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Case Report

Pemetrexed and cisplatin followed sequentially by gefitinib as neo-adjuvant therapy for stage IIB EGFR-mutation-positive lung adenocarcinoma patient: a case report and literature review

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Abstract: Early-stage non-small-cell lung cancer (NSCLC) patients with EGFR mutation positive have a poor prognosis even after complete resection, which raised growing demands for multimodal therapies. Sequential therapy with chemotherapy and EGFR-TKI for advanced EGFR mutation-positive NSCLC patients significantly prolonged PFS, but there has been no report of the efficacy and complications of it in neo-adjuvant therapy for early stage NSCLC patients with EGFR mutation positive. In this paper, the case of a 64-year-old Chinese female patient diagnosed with stage IIB lung cancer harboring EGFR mutation-positive was presented. After two cycles of neo-adjuvant therapy with pemetrexed and cisplatin followed sequentially by gefitinib, the primary lesion was remarkably shrunk. The patient underwent tumor resection and systematic mediastinal lymph node dissection followed by two cycles of adjuvant chemotherapy. The patient had been followed up for 37 months after adjuvant chemotherapy without recurrence or any other complication. And during this period, she didn't receive any anti-cancer therapy. In conclusion, pemetrexed plus cisplatin followed sequentially by gefitinib as neo-adjuvant therapy is effective and safe for early stage NCLC patients with EGFR mutation.

Keywords: Gefitinib, neo-adjuvant therapy, NSCLC, EGFR mutation

Introduction

Lung cancer remains the leading cause of cancer mortality worldwide, in which non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancer cases [1]. The survival rate of lung cancer varies considerately with the stage of cancer [2, 3]. To date, surgery has remained the treatment of choice for early-stage NSCLC, especially in patients with T3N0 NSCLC [4, 5], before the tumor cells develop distant metastasis [3]. Despite aggressive surgical management, stage IIB to IIIA NSCLC patients with a high recurrence rate display an adverse prognosis [6].

Theoretically, neo-adjuvant therapy potentially shrinks tumor, improves the chances of the complete resection, eradicates occult micro metastasis [7, 8], and significantly improves recurrence-free survival, time to distant recurrence and overall survival in resectable NSCLC [9]. After neo-adjuvant therapy, patients with potentially radical lobectomy are more likely to benefit from operation procedures [10]. Disease-free survival (DFS) is increasingly used as the primary end point in early-stage NSCLC randomized trials [6]. A large randomized Southwest Oncology Group Trial S9900 (354 patients) showed that when compared with surgery alone, neo-adjuvant chemotherapy may improve DFS and overall survival (OS) in the clinical stage of IB-IIIA NSCLC, excluding N2 disease and superior sulcus tumors [11]. In addition, aggregate data from randomized controlled trials also indicate neo-adjuvant chemotherapy could improve the overall survival in resectable NSCLC patients [12, 13].

Recently, EGFR mutations have been reported as a predictor of benefit to EGFR TKIs [14-19]. It has been suggested by several reports with

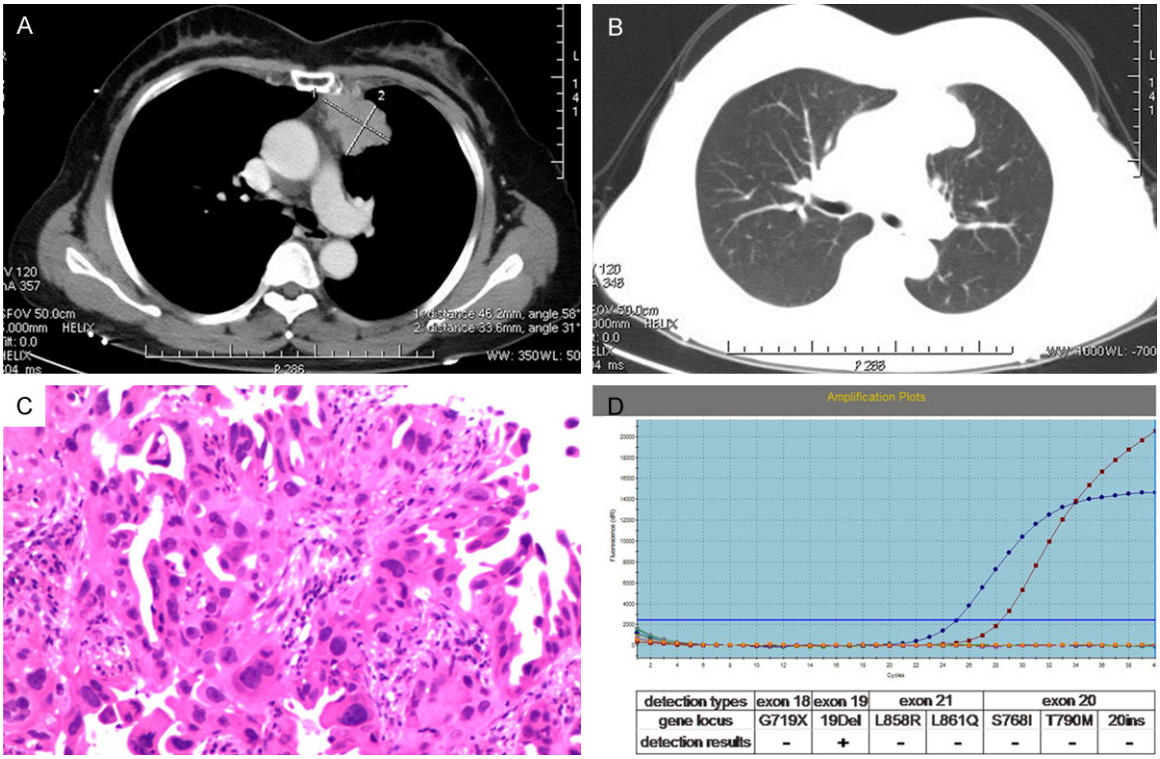

Figure 1. Imaging of patients before treatment. A. (mediastinal window) and B. (pulmonary window), chest computed tomography (CT) scan demonstrated an abnormal mass in the upper lobe of the left lung without lymph node enlargement. C. Immumohistochemical staining of biopsy tissue in the upper lobe of the left lung is histologically consistent with papillary adenocarcinoma, (magnification, 400 ×). D. EGFR molecular analyses of biopsy sample using Real-time fluorescent PCR showed the patient harbored deletion mutation in exon 19.

smaller sample sizes that preoperative EGFR-TKIs is safe and feasible to improve response rate of early-stage NSCLC [20, 21] and even results in N2 down-staging prior to attempted resection with locally advanced NSCLC harboring EGFR mutation [22, 23].

This report describes the clinicopathological features of a patient with stage IIB EGFR mutation-positive lung adenocarcinoma that exhibited remarkable therapeutic efficacy using pemetrexed plus cisplatin followed sequentially by gefitinib as neo-adjuvant therapy. Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Case report

A 64-year-old Chinese female was admitted to the Affiliated Cancer Hospital of Zhengzhou University (Zhengzhou, China) in November, 2012 due to a suspected mass in the left lung found by health examination. She was a retired white-collar worker, non-smoker or without the influence of secondhand smoke, without cough or fever. With an Eastern Cooperative Oncology Group (ECOG) performance status of 0, she had no family history of any hereditary illnesses. In addition, she did not have any other accompanying diseases and had not taken any medications. The physical examination did not reveal any significant abnormalities. Chest computed tomography (CT) scan revealed a mass in the upper lobe of the left lung with the size of 48 mm×31 mm in the largest dimension with no clear boundary with mediastinal pleura (**Figure 1A** and **1B**). Serum tumor markers included carcinoembryonic antigen (CEA): 10.47 ng/ml, cytokeratin 19 fragment antigen 21-1: 5.14 ng/ml and neuron-specific enolase (NSE): 16.89 ng/ml. The results of laboratory tests, isotope bone scan, the head MRI, and abdominal ultrasound didn't reveal any significant abnormalities. A computed tomography-guided percutaneous lung biopsy was performed on November 21, 2012, in which the histopathological diag-

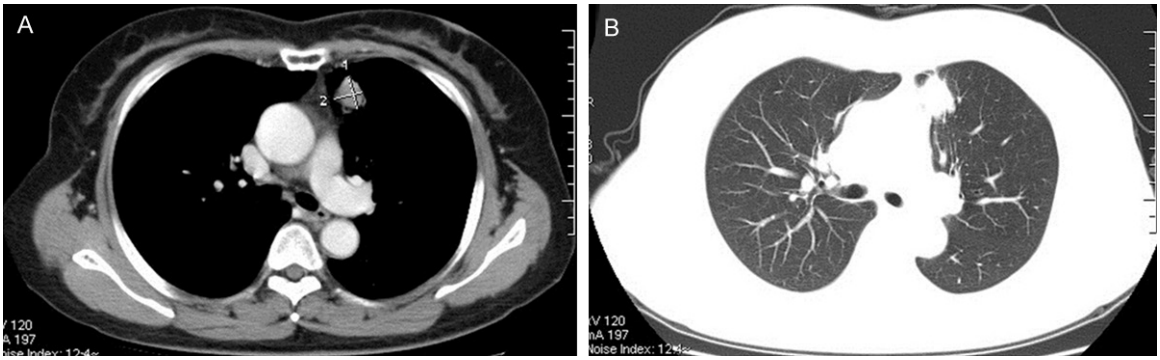

Figure 2. Chest computed tomography (CT) after neoadjuvant therapy. A. (mediastinal window) and B. (pulmonary window), CT scan showed that after 2 cycles of neo-adjuvant therapy, the mass was remarkably reduced.

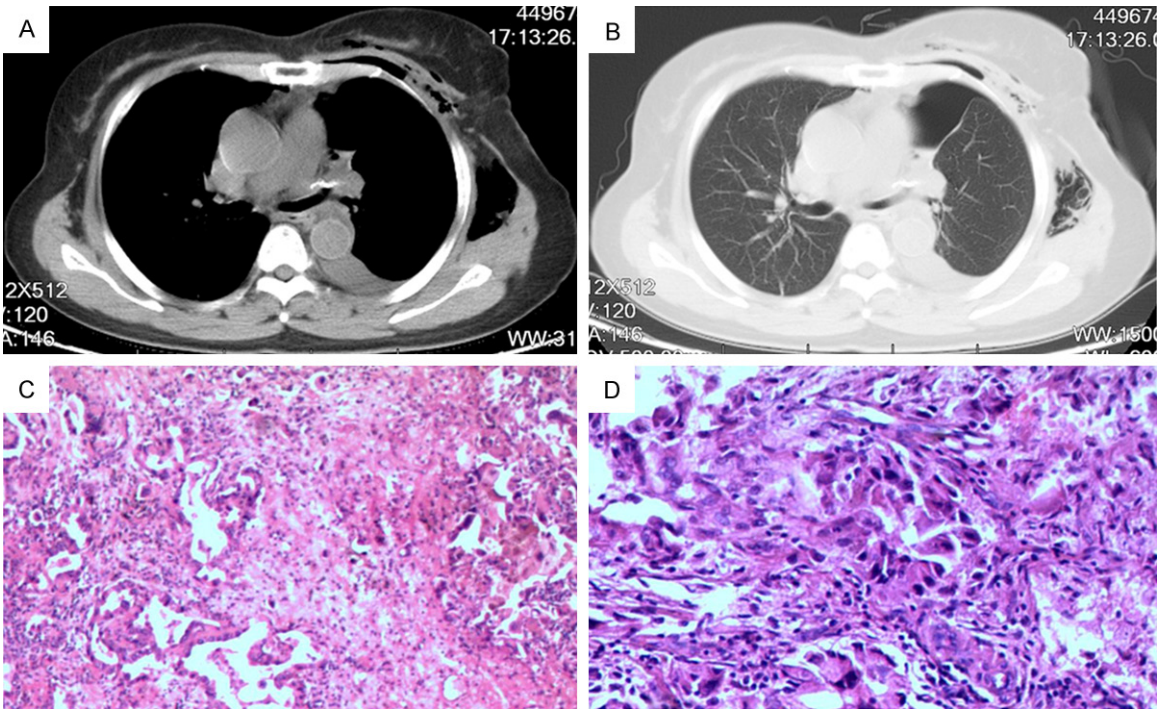

Figure 3. Postoperative CT and postoperative pathology. A. (mediastinal window) and B. (pulmonary window), postoperative CT scan showed that the patient underwent left upper lobe resection. C and D. Postoperative pathology confirmed that the lesion was adenocarcinoma (acinar and adherent growth pattern) (magnification, 400 ×).

nosis of the specimen prompted papillary adenocarcinoma (**Figure 1C**). EGFR molecular analyses of this obtained biopsy sample in exons 18 to 21 by virtue of Real-time fluorescent PCR revealed that the patient harbored deletion mutation in exon 19 (**Figure 1D**). Moreover, anaplastic lymphoma kinase (ALK) fusion protein was negative revealed by VENTANA ALK (D5F3) immunohistochemical staining. The patient with clinical stage IIB (cT3N0M0) [24] could consider surgical resection. Since the tumor indicated no clear boundary with mediastinal pleura, it was not easy to be resected completely. After consultation with the multidisciplinary team (MDT) which includes the cardiothoracic surgeon, medical oncologist and radiation oncologist, the patient underwent neoadjuvant therapy on November 29, 2012. Pemetrexed (500 mg/m^2) and cisplatin (75 mg/m^2) was intravenously administered and the intravenous hydration was infused at around 2000 mL and the patient received intravenous

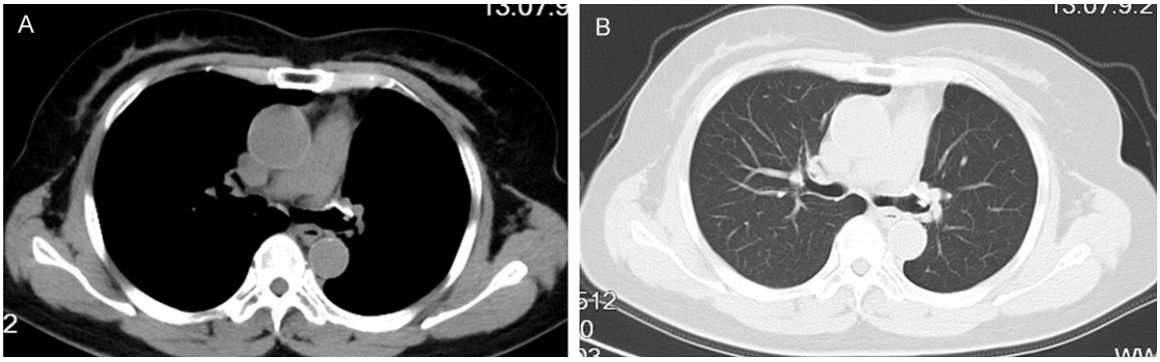

Figure 4. Chest computed tomography (CT) of the patient after she had been followed of 37 months. A. (mediastinal window) and B. (pulmonary window), without recurrence.

injection with diuresis on Day 1; gefitinib (250 mg/d) was taken orally on days 8-17, during which this treatment regimen was repeated every 3 weeks for 2 cycles. After neo-adjuvant therapy, chest CT showed that the primary tumor was significantly shrunk with the size of 17 mm×16 mm (**Figure 2A** and **2B**), which was evaluated as a partial response (PR) according to the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (version 1.1) [25]. But the biochemical examination results indicated that there was slight renal dysfunction--as serum creatine was 117 umol/L. In response, Shenkang injection had been employed until renal dysfunction got complete recovery.

As there were no surgical contraindications, the patient underwent left upper lobe resection combined with systematic mediastinal lymph node dissection and intercostal nerve cryotherapy on January 17, 2013 (**Figure 3A** and **3B**). Postoperative pathology was adenocarcinoma (acinar and adherent growth pattern) with the visceral pleura and the fine bronchus invasion. Also, the bronchial stump was tumor-free and there was no cancer invasion into the lymph nodes (0/15) (pT3N0M0) (**Figure 3C** and **3D**). Subsequently, the patient received two cycles of postoperative chemotherapy with lesser nephrotoxicity paclitaxel liposome (150 mg/m^2) every 3 weeks after complete recovery of the renal function. Serum creatinine was found to be stable around the normal values during the subsequent treatment. The patient had been followed for a duration of 37 months after adjuvant chemotherapy without recurrence or any other complication, during which she hadn't receive any anti-cancer therapy (**Figure 4A** and **4B**).

Discussion

The mechanisms underlying local recurrence and metastasis of early-stage NSCLC remain unclear, and driver gene mutations have been found to be associated with the response to targeted therapies and prognosis of NSCLC [26]. As a driver gene, EGFR is a transmembrane glycoprotein, ligands bound to its receptor triggers both activation of the TK domain, which includes an extracellular ligand-binding domain and an intracellular kinase domain, by initiating signaling pathways and attenuating some receptor signaling achieving equilibrium to drive normal cell growth or apoptosis and differentiation or dedifferentiation [27-30]. EGFR gene is located on the short arm of chromosome 7 (7p21), which is commonly amplified or overexpressed in NSCLC patients [31]. However, the overexpression of EGFR and its ligands in several carcinomas and their association with accelerated tumor progression provide a rationale for targeting this network employing tumor-selective strategies [30]. EGFR TKIs are small molecules that take effect by inhibiting EGFR autophosphorylation, receptor activation and signal transduction [32]. EGFR mutation was the robust predictive factor behind response to EGFR-TKI [33, 34]. A recent study partially demonstrates how they confer susceptibility on TKIs, and that the relative intensities of tyrosine-phosphorylated proteins induced in cells after transfection by EGFR mutant compared to wild-type EGFR were quantitatively and qualitatively different [18].

Currently, the combination treatment of TKIs and chemotherapy has gained growing popularity, which has two modes: the synchronous

mode in which TKI and chemotherapy are administered at the same time; and the sequential mode, in which they are given in an interleaved order [35]. However, concurrent combination does not improve treatment outcome in mutation-positive patients [36]. There may be two reasons behind this: firstly, chemotherapy has been found to activate the EGFR pathway and enhance phosphorylation and subsequent ubiquitination and degradation [37, 38]. Moreover, improper activation of EGFR TK results in increased tumor cell survival, proliferation and metastasis [39, 40]. Secondly, chemotherapy and EGFR-TKI have different mechanisms. Chemotherapy drugs acts by cytotoxicity, whereas gefitinib is cytostatic. The anti-tumor effect of TKIs, by arresting the cell cycle, may lower the sensitivity of cytotoxic agents [41-43]. Nonetheless, it is commonly known that sequential use of EGFR-TKI following chemotherapy is used as the first-line treatment for advanced NSCLC patients with an activating EGFR mutation-positive, which produced improved tumor response compared to EGFR TKI treatment alone [44] and significantly prolonged PFS compared to chemotherapy alone [44, 45].

EGFR-TKIs confer an excellent PFS benefit on patients as the first-line treatment for the advanced NSCLC patients with EGFR activating mutation, especially the high abundance of EGFR mutation [46-48]. The identification of patients with an EGFR activating mutation is crucial to the use of sequential neo-adjuvant treatment. Nevertheless, it still remains uncertain whether or not EGFR-TKI can be applied to neo-adjuvant therapy to improve DFS and OS for early stage NSCLC patients. Therefore, assessment of new therapy is of considerable interest for early NSCLC patients. Several reports showed that neo-adjuvant TKI therapy boasts low toxicity and sufficient activity [20, 21] and would not affect operational difficulty and healing of wounds [49]. Neo-adjuvant EGFR-TKI in operable patients offers a unique opportunity to evaluate pathological changes induced by targeted therapy. Subsequently, pathological features of specimens from patients undergoing surgeries after neo-adjuvant therapy demonstrated that typical structural changes varied accordingly, such as deceleration in tumor cell proliferation, reduction of tumor cellularity, and a noticeable replacement of tumors by fibrotic scar tissues [21, 50]. As we all know the sequential combination of cytotoxic chemotherapy and cytostatic EGFR-TKI delivers a high disease control rate and favorable PFS for advanced NSCLC patients harboring activating EGFR mutation [44, 51]. The preclinical study indicated that the G1 phase arrest induced by EGFR-TKI might have interfered with the cell cycle-dependent cytotoxic chemotherapy resulting in significantly enhanced apoptosis, when the sequential combination of chemotherapy and EGFR-TKI was used [52]. However, the efficacy of sequential combination regimen in neo-adjuvant therapy for early stage NSCLC patients with EGFR mutation remains unknown.

In the present case, a 64-year-old Chinese female patient with EGFR mutation positive who was divided into clinical stage of T3N0M0 and stage IIB in the UICC TNM staging system [7, 53, 54], which exhibits a poor prognosis after conventional management strategies. We administered two cycles of neo-adjuvant therapy with pemetrexed and cisplatin followed sequentially by gefitinib. After two cycles of this therapy, the patient was evaluated as partial response (PR) according to the RECIST 1.1 [25]. It is commonly known that adjuvant chemotherapy has become standard regimen in early stage NSCLC, at least for stage II and resected IIIA NSCLC [55]. Also, DFS rate was significantly improved in early-stage NSCLC patients who received adjuvant chemotherapy after complete surgical resection [56-58]. Since the patient exhibited chemotherapy contraindications-renal dysfunction after neo-adjuvant therapy, which was an acceptable level of toxicity, we had to delay the time of adjuvant chemotherapy until the patient's renal dysfunction was complete recovered. She received two cycles of adjuvant paclitaxel liposome chemotherapy with lesser nephrotoxicity. The data suggest that pemetrexed and cisplatin followed sequentially by gefitinib as neo-adjuvant therapy could remarkably reduce the size of the tumor so that resection is completely more easily. This case report may provide further information benefiting multi-angle disease treatment and research.

Cisplatin-based chemotherapy is the standard first-line regimen for advanced NSCLC patients [59]. Unfortunately, nephrotoxicity is the main

dose-limiting side effect of cisplatin [60-62]. It is well known that renal dysfunction, including slight impairments, which is caused by ≥50 mg/m^2 of administration, could occur in approximately one-third of patients who have undergone therapy [60, 63], even when hydration and diuresis were used adequately [64, 65]. One of the clinical signs of kidney damage is an increase of serum creatinine [66]. Furthermore, a recent research was directed towards the understanding of the molecular and cellular mechanism. According to the research, Cisplatin nephrotoxicity was the composite result of the transport of Cisplatin into renal epithelial cells to activate complex signaling pathways that lead to tubular cell injury and activation of a multiple cell death [67].

To the best of our knowledge, this is the first report on the efficacy and complication of pemetrexed and cisplatin followed sequentially by gefitinib as neo-adjuvant therapy for early stage NSCLC patient with EGFR mutation.

Neo-adjuvant sequential administration of pemetrexed and cisplatin followed by gefitinib in this EGFR mutation positive patient in early stage resectable NSCLC could remarkably reduce the size of tumor so that resection can be completed more easily. Pemetrexed and Cisplatin followed sequentially by gefitinib may potentially become a standard treatment for the early stage NSCLC in the future and some patients may benefit moderately, but whether this treatment could prolong DFS and overall survival or not needs long term follow-up in the future.

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Disclosure of conflict of interest

None.

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