

The clinical efficacy of preoperative induction therapy of icotinib in local advanced non-small cell lung cancer

Chuan Li, Ronghua Yang, Kaihua Tian, Wenjie Jiao

The Thoracic Surgery Department of Affiliated Hospital of Qingdao University, Qingdao 266003, China

Abstract: Numerous studies suggest the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKI) including gefitinib, erlotinib and icotinib have fairly effective anti-tumor activity in local advanced Non-Small Cell Lung Cancer (NSCLC) with mutation or amplification of EGFR gene. We reported two cases of surgical resection after clinical stage downgrading by taking orally icotinib preoperatively in patients with local advanced NSCLC. Both of the patients had mediastinal lymphadenopathy with high FDG uptake and were staged as clinical IIIa. After the induction treatment of icotinib, they both acquired tumor regression and underwent resection of residual disease. The induction treatment did not increase after operative complications in the two patients. We believe that it is significant and necessary to discuss the role of preoperative neoadjuvant therapy of icotinib in patients with local advanced non-small cell lung cancer harboring EGFR gene mutation in future clinical trials.

Keywords: EGFR-TKI; Icotinib; NSCLC; Induction Therapy; Surgical Resection

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Corresponding Author: Chuan Li

1. Introduction

Lung cancer is the first cause of cancer-related death for both men and women worldwide, with a responsibility for the more mortality than a combination of those caused by colorectal cancer, breast cancer and prostate cancer[1]. Non-Small Cell Lung Cancer (NSCLC) accounts for approximately 85% of all the lung cancers and most cases are presented as advanced stage at the first visit[2].

Over the last decade, Epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI), as a targeted therapy regimen, has appeared excellent anti-tumor efficacies in local advanced Non-Small Cell Lung Cancer (NSCLC) with mutation or amplification of EGFR gene[3-5]. EGFR-TKI has been recommended to be the first-line drug for the advanced non-small cell lung cancer patients with EGFR gene mutation[6]. Up to date, there are three target agents: gefitinib, erlotinib and icotinib available in the diseases management. Compared with erlotinib and gefitinib, icotinib shows the same clinical efficacy and higher management safety[7].

In this report, we presented two cases with local advanced non-small cell lung cancer harboring EGFR gene mutation, which underwent lobectomy eventually after the induction treatment of icotinib.

2. Patient one

This was a non-smoking Chinese woman aged 60 years old. She went to see a doctor first time because of her irritating cough for one month. Her chest CT scan revealed a mass of size around 4×3cm in the right upper lobe as well as the hilar and mediastinal lymphadenopathy. Percutaneous Fine-Needle Biopsy of the tumor confirmed a diagnosis of peripheral

adenocarcinoma of the right upper lobe, cT2aN2M0, stage IIIa. After giving consent, she got intravenously cisplatin and paclitaxel chemotherapy two cycles firstly. After admission, she underwent a whole-body [¹⁸F] Fluorodeoxyglucose Positron Emission Tomography-Computed Tomography (¹⁸F-FDG PET-CT) scan which revealed that her primary tumor and the hilar and mediastinal lymph nodes had no significant change compared with before treatment (Figure 1).

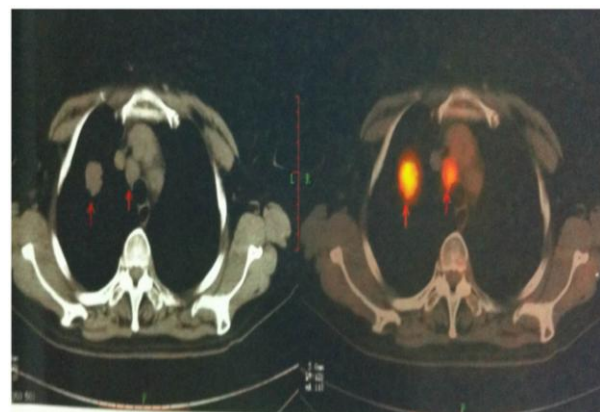


Figure 1. PET-CT (¹⁸F-FDG) scan demonstrated a primary tumor of SUNmax 7.4 and the enlarged hilar and mediastinal lymphadenopathy with high FDG uptake.

There weren't evidences of metastases in rest part of body. To seek an alternative treatment, the EGFR gene in the fine-needle biopsy specimen of lung tumor was characterized and indicated a mutation in the 19th exon. So the patient took orally icotinib at dose of 125mg, three times per day. Four weeks later, the chest CT scan showed the lung tumor as well as the hilar and

mediastinal lymph nodes shrank significantly (Figure 2). In the period, no severe harmful events were seen except for slight rash and initial several times diarrheas. Consequently the patient underwent an operation of the right upper lobe resection and comprehensive lymph node dissection. The postoperative pathologic check of the resected specimens confirmed the

diagnosis of adenocarcinoma in the right upper lobe and metastases in hilar and mediastinal lymph nodes. pT2aN2M0, stage IIIa (Figure 3). The patient continued to take icotinib postoperatively and was followed-up her chest CT scan showed no recurrence of the disease four years later.

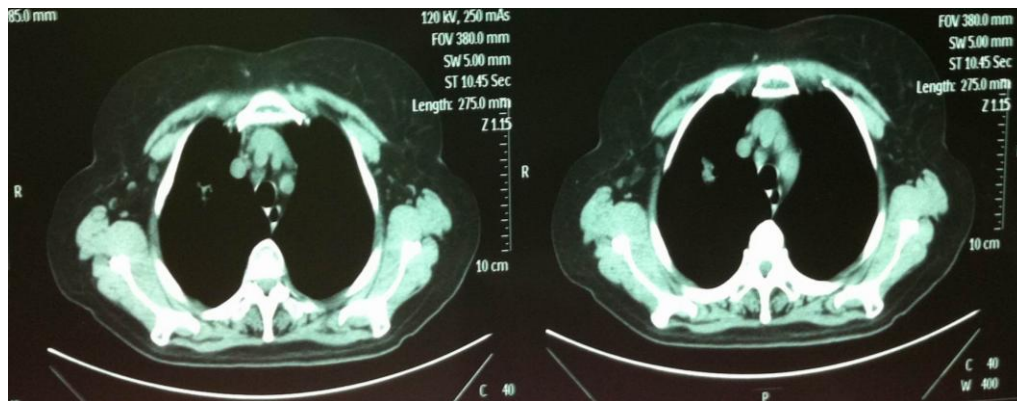


Figure 2. Chest CT scan showed the primary tumor and the hilar and mediastinal lymph nodes shrank significantly after icotinib induction treatment.

3. Patient two

This was a non-smoking Chinese woman aged 56 years old. She went to see a doctor at the first time because of productive cough and short of breathing for two months. Her chest CT scan showed a patchy consolidation lesion and some scattered nodules in the lower and middle lobes of the right lung as well as mediastinal lymphadenopathy. The bronchoscopy biopsy confirmed the diagnosis of adenocarcinoma of her right lung, so the clinical stage was cT4N2M0, stage IIIa. The pulmonary function testing revealed a restrictive ventilatory dysfunction (Table 1). She couldn't withstand a double lobectomy in this case. After giving consent, the EGFR gene of bronchoscopy biopsy specimen of her lung tumor was characterized and indicated a mutation in the 19th exon. So she took orally icotinib at dose of 125mg, 3 times per day. Eight weeks later her respiratory symptoms relieved and chest CT scan showed that the scale of the lesions in her right lung significantly reduced comparing with the previous imaging. Just a small soft tissue mass and little residual nodules left within her right lower lobe. The pulmonary function testing results became almost be in the normal range (Table 2). In the period, no severe advent events were seen except for dry skin and rash of grade I-II. Subsequently the patient underwent a resection of the right lower and middle lobes and comprehensive lymph node dissection. The postoperative pathologic check of the resected specimens confirmed the adenocarcinoma and no metastatic evidence in mediastinal lymphadenopathy, pT4N0M0, stage IIIa. The patient continued to take

icotinib and was followed-up postoperatively. Her chest CT scan showed no recurrence of the disease four years later.

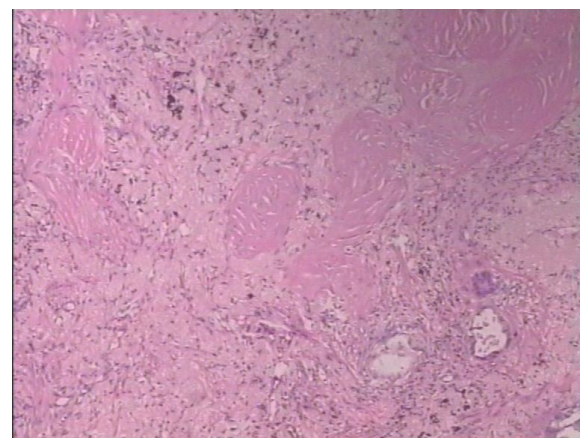


Figure 3. Hematoxylin and eosin staining of the removed tumor tissue (Magnification, 100) confirmed the diagnosis of adenocarcinoma and showed extensive fibrosis of the tumor tissue and a few carcinoma cells infiltrating into the lung mesenchyme.

4. Discussion

Since the first EGFR-TKI agent gefitinib came to the market in 2002, some clinical test studies and clinical experiences have confirmed the significant efficacies of EGFR-TKI on the advanced NSCLC with EGFR gene mutation[4,5,7,8]. EGFR-TKIs have been commended as the first-line treatment of the advanced

NSCLC with EGFR gene mutation by the NCCN guide of NSCLC since 2012. Icotinib was invented by Chinese and came to utilization in clinic in 2011. From then on over ten thousands inoperable patients with advanced NSCLC have taken orally icotinib in the first stage treatment, the second stage treatment and maintenance treatment. Icotinib has been confirmed its equal clinical efficacy to gefitinib and erlotinib. Besides, icotinib management shows higher clinic safety and wider treatment window than the other ones[3,7].

Table 1. Pulmonary function testing results before Icotinib treatment

Spirometry	Pred(L)	Best(L)	Best/Pred(%)
FVC	2.77	2.10	76
FEV1	2.27	1.88	83
MVV	95	65	69

In patients with local advanced NSCLC, preoperative new adjuvant chemotherapy aiming to regress the disease and downgrade the stage has been widely known and accepted[9,10]. However conventional cytotoxic chemotherapy usually develops severe advent events, such as neurotoxicity, renal dysfunction, neutropenia, even myelosuppression, which often lead in the termination of new adjuvant treatment. Early clinical trial data revealed that EGFR-TKI was well tolerated and less toxic compared with cytotoxic drugs[11-13]. In this report, the main toxicities of icotinib were rash and diarrhea of grade I-II, and the both patients could tolerate them throughout. So the favorable tolerance and safety of EGFR-TKIs can seemly open a new path to induction treatment for the patients with advanced NSCLC with EGFR gene mutation.

Table 2. pulmonary function testing results after Icotinib treatment

Spirometry	Pred(L)	Best(L)	Best/Pred(%)
FVC	2.80	2.59	92
FEV1	2.29	2.34	102
MVV	95	81	85

Up to now, there were a few case reports of taking EGFR-TKI agent, gefitinib or erlotinib, as preoperative induction treatment in patients with local advanced NSCLC harboring EGFR gene mutation [14,15]. These cases suggested EGFR-TKIs used preoperatively could induce the tumor regressed. A prospective clinical phase II trial of the preoperative induction treatment of erlotinib in stage IIIA (N2) lung cancer was reported at

the ASCO annual meeting in 2012[16]. The study has got an initial satisfactory result. But none systemic clinical study of the induction treatment of EGFR-TKI agents has been reported so far.

Here we reported two cases of patients who suffered with stage IIIa NSCLC and got icotinib induction treatment before their operations. To the best of our knowledge, this is the first report on taking icotinib alone as a preoperative induction treatment for inoperative NSCLC with stage IIIA (N2). The both patients had the local advanced lung cancer and were not recommended to surgical resection at first. Mutations of EGFR gene were identified in their biopsy specimens of tumors, which suggested their tumors would be responsive to EGFR-TKI. So they took orally icotinib as an induction treatment. Both of them dramatically attained a tumor regression and luckily got tumor resection at last. In the treatments, icotinib played an evident role in downgrading the clinical stage of the local advanced NSCLC. The biological effects investigated in the two cases include as follows: lung tumors and peripheral lesions regression; hilar and mediastinal lymph nodes shrinking; the number of carcinoma cells in the surgical specimen reducing histologically; lymphocytes and macrophage infiltrating in pulmonary parenchyma; excessive fibrosis of the tumor tissue; wall thickening and lumen narrowing of vessels in pulmonary mesenchyme. Interestingly, the pulmonary function of one of the two cases got improved evidently and the patient could sustain the bilobectomy in the end.

Although many literatures and this study showed the preoperative induction treatment efficacy of EGFR-TKIs is obvious and the patients presented well tolerant to its. And also the postoperative following-up demonstrated that most patients had a satisfactory recent result. But taking EGFR-TKIs preoperatively as a new adjuvant therapy to induce tumors regressed was still staying at the level of experience of cases rather than a conventional treatment option. Furthermore, sometimes the results of the postoperative pathological check revealed the tumors resection uncertain or uncompleted.

Therefore the preoperative neoadjuvant therapy of EGFR-TKIs in patients with local advanced NSCLC harboring EGFR gene mutation needs large scale randomized clinical trials to testify its efficacy and feasibility. There are still some issues need to be explored further. What is the reasonable period of taking EGFR-TKI before surgical interfering? When a patient should undergo surgical resection after taking EGFR-TKI as a preoperative neoadjuvant therapy? Whether and how EGFR-TKIs would continue to be used postoperatively are still far to the all-recognized standards. However we believe that with the progress of the clinical study of EGFR-TKIs in preoperative neoadjuvant therapy of advanced NSCLC harboring

EGFR gene mutation, its clinical application prospect could be expected definitely.

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