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1 例晚期 EGFR 阳性非小细胞肺癌的联合治疗

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[摘　要] 上海市胸科医院(上海交通大学附属胸科医院)收治了1例EGFR阳性非小细胞肺癌(non-small cell lung cancer，NSCLC)患者，男，48岁，因“胸闷、胸痛、气促2周”于2015年6月16日入院。胸部CT见右侧胸膜多发结节影、右下叶阴影、右侧胸腔积液。右侧胸腔闭式引流包埋病理提示腺癌。胸水基因检测结果示：EGFR19外显子缺失突变(19del)。一线治疗采用标准含铂双药化疗联合EGFR-TKI靶向治疗，后以单药培美曲赛联合靶向维持，疗效达部分缓解(partial regression，PR)，无进展生存(progression-free survival，PFS)达15个月，二线治疗加用贝伐珠单抗后疾病稳定(stable disease，SD)，PFS达18个月，三线治疗采用三代EGFR-TKIs联合贝伐珠单抗，最佳疗效完全缓解(complete regression，CR)，患者目前仍在随访中，总生存期(overall survival，OS)已超50个月。联合治疗可显著延长晚期NSCLC患者的生存。

[关键词] 晚期；非小细胞肺癌；EGFR阳性；联合治疗

Combination therapy in the treatment of advanced EGFR-mutated non-small cell lung cancer: A case report

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Abstract A 48-year-old male with EGFR-positive non-small cell lung cancer (NSCLC), presented with chest tightness, chest pain, and shortness of breath for the past two weeks was admitted into the Shanghai Chest Hospital on June 16, 2015. Chest CT showed multiple nodules on the right pleura, shadow in the right lower lobe, and right-sided pleural effusion. Pathological and histochemical analysis of pleural effusion suggested lung adenocarcinoma. The genetic test showed EGFR 19 exon deletion mutation (19del). The patient was diagnosed with advanced EGFR-mutated lung adenocarcinoma and treated with standard platinum-based chemotherapy combined with EGFR-TKIs as the first-line regimen followed by pemetrexed and gefitinib as a maintenance therapy. Partial regression (PR) was observed and progression-free survival (PFS) achieved 15 months for the first-line. Bevacizumab was additionally administered in the second-line and stable disease (SD) with a PFS of 18 months were observed.

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EGFR 790 mutation was displayed after disease progression. The third-line treatment was composed of third-generation EGFR-TKIs and bevacizumab. Chest CT showed a complete regression (CR) and the patient is still under follow-up. The overall survival (OS) has exceeded 50 months. Combination therapy provides survival benefit in the treatment of advanced EGFR-mutated NSCLC.

Keywords advanced; non-small cell lung cancer; EGFR mutation; combination therapy

肺癌是目前世界范围内发病率及病死率最高的肿瘤，非小细胞肺癌(non-small cell lung cancer，NSCLC)约占所有肺癌的85%，腺癌是NSCLC的主要类型[1-3]。基因检测技术的发展为NSCLC提供了准确的分子分型及靶向治疗的依据[4]。靶向治疗的不断发展使晚期NSCLC患者的生存期明显延长[5]。对于晚期EGFR敏感突变阳性肺腺癌患者，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)是目前的标准一线治疗方式[6]。但治疗过程中不可避免地会出现耐药、进展，如何延缓EGFR-TKIs耐药、使疗效最大化、延长无进展生存(progression-free survival，PFS)是临床亟待解决的问题。除研发新一代TKIs外，联合用药是最常用的策略。本病例为晚期EGFR阳性NSCLC，采用多线联合治疗总生存期(overall survival，OS)已超4年。

1 临床资料

患者，男，48岁，因“胸闷、胸痛、气促2周”于2015年6月16日入上海市胸科医院治疗。胸部CT示：右侧胸膜、纵隔胸膜及膈胸膜多发结节状影，右肺下叶阴影，右侧胸腔积液。肺癌肿瘤标志物癌胚抗原升高，行右侧胸腔闭式引流，胸水包埋病理考虑为腺癌。同期骨扫描未见明显转移性骨肿瘤病变，头颅MRI及腹部B超未见明显异常。胸水沉渣包埋组织基因检测提示EGFR19外显子缺失突变(19del)、ALK阴性、ROS1阴性。胸水引流后胸部CT见图1。

1.1 临床及病理诊断

依据胸水沉渣包埋组织病理、影像学等辅助检查及基因检测结果，该患者诊断为原发性，周围型，右下叶，腺癌，C-T2N1M1a，IV期，PS 1，EGFR 19del。

1.2 治疗

1.2.1 一线治疗

患者入院时胸闷、胸痛、气促症状明显，于培美曲赛/卡铂标准含铂双药化疗后症状得到改善，1周后基因检测结果提示EGFR 19del，予一代EGFR-TKIs吉非替尼口服靶向治疗，即一线治疗采用的是化疗联合靶向治疗。两疗程含铂双药化疗(每月1次)后评估疗效达部分缓解(partial regression，PR)，但患者出现骨髓抑制3度，遂调整至培美曲赛单药化疗(每月1次)，后未再出现骨髓抑制，仅见皮疹I度不良反应。治疗持续至2016年9月，患者再次出现胸痛明显，复查胸部CT见右侧胸膜结节增大，提示疾病进展(progression disease，PD)，一线治疗PFS达15个月。一线治疗期间胸部CT情况见图2。

1.2.2 二线治疗

考虑患者为胸膜局部进展，二线治疗在一线维持治疗基础上加用贝伐珠单抗(每月1次)，患者用药期间未出现除皮疹I度外其他不良反应，治疗期间最佳疗效疾病稳定(stable disease，SD)。二线治疗PFS达18个月，胸部CT随访结果见图3。至2018年3月再次出现胸痛，胸部CT见胸膜结节增大，提示PD。

1.2.3 三线治疗及随访

血基因检测提示EGFR T790M突变，三线治疗采用奥西替尼联合贝伐珠单抗，最佳疗效达完全缓解(complete regression，CR)，胸部结节完全消失。2019年5月三线治疗后14个月患者出现蛋白尿2+，停用贝伐珠单抗后好转，目前仍在随访中，未达PD(图4)。三线治疗PFS至2019年9月已达51个月。

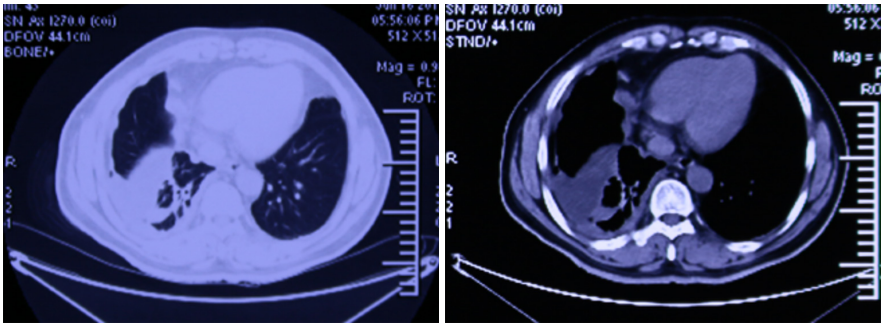
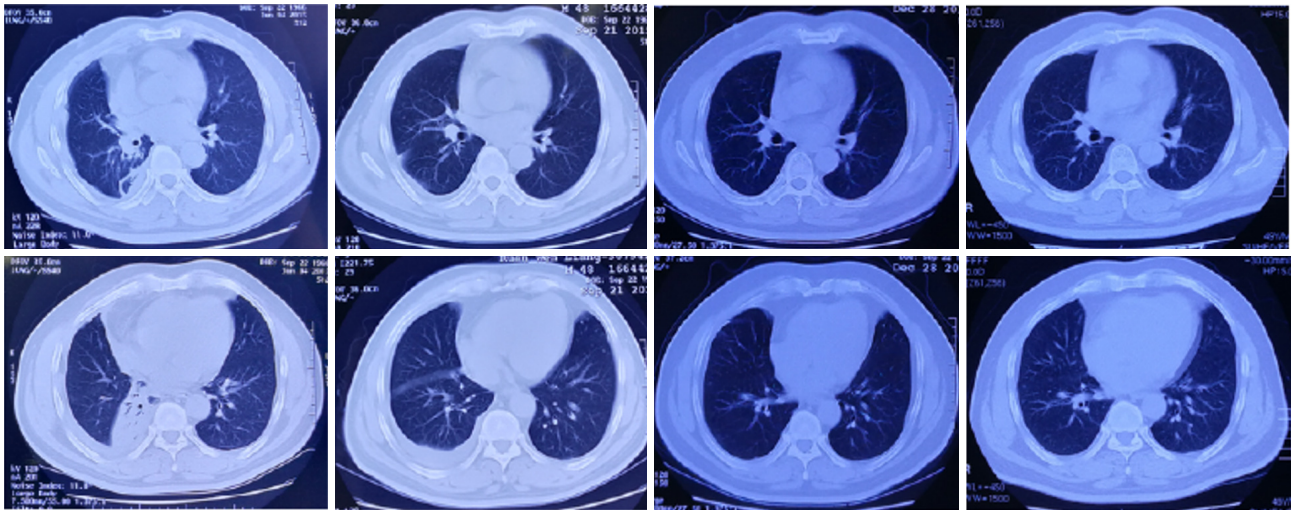


图1 胸部CT见右侧胸膜、纵隔胸膜及膈胸膜多发结节状影，右肺下叶阴影(左图：肺窗，右图：纵隔窗)

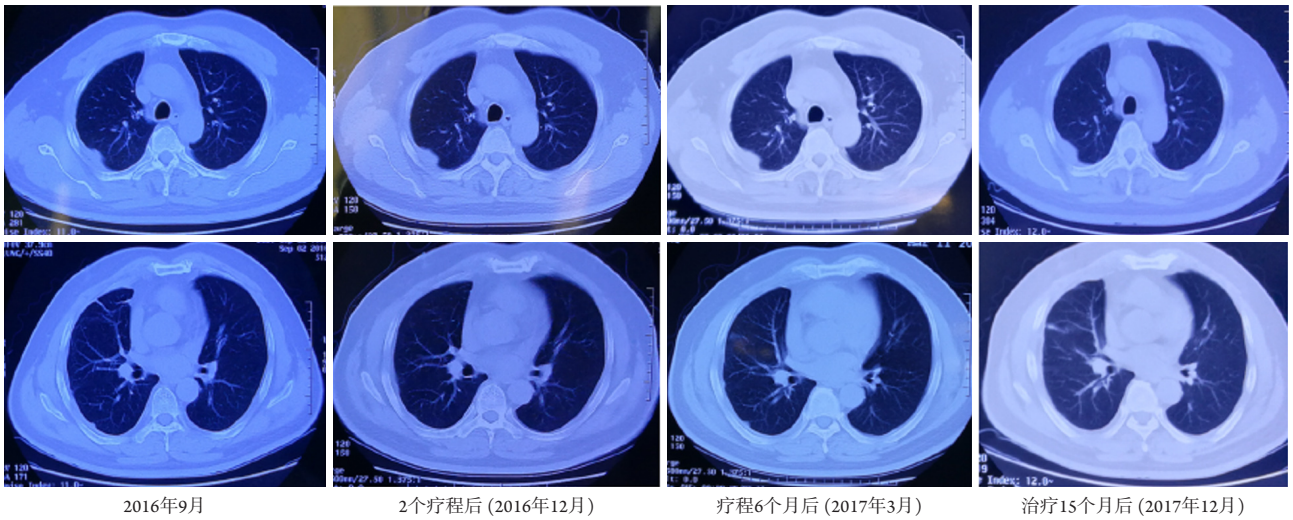
Figure 1 Chest CT shows multiple nodules on the right pleura, shadow in the right lower lobe, and right-sided pleural effusion (left: lung window, right: mediastinum window)



基线 (2015年6月) 2个疗程后 (2015年9月) 疗程6个月后 (2015年12月) 治疗12个月后 (2016年6月)

图2 一线治疗胸部CT随访显示治疗后胸部病灶明显缩小，疗效达PR

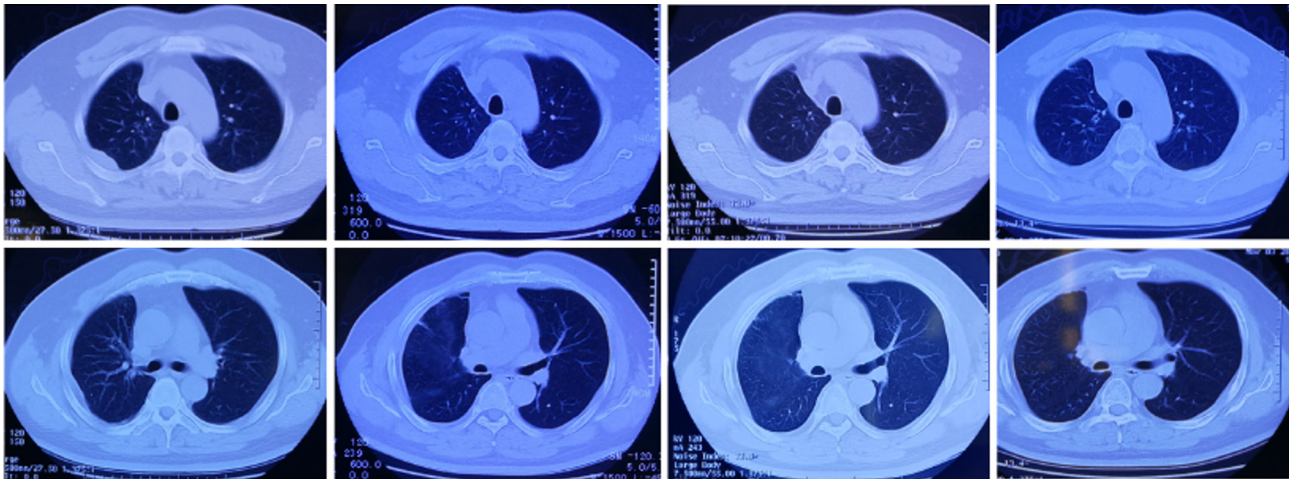
Figure 2 Chest CT results during the first-line display a significant tumor shrinkage which indicates a partial regression



2016年9月 2个疗程后 (2016年12月) 疗程6个月后 (2017年3月) 治疗15个月后 (2017年12月)

图3 二线治疗胸部CT随访显示病灶维持稳定

Figure 3 Chest CT results during the second-line show that the lesions remain stable



治疗前 (2018年3月)　治疗2个月后 (2018年6月)　治疗6个月后 (2018年10月)　治疗1年后 (2019年5月)

图4 三线治疗胸部CT随访显示病灶消失，疗效评价为CR

Figure 4 Chest CT results during the third-line show a complete regression

2 讨论

对于EGFR敏感突变的晚期NSCLC患者，联合用药是延缓EGFR-TKIs耐药、延长患者生存的重要策略。既往研究[7-9]显示：EGFR-TKIs与化疗或与抗血管生成药物联合可明显改善预后。该病例患者历经三线治疗，采用联合治疗的手段，获得了长期生存。

EGFR-TKIs联合化疗具有抑制NSCLC增殖、延缓耐药的协同作用[10-12]。EGFR-TKIs目前是EGFR敏感突变晚期NSCLC的标准一线治疗方案。既往研究[5,7-9]显示：一、二代EGFR-TKIs治疗的PFS为9~13个月，耐药进展不可避免。但一代EGFR-TKIs例如吉非替尼、厄洛替尼等联合传统化疗较单药EGFR-TKIs治疗客观缓解率(objective response rate，ORR)提高、显著延长PFS达15~17个月，OS也有明显延长[7-9]。基础研究[10-12]显示：MAPK，PI3K/AKT，ERK5，TGF-β，SAPK/JNK及端粒酶信号通路在NSCLC发生发展过程中起重要作用，而联合治疗可抑制相关通路，从而抑制肿瘤生长。值得注意的是，在吉非替尼联合培美曲赛/铂类一线晚期NSCLC的临床试验中，有10%的患者出现了3/4级骨髓抑制[9]，而本病例中患者在2个疗程联合治疗后，同样出现3度骨髓抑制，白细胞、血小板下降，将后续化疗药物调整为培美曲赛单药后未再出现骨髓抑制的不良反应，而一线治疗的PFS也达15个月，与既往联合治疗的PFS相符。

贝伐珠单抗为抗血管生成药物。在肿瘤的发生、发展和转移环节中，血管内皮生长因子(vascular endothelial growth factor，VEGF)是影响肿瘤与环境之间相互作用的重要介质，VEGF通过与VEGF受体(VEGF receptor，VEGFR)结合，促进肿瘤异常血管内皮细胞的增生、迁移，并增加异常血管通透性，而抗血管生成剂起到修剪和正常化肿瘤新生血管的作用，贝伐珠单抗是人源化的抗VEGF药物，通过结合VEGF使VEGFR丧失活化的机会，从而发挥抗血管生成的作用[13-14]。BEYOND试验[15]证实了贝伐珠单抗在一线治疗中的疗效。在二线治疗中，多中心II期临床试验[16-17]显示：贝伐珠单抗联合培美曲赛等化疗方案是有效且可耐受的，疾病控制率可达50%~73%，中位PFS达4.1~5.8个月。此外，鉴于VEGF在肺癌恶性胸腔积液(malignant pleural effusion，MPE)发病机制中的关键作用，贝伐珠单抗已被证实能有效抑制MPE的累积。贝伐珠单抗联合化疗治疗MPE疗效显著高于单纯化疗，且毒性可耐受[18-20]。本病例患者二线应用贝伐珠单抗联合治疗后，疗效为SD，二线PFS达到18个月，显示出贝伐珠单抗联合治疗的疗效。在治疗过程中，未出现贝伐珠单抗相关的常见不良反应，例如高血压、肾功能损害、出血等，可能和应用中调整了用药间隔时间和剂量相关。本病例中用药间隔从临床试验常规每3周1次调整到每月1次，用药剂量从常规15 mg/kg调整到5 mg/kg。

患者在二线治疗进展、发现EGFR T790M耐药基因后，三线治疗采用的是三代EGFR-TKIs奥西替尼联合贝伐珠单抗。早期的基础研究[21]显

示：贝伐珠单抗联合EGFR-TKIs，即抑制VEGFR和EGFR双通路能有效阻断EGFR-TKIs耐药进展。基于此，奥西替尼联合贝伐珠单抗的I/II期临床研究(WJOG8715L)目前正在进行中[22]。本病例中，三线奥西替尼联合贝伐珠单抗治疗后，胸膜病灶基本消失，最佳疗效达到CR，但是在治疗过程中，出现了蛋白尿2+，考虑为贝伐珠单抗常见的不良反应，停用贝伐珠单抗后好转。既往研究[15]显示：肾功能受损是贝伐珠单抗除高血压、出血外常见的不良反应，肾功能损害中常见蛋白尿(>3.5 g/d)，其他症状包括微血尿、血清肌酐水平增高，甚至急性肾衰竭和无尿，这些症状在贝伐珠单抗停药后预后相对较好，提示我们在治疗过程中应密切检测，早期识别贝伐珠单抗引起的不良反应。本病例三线治疗PFS至今已达17个月，仍在治疗随访中，总体OS已达51个月。

本病例体现了联合治疗延缓耐药、延长晚期EGFR阳性NSCLC生存预后的作用。该患者经历联合治疗模式包括EGFR-TKIs联合化疗、抗血管生成药物联合化疗、三代EGFR-TKIs联合抗血管生成药物等，患者的总OS已达4年之久，目前仍在三线治疗随访期间。在联合治疗过程中，临床医生不仅需要关注疗效，也需要同时关注毒性反应及药物经济学因素。本病例联合治疗毒性可耐受，也得益于靶向药物及抗血管生成药物的慈善援助项目，患者的经济负担大为减轻，这些因素都是患者获得长期生存的重要原因。

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