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CASE REPORT

Anti-angiogenesis Therapy in Lung Cancer: a Practical Approach

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ABSTRACT

In advanced pulmonary carcinoma, determination of epidermal growth factor receptor (EGFR) mutation status, histology, and anaplastic lymphoma kinase (ALK) *mutation status can be highly instructive for guiding the course of treatment. EGFR mutation status is a strong predictor of response to EGFR tyrosine kinase inhibitor therapy; non-squamous cell carcinoma predicts response to pemetrexed; and targeted therapy now exists for non–small-cell lung cancer that is positive for the* ALK *gene mutation. A patient case of advanced non–small-cell lung cancer is presented to provide a practical context for discussing management. The patient is a 55-year-old female never-smoker who presented with a dry, persistent cough, right scapular and persistent upper- / mid-thoracic back pain, and significant, gradual weight loss. She required urgent surgery to relieve spinal cord compression. The diagnosis of primary adenocarcinoma of the lung, positive for CK7 and TTF-1, and negative for CK20, was made following physical examination, imaging, and pathological investigations. The patient was initially treated with standard platinum-based chemotherapy, to which bevacizumab was added following disease progression — a strategy that met with good response and tolerability. Upon disease progression and determination of* ALK*-positive non–small-cell lung cancer, targeted therapy with crizotinib was initiated, which showed good partial response until the last follow-up in July 2013. The evidence-based rationale for the treatment approach adopted for this patient is described.*

Key Words: *Adenocarcinoma; Carcinoma, non-small-cell lung; Platinum; Receptor, epidermal growth factor; Treatment outcome*

中文摘要

肺癌的抗血管生成療法：一個實用的門徑

何重文

在晚期肺癌中，判斷表皮生長因子受體（EGFR）突變狀態、組織學和間變性淋巴瘤激酶突變狀態，對治療過程具相當的指導性。EGFR突變狀態是對EGFR酪氨酸激酶抑制劑治療反應的一個強力預測因素；非鱗狀細胞癌可預測對培美曲塞（pemetrexed）的反應；而對於間變性淋巴瘤激酶（*ALK*）基因突變呈陽性的非小細胞肺癌，現已有標靶治療可以使用。本文報導一個晚期非小細胞肺癌患者的病例，作為討論病人治療的實用背景。一名55歲、從不吸煙的女性，出現持續乾咳、右肩胛疼痛、上／中胸背部持續疼痛、以及顯著的體重逐步下降。患者需要接受緊急手術以舒緩脊椎壓迫。在身體檢查、影像及病理化驗後，診斷為CK7及TTF-1陽性、CK20陰性的原發性腺癌。患者起初以鉑類為基礎的標準化療進行治療；當疾病惡化，加入了貝伐株單抗（bevacizumab），作為達致良好反應及耐受性的策略。疾病出現惡化並判斷為*ALK*陽性非小細胞肺癌後，患者開始接受克里唑蒂尼（crizotinib） 標靶治療；直至2013年7月的最後一次跟進，患者有良好的局部反應。本文敍述了這名患者治療方案的循證理據。

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CASE REPORT

A 55-year-old woman presented with dry cough for 3 months; right scapular and upper- / mid-thoracic back pain for 2 months; and significant, gradual weight loss of around 10 lbs. She was a never-smoker, with a history of hypertension and Graves' disease. The Graves' disease had been treated with thyroidectomy and subsequent T4 replacement hormone therapy. She was also a hepatitis B carrier and was on entecavir. She had good performance status (PS 1).

Physical examination revealed shotty left supraclavicular lymph nodes, dullness in the chest, reduced entry of air to the left lung base, and bilateral mild lower limb weakness at the sensory level of T6. Magnetic resonance imaging of the spine showed multiple vertebral metastases, predominantly involving the thoracic and lumbar spine. In particular, there was significant T3 vertebral collapse with epidural spinal cord compression. The positron emission tomography–computed tomography (PET-CT) scan showed a hypermetabolic primary mass in the left lower lobe and multiple hypermetabolic mediastinal lymph nodes.

The spinal cord compression warranted urgent surgery which involved posterior spinal fusion, laminectomy for decompression, and excision of the extradural lesion at the thoracic spine. Based on pathological findings, the patient was diagnosed with primary adenocarcinoma of the lung that was positive for CK7 and TTF-1, but negative for CK20.

Treatment

Post-surgery, the patient received radiotherapy to the thoracic spine, and zoledronic acid every 4 weeks. Bone tumour biopsy, performed to determine her epidermal growth factor receptor (EGFR) mutation status, was inconclusive and failed to establish a definitive EGFR mutation status. Thus, the patient was initiated on standard platinum-based doublet chemotherapy with pemetrexed/cisplatin every 3 weeks. Treatment with EGFR tyrosine kinase inhibitor (TKI) was not attempted.

Following three cycles of chemotherapy, there was very significant improvement in the primary lung adenocarcinoma in the left lower lobe, in terms of both size and metabolic activity. There was also some response in the bone lesions, including resolution of the right rib lesion and muscle activity adjacent to the right scapula. However, simultaneously, there was worsening of bone lesions at T11, L5 and the left posterior ilium. There was also worsening in the right femoral head lesion and the left acetabulum lesion, and new bone lesions were detected by PET-CT, indicating disease progression. Nevertheless, the tumour bulk, as a whole, appeared to be significantly reduced as a result of chemotherapy.

At this stage, the following treatment options were considered for the patient: continuing with pemetrexed/cisplatin; switching to second-line chemotherapy (eg, docetaxel); switching to EGFR TKI therapy; or adding on bevacizumab (BEV) to pemetrexed/cisplatin. It was decided to add BEV 7.5 mg/m^2 to the existing chemotherapy starting cycle 4. The rationale for continuing with the standard chemotherapeutic regimen was based on the marked improvement in the overall tumour bulk and favourable response in some of the bone lesions.

After completing 6 cycles of induction chemotherapy, PET-CT showed that the primary adenocarcinoma in the left lower lobe was, essentially, no longer metabolically active. The L3 and L5 bone lesions also resolved, as did the ones in left posterior ilium. Further improvements were also noted in the primary left lower lobe tumour, bilateral lung lesions, pretracheal node and multiple bone metastases.

The patient continued with maintenance therapy with BEV/pemetrexed every 3 weeks. This was very well tolerated, with the patient showing only mild hypertension, which was controlled using a single antihypertensive drug. She had excellent performance status and quality of life. However, after around 1 year, in August 2011 (at cycle 15 of maintenance treatment), disease progression, predominantly in the bone, was detected by PET-CT reassessment. There were some differences in opinion regarding subsequent therapy, due to the lack of evidence in this setting and the patient's indeterminate EGFR mutation status. Erlotinib was initiated, and zoledronic acid was switched to denosumab, upon documented disease progression by PET-CT. Upon further disease progression by PET-CT showing more prominent left lower lobe primary tumour, treatment with BEV/gemcitabine/carboplatin for three cycles was initiated without inducing objective response.

The patient then underwent bronchoscopy with transbronchial lung biopsy, which allowed confirmation

of adenocarcinoma that was positive for the anaplastic lymphoma kinase (*ALK*) gene rearrangement (determined by fluorescence in-situ hybridisation). Thus, treatment was changed again in January 2012 to the targeted agent crizotinib, which elicited a good partial response. Breakthrough brain metastases were diagnosed in November 2012, which were treated effectively with whole-brain radiotherapy (WBRT). Crizotinib was continued following WBRT, until present. In her last follow-up in July 2013, the patient had excellent performance status (PS 0).

DISCUSSION

Rationale for Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor Versus Platinum-based Doublet Chemotherapy

In the current case, an attempt was made to determine the patient's tumour EGFR mutation status, as such information can help to decide whether there is an indication for EGFR TKI therapy. The rationale is based on data from several studies that have shown EGFR mutation status to be a strong predictor of improved outcomes with EGFR TKI therapy.

In the landmark phase III, open-label IPASS study, previously untreated East Asian patients with advanced pulmonary adenocarcinoma, who were never-smokers or former light smokers, were randomised to receive either gefitinib or carboplatin-paclitaxel.[1] The primary endpoint was progression-free survival (PFS). At 12 months, PFS was 24.9% with gefitinib and 6.7% with carboplatin-paclitaxel. Thus, gefitinib demonstrated both non-inferiority and superiority to carboplatin-paclitaxel in the primary endpoint (hazard ratio [HR] for progression or death = 0.74; 95% confidence interval [CI], 0.65-0.85; $p < 0.001$). Moreover, in the subgroup of patients with EGFR mutation-positive tumours, PFS was significantly longer in those treated with gefitinib than with carboplatin-paclitaxel (HR for progression or death = 0.48; 95% CI, 0.36-0.64; $p < 0.001$). In comparison, PFS in the subgroup without EGFR mutations was significantly longer with carboplatin-paclitaxel than with gefitinib (HR for progression or death with gefitinib = 2.85; 95% CI, 2.05–3.98; $p < 0.001$).

Patients with EGFR mutation-positive tumours receiving gefitinib also showed significantly higher objective response rate (ORR; secondary endpoint) than those receiving standard chemotherapy (71.2% vs. 47.3%, respectively; odds ratio [OR] = 2.75; $p < 0.0001$). However, there was practically no ORR with gefitinib in patients with EGFR mutation-negative tumours versus standard chemotherapy (1.1% vs. 23.5%, respectively; OR = 0.94; $p < 0.0013$).

Similarly, the OPTIMAL study, an open-label, randomised, multicentre, phase III trial of mainland Chinese patients with EGFR mutation-positive stage IIIB or IV non–small-cell lung cancer (NSCLC), also showed that the EGFR TKI erlotinib conferred significantly greater PFS benefit than standard chemotherapy with gemcitabine plus carboplatin (median PFS, 13.1 vs. 4.6 months; HR = 0.16; 95% CI, 0.10-0.26; $p < 0.0001$).[2]

Finally, non-squamous histology in NSCLC can be a predictor of response with the chemotherapeutic agent pemetrexed. This was first demonstrated in a non-inferiority, phase III, randomised study by Scagliotti et al,[3] which compared the overall survival (OS) in chemotherapy-naive patients with stage IIIB or IV NSCLC treated with cisplatin/gemcitabine or cisplatin/pemetrexed. The study results showed that OS with cisplatin/pemetrexed was non-inferior to cisplatin/gemcitabine (median OS, 10.3 vs. 10.3 months; HR = 0.94; 95% CI, 0.84-1.05). Furthermore, OS was statistically superior with cisplatin/pemetrexed versus cisplatin/gemcitabine in patients with adenocarcinoma (12.6 vs. 10.9 months) and large-cell carcinoma histology (10.4 vs. 6.7 months; $p = 0.03$). In contrast, patients with squamous cell histology showed significantly longer OS with cisplatin/gemcitabine versus cisplatin/pemetrexed (10.8 vs. 9.4 months; $p = 0.05$).

In the present case, a decision to initiate standard chemotherapy with pemetrexed as a component was made based on the histological findings and failure to establish a definitive EGFR-mutation status.

Rationale for Adding Bevacizumab to Pemetrexed/Cisplatin

Upon disease progression with standard chemotherapy, the patient was initiated with treatment with BEV plus pemtrexed/cisplatin. BEV is a humanised monoclonal antibody that targets vascular endothelial growth factor (VEGF), which promotes tumour angiogenesis. Increased VEGF expression is common in NSCLC, and associated with adverse clinical outcomes. The rationale for adding BEV to standard chemotherapy in this patient was based primarily on evidence from two

landmark phase III clinical trials (E4599 and AVAiL), as well as supporting information from the phase IV post-marketing SAiL study.[4-7] Without losing disease control of the main tumour bulk from the initial 3 cycles of pemetrexed/cisplatin, adding BEV to the same chemotherapy backbone in this patient helped enhance the efficacy of chemotherapy.

The E4599 phase III trial randomised patients with recurrent or advanced NSCLC (stage IIIB or IV) to receive paclitaxel/carboplatin alone or paclitaxel/carboplatin plus BEV in the first-line setting.[4] Chemotherapy was administered every 3 weeks for 6 cycles, and BEV was administered every 3 weeks, until there was evidence of disease progression or unacceptable toxicity. The primary endpoint was OS. Patients receiving chemotherapy-plus-BEV showed significantly longer OS (median OS, 12.3 vs. 10.3 months; HR for death = 0.79; p = 0.003), PFS (median PFS, 6.2 vs. 4.5 months; HR for disease progression = 0.66; p < 0.001) and higher response rates (35% vs. 15%; p < 0.001) versus chemotherapy alone.

The randomised phase III AVAiL study also investigated the efficacy and safety of a standard chemotherapy doublet (gemcitabine/cisplatin) plus low-dose BEV, or high-dose BEV, or placebo, in patients with advanced non-squamous NSCLC.[5,6] The trial, however, was not powered to show a difference in efficacy between the two doses of BEV. The primary endpoint of PFS was significantly prolonged in the low-dose and high-dose BEV groups compared with the chemotherapy/placebo group. The HR for PFS was 0.75 (median PFS, 6.7 vs. 6.1 months with placebo; p = 0.003) in the low-dose group and 0.82 (median PFS, 6.5 vs. 6.1 months with placebo; p = 0.03) in the high-dose group versus placebo. The ORR were 20.1%, 34.1% and 30.4% for placebo, chemotherapy plus low-dose BEV, and chemotherapy plus high-dose BEV, respectively.

Thus, both E4599 and AVAiL were positive trials to support the addition of BEV to standard chemotherapy in BEV-eligible patients with advanced NSCLC. Data from the phase IV postmarketing SAiL trial have further confirmed the findings of E4599 and AVAiL.[7] Across these phase III and phase IV trials, PFS and OS with first-line BEV plus standard chemotherapy have remained consistent, ranging from 6.2 to 7.8 months for PFS, and 12.3 to 14.6 months for OS.[4-7] The ARIES registry in the USA is an ongoing observational study designed to follow patients with locally advanced or metastatic NSCLC (excluding predominantly squamous histology) or metastatic or locally advanced and unresectable colorectal cancer who are receiving BEV in combination with first-line chemotherapy. This registry should provide further evidence on the utility of BEV combination treatment strategies in these settings.

CONCLUSION

In this case of primary pulmonary adenocarcinoma of indeterminate EGFR mutation status, the addition of BEV to standard pemetrexed/platinum chemotherapy enhanced disease control beyond that achieved with standard chemotherapy alone. EGFR mutation status can provide invaluable information with regard to response to EGFR TKI treatment and attempts should be made to determine this in patients with advanced NSCLC. Similarly, histological findings can provide guidance on whether patients will respond to pemetrexed treatment. Clinical trials have also shown that the addition of BEV to standard chemotherapy is effective in prolonging both PFS and OS in the setting of advanced pulmonary adenocarcinoma with either EGFR wild-type or unknown mutation status. Although the current case received this as second-line treatment with good response, BEV added to standard chemotherapy can be considered as an upfront, first-line option in appropriate, BEV-eligible patients with non-squamous NSCLC, based on positive data from clinical trials. In general, very careful selection of patients is crucial to ensure that the risk-to-benefit ratio of this treatment regimen is maximised. Finally, when NSCLC is established as being *ALK*-positive, as in the current case, targeted therapy with agents such as crizotinib may elicit a good partial response and should be considered.

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