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驱动基因阳性的晚期肺腺癌精准治疗 1 例

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[摘　要]　现报告1例表皮生长因子受体(epidermal growth factor receptor，EGFR)基因19号外显子缺失突变阳性晚期肺腺癌病例的诊疗过程。患者入院后，根据其疾病分期以及基因突变情况，给予一线EGFR抑制剂吉非替尼治疗后部分缓解，进展后培美曲塞联合顺铂标准化疗也有部分缓解，很快再次进展，随后加入AURA17临床研究，奥希替尼治疗后部分缓解，4个月后复查进展，最后因多脏器功能衰竭死亡，总生存期约20个月。此病例的诊疗过程提示基因检测在晚期肺癌全程管理中的重要性。

[关键词]　非小细胞肺癌；表皮生长因子受体；酪氨酸激酶抑制剂；靶向治疗

Precision treatment of advanced lung adenocarcinoma with driver gene positive: A case report

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Abstract　The diagnosis and treatment of an advanced lung adenocarcinoma case with exon 19 deletion of EGFR gene positive is reported. First-line treatment with EGFR inhibitor gefitinib was administrated for the patient based on disease stage and genetic mutation state. After this treatment, the patient gained partially response. After 9.5 months, she progressed again and accepted standard chemotherapy, pemetrexed combined with cisplatin, which also showed partial response. But it soon made progress again. Fortunately, the patient could attend the AURA17 study, partial remission was achieved after treatment with osimertinib. Four months later, the patient's disease progressed. Finally, she died of multiple organ failure and overall survival was 20 months. The diagnosis and treatment of this case suggests the importance of genetic testing in the overall management of advanced lung cancer.

Keywords　non-small cell lung cancer; epidermal growth factor receptor; tyrosine kinase inhibitors; targeted therapy

肺癌是全球发病率和病死率最高的恶性肿瘤之一，其中非小细胞肺癌(non-small cell lung cancer，NSCLC)占80%~85%，80%的NSCLC为晚期肺癌患者[1]。随着分子基因检测技术和抗肿瘤药物研发的进展，对于驱动基因阳性的NSCLC患者，分子靶向治疗已经被美国国立综合癌症网络(National Comprehensive Cancer Network，NCCN)指南和中国临床肿瘤学会(Chinese Society of Clinical

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Oncology，CSCO)指南推荐为一线治疗。表皮生长因子受体(epidermal growth factor receptor，EGFR)是亚裔人群肺腺癌发生频率最高的驱动基因[2]，EGFR酪氨酸激酶抑制剂(tyrosine kinase inhibition，TKI)能竞争性地与ATP结合位点结合从而阻断配体激活EGFR以及下游的信号通路，最后致抗肿瘤作用。临床研究[3-7]显示TKI一线治疗EGFR敏感突变的晚期NSCLC患者缓解率(response rate，RR)和无进展生存期(progression-free survival，PFS)均明显优于化疗组。现将南京医科大学附属杭州医院收治的1例晚期肺腺癌病例的诊疗过程报告如下。

1 临床资料

患者，女，63岁，否认吸烟史。因咳嗽咳痰、痰中带血丝2个月于2014年8月就诊南京医科大学附属杭州医院，2014年8月5日查胸部CT(平扫+增强)提示：右肺上叶前段占位，肺癌考虑，伴右肺多发结节灶、纵隔及右肺门肿大淋巴结伴纵膈小结节。上腹部CT(平扫+增强)示：贴近右肝后段的胸膜处异常密度灶，考虑胸膜转移。头颅MRI以及骨ECT均未见明显占位。于2014年8月6日行CT引导下右肺肿块穿刺术，术后病理示中分化腺癌，免疫组织化学：CK(+)，TTF-1(+)，CK7(+)，CK20(−)，CEA(+)，CDX2(局部+)，TG(−)。EGFR基因检测(ARMS法)提示：19外显子缺失，18，20，21外显子无突变。诊断：右肺腺癌伴右肺内、纵膈淋巴结及胸膜转移(T4N2M1，IV期)，EGFR基因敏感突变型。于2014年8月14日开始口服吉非替尼片250 mg，每日一次。1月后复查胸部CT提示右上肺病灶明显缩小，评估PR，定期复查维持PR。2015年5月29日胸部CT提示疾病进展(图1)。2015年5月31日起予培美曲塞0.6 g d1+顺铂50 mg d1~2每周3次，静脉化疗4周期，2周期后复查胸部CT提示左肺部明显缩小，疗效PR，4周期后(2015年8月17日)复查胸部CT提示肺部病灶进展。之后患者加入奥希替尼中国注册研究——AURA17临床研究，再次活检，组织EGFR基因示：19外显子缺失突变，20外显子T790M，筛选成功。2015年9月4日开始奥希替尼(AZD9291)80 mg，每日1次口服，6周评估PR，12周维持PR，18周(2016年1月)时查胸部CT(图2)提示靶病灶进展，腹部CT提示腹腔积液，评估PD，终止用药。引流腹水找脱落细胞，病理提示低分化腺癌。腹水蜡块切片行基因二代测序提示：EGFR基因19外显子缺失(36.77%)，PIK3CA+(13.87%)。2016年1月12日开始顺铂60 mg d1，d8+人血管内皮抑制素(恩度)60 mg d1，d8腹腔化疗后腹水消失。2016年1月21日开始多西他赛40 mg d1，d8静脉化疗。2016年2月17日出现胸水，予顺铂联合恩度胸腔灌注，胸水消失。2016年3月17日肺部病灶再次进展，腹胀明显，腹部可及包块，腹部CT提示腹腔内广泛转移(图3)，疾病迅速进展，2016年4月12日死亡。

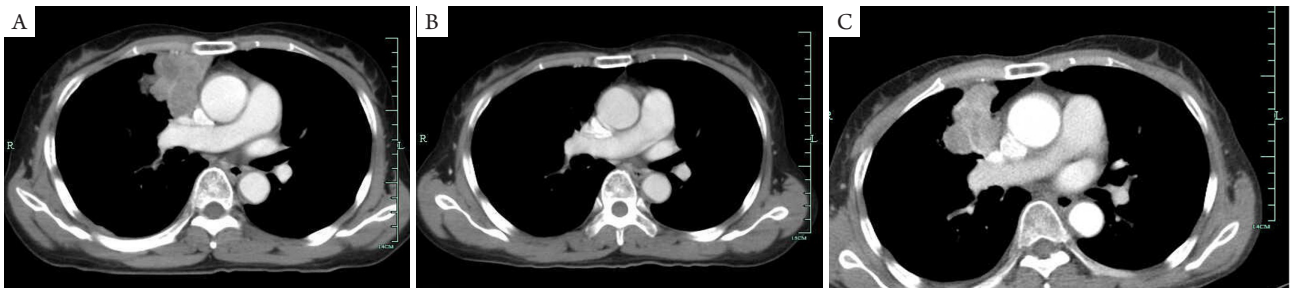

图1 吉非替尼治疗前后胸部CT

Figure 1 Chest computed tomography (CT) before and after the treatment with gefitinib

(A)患者初诊时；(B)吉非替尼治疗1个月后；(C)吉非替尼治疗9.5个月后耐药。

(A) Initial diagnosis of the patient; (B) 1 month after treatment with gefitinib; (C) Resistance to gefitinib after 9.5 months of treatment.

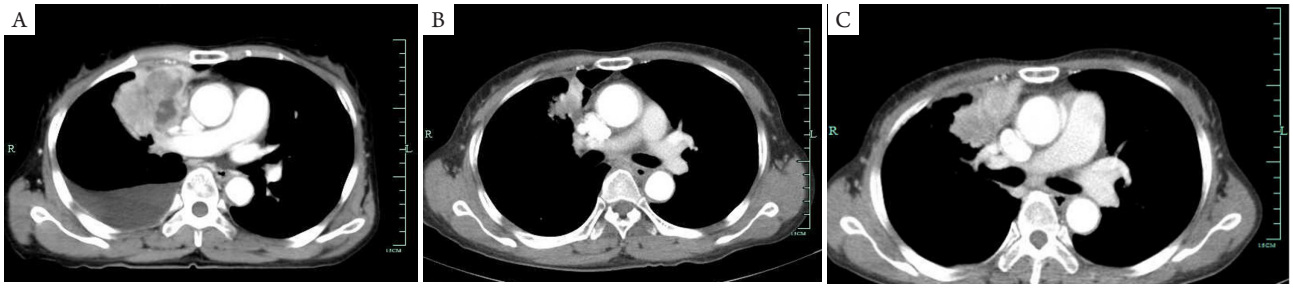

图2 奥希替尼治疗前后胸部CT

Figure 2 Chest CT before and after treatment with osimertinib

(A)奥希替尼治疗前；(B)奥希替尼治疗6周后，(C)奥希替尼治疗18周后耐药。

(A) Before the treatment with osimertinib; (B) Six weeks after the treatment with osimertinib; (C) Resistance to osimertinib after 18 weeks of treatment.

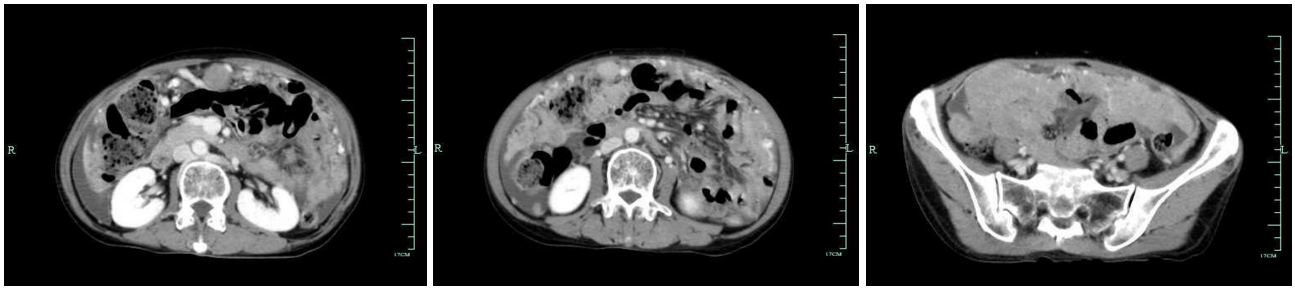

图3 腹部CT提示腹腔内广泛转移瘤伴肠管受累

Figure 3 Abdominal CT showed the tumor spread widely in the abdominal cavity and involved the bowel

2 讨论

患者首诊为晚期肺腺癌，EGFR基因突变敏感型，根据NCCN指南和2015年中国原发性肺癌诊疗规范，予一线吉非替尼治疗，9.5个月后出现进展，虽然靶向治疗疗效有目共睹，但是不可避免的会面临耐药问题，有数据[8]显示：绝大多数患者在EGFR-TKI治疗6~12个月后出现耐药，EGFR-TKI的耐药可分为原发性耐药、获得性耐药以及适应性耐药。本例患者吉非替尼用药后9.5个月出现进展，考虑获得性耐药[9]。耐药后患者检测组织EGFR基因提示20外显子T790M突变。研究[10]表明：约50%的患者耐药性是由T790M二次突变介导的，T790M二次突变也是继发性耐药可能的机制之一。AURA3临床研究[11]显示：对于具有T790M突变的一线TKI治疗后耐药的晚期NSCLC患者，奥希替尼治疗组的中位PFS为10.1个月，显著高于化疗组的4.4个月(HR：0.30，95%CI：0.23~0.41)，奥希替尼、化疗组的ORR分别为71%和31%(OR=5.39，95%CI：3.47~8.48)。目前奥希替尼已经被美国和中国食品药品监督管理局批准用于T790M二次突变晚期NSCLC的靶向治疗，并被NCCN指南和CSCO指南优先推荐。本例患者在2015年有幸参与奥希替尼中国注册临床研究AURA17研究，免费获得奥希替尼治疗，疾病再次快速进展后，腹水蜡块切片行二代测序提示：EGFR基因19外显子缺失(36.77%)，PIK3CA+(13.87%)。奥希替尼耐药机制复杂[12]，包括T790M突变丢失，EGFR获得性突变如C797S突变，MET扩增，细胞周期基因变异，HER2扩增，PIK3CA扩增/突变，致癌基因融合，BRAF V600E突变等，甚至有些耐药机制仍然不明。本例患者奥希替尼耐药机制为T790M丢失和PIK3CA突变，PIK3CA突变致下游信号通路的激活促进恶性肿瘤的发展和转移，其丰度高提示患者预后不佳，患者三代TKI疗效不佳，可能与PIK3CA下游通路的激活有关。

对于EGFR基因敏感突变的晚期NSCLC患者，一线TKI治疗是目前标准的治疗，相比较以铂类为基础的双药化疗，显著延长了患者的无进展生存期。目前TKI有一代、二代和三代，FLAULA研究[13]提示三代TKI优于一代TKI，而且众多临床研

究提示一代TKI联合抗血管治疗[14-16]或化疗[17-18]较单独TKI显著延长了PFS，而OS是否真正获益需要更多研究证实。因此，选择哪一代TKI治疗或者是否选择更激进的联合治疗，仍需要筛选更合适的病例进一步研究。此外，三代TKI奥希替尼的耐药机制复杂，针对奥希替尼耐药后的治疗仍需要探索和研究。

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