地医院随访观察，疾病持续缓解中。

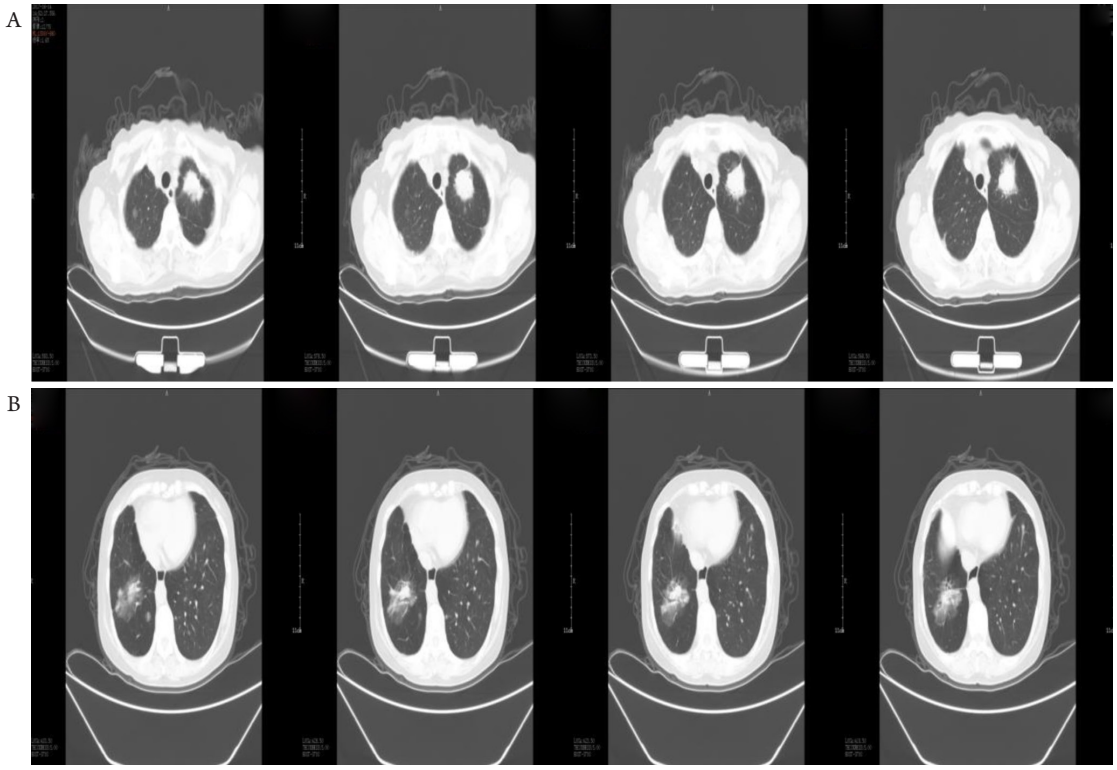

图1 易瑞沙靶向治疗前肺部病灶情况

Figure 1 Pulmonary lesions before target therapy with Iressa

(A)2017年6月14日左肺上叶最大层面约3.6 cm × 3.2 cm；(B)2017年6月14日右肺最大层面约5.9 cm × 3.5 cm。

(A) On June 14, 2017, the largest section of the upper left lung was about 3.6 cm × 3.2 cm; (B) On June 14, 2017, the largest section of the right lung was about 5.9 cm × 3.5 cm.

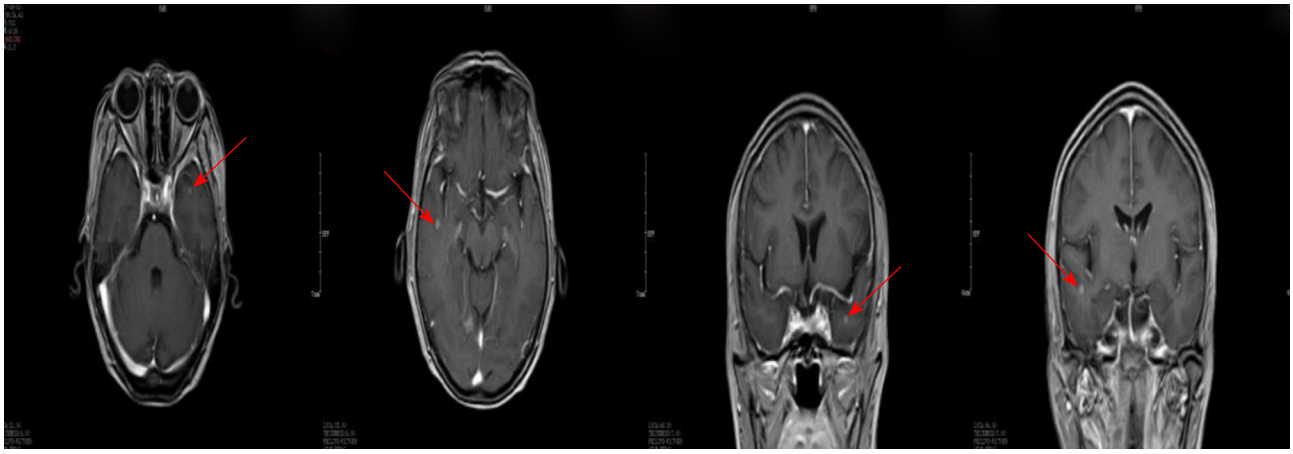

图2 头颅MRI提示双侧颞叶转移灶(箭头)

Figure 2 MRI of head indicates bilateral temporal lobe metastasis (arrows)

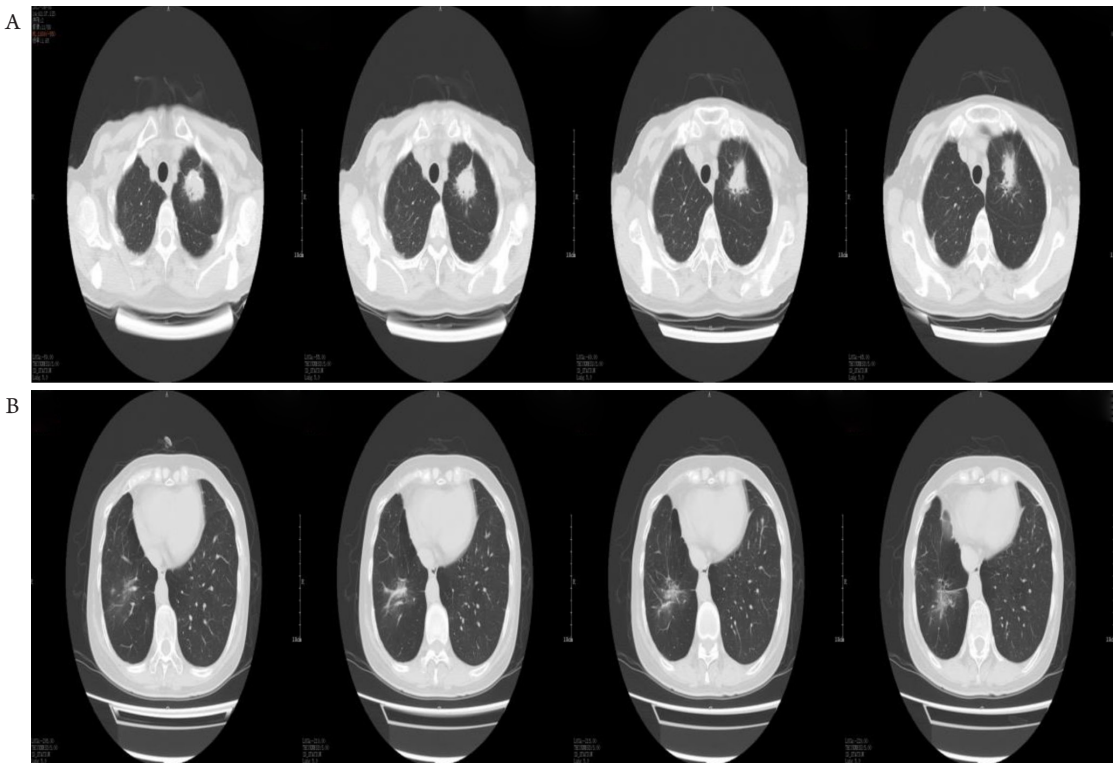

图3 易瑞沙靶向治疗后肺部病灶情况

Figure 3 Pulmonary lesions after targeted treatment with Iressa

(A)2017年8月5日左肺上叶最大层面约3.1 cm × 2.5 cm；(B)2017年8月5日右肺最大层面约1.9 cm × 2.0 cm。

(A) On August 5, 2017, the largest section of the upper left lung was about 3.1 cm × 2.5 cm; (B) On August 5, 2017, the maximum level of right lung was about 1.9 cm × 2.0 cm.

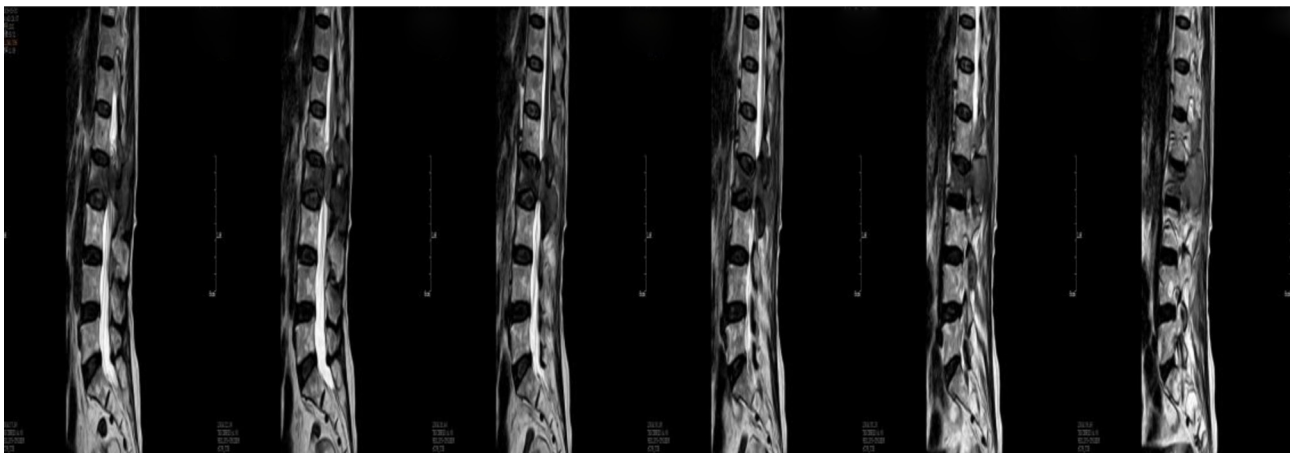

图4 腰椎MRI提示腰椎骨转移伴局部软组织肿块形成

Figure 4 MRI of the lumbar spine suggests bone metastasis with local soft tissue mass formation

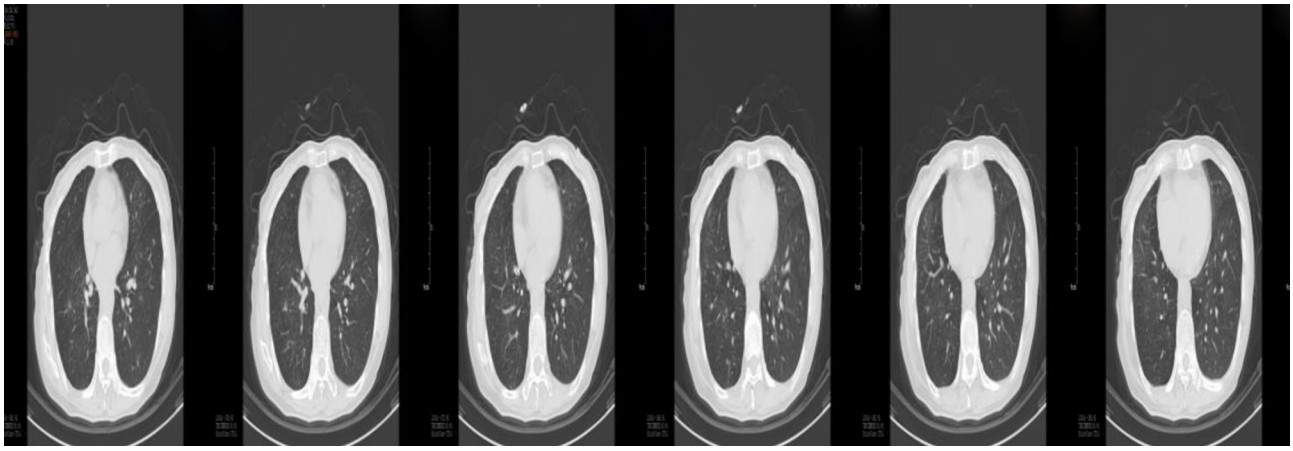

图5 胸部CT提示两肺新见多发粟粒结节及结节灶

Figure 5 Chest CT shows multiple miliary nodules and nodular foci in both lungs

2 讨论

肺癌的分型由过去单纯的病理组织学分类，进一步细分为基于驱动基因的分子亚型[5-7]。对于晚期或转移性NSCLC患者，病理学诊断后保留足够组织标本进行分子检测。对非鳞癌组织标本进行分子学检测(基因测序)和PD-L1表达检测，根据检测结果分为以下7类作出治疗推荐：1)*EGFR*敏感突变阳性；2)*ALK*阳性；3)*ROS1*阳性；4)*BRAF V600E*阳性；5)*NTRK*融合突变阳性；6)PD-L1≥1%且*EGFR*、*ALK*阴性或未知；7)*EGFR*，*ALK*，*ROS1*，*BRAF V600E*，*NTRK*阴性或未知，PD-L1<1%或未知[8]。

相比西方国家，中国NSCLC患者具有更高的EGFR突变率，尤其在不吸烟肺癌患者中[9-13]。亚裔人群和我国的肺腺癌患者*EGFR*敏感突变阳性率为40%~50%[9-10,14]。*EGFR*突变主要包括4种类型：外显子19缺失突变、外显子21点突变、外显子18点突变和外显子20插入突变[11]。最常见的*EGFR*突变为外显子19缺失突变(19DEL)和外显子21点突变(21L858R)，均为表皮生长因子受体激酶抑制剂(EGFR-TKI)的敏感突变，18外显子G719X、20外显子S768I和21外显子L861Q突变亦均为敏感突变，20外显子的T790M突变与第1，2代EGFR-TKIs获得性耐药有关，还有许多类型的突变临床意义尚不明确[9,12]。

*EGFR*突变阳性晚期NSCLC患者一线治疗的多个随机对照研究[15-18]显示：吉非替尼、厄洛替尼、埃克替尼和阿法替尼对比化疗均可显著改善患者的PFS，且3级及以上不良反应显著低于化疗。

对于*EGFR*突变阳性NSCLC伴有脑转移的患者，既往多个回顾性研究、II和III期临床研究分析均显示，EGFR-TKIs单药治疗脑转移取得了好的疗效。吉非替尼单药治疗*EGFR*基因敏感突变的肺腺癌伴脑转移患者的ORR为87.8%，中位颅内PFS为14.5个月，中位OS为21.9个月，吉非替尼治疗可显著延迟脑转移患者至放疗时间，中位至挽救性放疗时间为17.9个月[19]。

III期临床研究FLAURA[20]对比了三代EGFR-TKIs奥希替尼与第1代药物一线治疗*EGFR*突变阳性晚期NSCLC的疗效和安全性，结果显示奥希替尼显著延长PFS，降低疾病进展风险54%(18.9个月vs 10.2个月)，且安全性良好，3级及以上不良事件发生率少于标准治疗组(34% vs 45%)。FLAURA研究[21]显示：亚洲人群中位PFS分别是16.5个月和11个月，3级及以上不良事件发生率为40%和48%。

EGFR-TKIs耐药患者，建议再次活检进行*EGFR T790M*检测。*T790M*突变是第1代EGFR-TKIs主要耐药机制之一，约占50%[22-24]。不能获取肿瘤标本的患者，建议行外周血游离肿瘤DNA(cell-free/circulating tumor DNA，cf/ctDNA)*EGFR T790M*检测。BENEFIT研究、AURA3研究以及FLAURA研究[25-27]的ctDNA分析结果证明检测外周血基础上*EGFR*敏感突变和*T790M*耐药突变是可行的。

EGFR-TKIs耐药后，根据患者临床进展模式选择治疗已被广泛认可，将EGFR-TKIs进展患者分为3种类型[28]：局部进展、缓慢进展和快速进展。对于局部进展患者，多个回顾性分析[29-34]显示继续原EGFR-TKIs治疗联合局部治疗可获得PFS2或TTP2 4.0~10.9个月，亚组分析显示孤立进展或颅内进展患者预后更佳。对于缓慢进展患者，继续应用

原EGFR-TKIs治疗是可选方案之一，前瞻性研究ASPIRATION[35]探索了*EGFR*突变晚期NSCLC患者缓慢进展后继续使用厄洛替尼的疗效，显示继续用药患者中位PFS在11个月(PFS1)的基础上延长到14.1个月，获得3.1个月的PFS2；其他观察性研究以及回顾性分析亦有相似的结论[36-37]。

第3代EGFR-TKIs奥希替尼作用于*T790M*突变靶点。对比奥希替尼和铂类双药化疗治疗TKI耐药后*T790M*阳性的NSCLC的随机III期AURA3临床研究[38]显示：奥希替尼显著延长PFS时间(中位10.1个月vs 4.4个月)。奥希替尼可用于EGFR-TKI治疗进展、并经检测确认存在*EGFR-T790M*突变阳性的局部晚期或转移性NSCLC患者。对于耐药患者，若*T790M*突变检测明确耐药机制*T790M*突变阳性，都推荐使用奥希替尼进行治疗。

分子靶向治疗为晚期肺癌患者提供了更多的治疗手段和更多的期待，在临床工作中，要根据患者的实际情况包括经济能力进行个体化治疗，更好的使用EGFR-TKIs，并与手术、放疗及化疗等手段综合应用，以期最大程度地改善患者生活质量，延长患者生存期。

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