

## RESEARCH ARTICLE

# Systematic Analysis of Icotinib Treatment for Patients with Non-Small Cell Lung Cancer

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### Abstract

**Purpose:** This analysis was conducted to evaluate the efficacy and safety of icotinib based regimens in treating patients with non-small cell lung cancer (NSCLC). **Methods:** Clinical studies evaluating the efficacy and safety of icotinib-based regimens with regard to response and safety for patients with NSCLC were identified using a predefined search strategy. Pooled response rates of treatment were calculated. **Results:** With icotinib-based regimens, 7 clinical studies which including 5,985 Chinese patients with NSCLC were considered eligible for inclusion. The pooled analysis suggested that, in all patients, the positive response rate was 30.1% (1,803/5,985) with icotinib-based regimens. Mild skin itching, rashes and diarrhea were the main side effects. No grade III or IV renal or liver toxicity was observed. No treatment-related death occurred in patients treated with icotinib-based regimens. **Conclusions:** This evidence based analysis suggests that icotinib based regimens are associated with mild response rate and acceptable toxicity for treating Chinese patients with NSCLC.

**Keywords:** Icotinib - NSCLC - chemotherapy - response rate - toxicity

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### Introduction

Lung cancer is a serious problem for human being. Many patients with lung cancer will be diagnosed with advanced disease and will be systemically treated with palliative chemotherapy. For clinical practice, many patients with advanced non-small-cell lung cancer (NSCLC) would receive palliative chemotherapy, in which platinum doublets were still recommended as first-line, pemetrexed or docetaxel as second-line, and erlotinib as second- or third-line therapy (Fossella et al., 2000; Shepherd et al., 2000; Schiller et al., 2002; Hanna et al., 2004; Shepherd et al., 2005; Feld et al., 2006; Scagliotti et al., 2007). Significant improvements were achieved in the treatment of advanced NSCLC since 2010. Treatment strategies are now heavily influenced by histologic type of NSCLC (Ellis et al., 2011), and multiple trials have examined the sequence of subsequent lines of therapy, especially, epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIS) vs. chemotherapy. More important, findings of molecular abnormalities, e.g., mutations of the EGFR gene (Lynch et al., 2004; Paez et al., 2004) and translocations of the ALK (Soda et al., 2007) gene have identified a group of patients who appear to derive significantly greater benefit from molecularly targeted therapies.

Icotinib hydrochloride (BPI-2009H), an orally active, EGFR-TKI, is suggested to have similar antitumor activity

to gefitinib and erlotinib in patients with advanced NSCLC (Zhao et al., 2011; Tan et al., 2012). Based on preclinical and clinical data, icotinib is associated with an inhibition of the growth of human cancer cell lines that overexpress EGFR and demonstrated good tolerance in clinical settings (Liu et al., 2009).

As the toxicity of icotinib is less common than that of cytotoxic agents, the utility as a first-line treatment for patients with NSCLC with poor PS is proposed. Patients from East-Asian origin with adenocarcinoma are considered to be significantly associated with a favorable response to EGFR TKIs (Fukuoka et al., 2003; Kris et al., 2003).

According to this background, we hypothesize that icotinib originated regimen could be established as an optimal schedule in treating Chinese patients with non-small-cell lung cancer.

### Materials and Methods

#### Search strategy

We searched PUBMED, by using the following search terms: (non-small-cell lung cancer) and (icotinib). All clinical studies evaluating the impact of icotinib on the response or survival and side effects for Chinese patients with non-small-cell lung cancer published in English prior to May 2015 were identified. If samples of two studies overlap, only the newest one was included. Additional

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articles were obtained from references within the articles identified by the electronic search. We did not consider meeting abstracts or unpublished reports.

#### *Inclusion and exclusion criteria*

We reviewed abstracts of all citations and retrieved studies. The following criteria were used to include published studies: (1) clinical studies, combined with cisplatin, carboplatin, or other medications that were used for patients with NSCLC; (2) The study was performed in accordance with the Helsinki Declaration (1964, amended in 1975 and 1983) of the World Medical Association. Eligibility criteria included histologically or cytologically verified non-small-cell lung cancer, the presence of at least one bidimensionally measurable lesion, a performance status (WHO) of less than 2. Studies were excluded if one of the following existed: (a) duplicate data; (b) no sufficient data were reported.

#### *Data collection and analysis*

Selection of trials and data extraction: The titles and abstracts of publications identified according to the above search strategy were assessed independently for inclusion by two authors, the full text was selected for further assessment if the abstract suggests relevance. Disagreement was resolved by discussion. Data was extracted by independent authors. The following recorded data were extracted: author, publication data, country of the first or corresponding author, the number of patients. Outcome presented in at least 3 studies were extracted for combined analysis.

## **Results**

There were 51 papers relevant to the search words by the end of May 2015. Via steps of screening the title and reading the abstract, 7 studies were identified (Yang et al., 2013; Chen et al., 2014; Hu, et al., 2014; Pan et al., 2014; Shao et al., 2014; Zheng et al., 2014a; 2014b). All these studies had been carried out in China. The following outcomes were presented in at least all studies and extracted for combined analysis: response rate, including the rate of complete or partial response (CR or PR) and toxicities. Characteristics of studies included in this analysis are presented as short-term outcomes: the response rate of Hu, et al. was 30.0% (1665/5549), of Zheng et al. was 33.3 % (14/42), of Zheng et al. was 42.1 % (16/38), of Chen et al. was 23 % (19/82) , of Pan et al. was 43.5 % (30/69) , of Shao et al. was 22.1 % (33/149) , and of Yang et al. was 46.4 % (26/56). Totally, 5985 patients were enrolled and 1803 patients achieved CR or PR, the pooled response rate thus was 1803/5985 (30.1%). Major adverse effects were mild skin itching, rash, and diarrhea. No grade III or IV renal or liver toxicity were observed. No treatment related death occurred in patients with icotinib based regimens.

## **Discussion**

Although there is a continuous decline trend in lung cancer death rates among Western countries (Jemal et al.,

2011). In other area, especially in developing countries, i.e., China and other Asian, or African countries, the rates are still increasing (Jemal et al., 2011). NSCLC accounts for more than 85% of all lung cancer patients (Govindan et al., 2006), and approximately 40% of these patients are first diagnosed at an advanced stage (Ramalingam et al., 2008). The lack of effective therapies in patients with advanced NSCLC and extremely those with poor PS (particularly PS 3-4) is a major clinical problem. Based on report from National Comprehensive Cancer Network guidelines, 4-6 cycles of platinum-based doublet chemotherapy is recommend as first-line treatment for patients with NSCLC (National Comprehensive Cancer Network et al., 2013), that generally consists of cisplatin or carboplatin with another cytotoxic agent, sometimes in combination with a biologic agent, e.g., bevacizumab (B). Currently the recommended second-line or third-line treatments for NSCLC patients include docetaxel, erlotinib, pemetrexed or gemcitabine (Shepherd et al., 2000; Hanna et al., 2004; Shepherd et al., 2005; Leighl et al., 2012).

However, it is important to notice that combination chemotherapy regimens using a platinum doublet result in median overall survival of 8-11 mo (Cappuzzo et al., 2010). Obviously, clinical outcomes in patients with NSCLC continue to be poor, with an overall survival of 7 to 9 months, and objective response rate of less than 10% (Hotta et al., 2007). Therefore, novel treatment strategies for advanced NSCLC patients failing the first-line therapies are urgently required. The use of cytotoxic chemotherapy as the initial treatment for patients who are not suitable for molecular targeted therapy due to EGFR mutation status is supported by results from previous trial (Gridelli et al., 2012). Patients in that trial were randomly divided into first-line erlotinib followed by chemotherapy (cisplatin plus gemcitabine) till progression or the same first-line chemotherapy followed by erlotinib till progression. Overall survival was significantly longer in unselected patients assigned to initial chemotherapy followed by second-line erlotinib. For patients known to be EGFR mutation negative, overall survival was significantly longer with initial chemotherapy.

Currently, there is a trend that for those patients with an EGFR mutation or ALK rearrangement, use of a specific inhibitor directed at that target would be indicated either as the initial treatment or as a therapy when progressive disease is diagnosed. EGFR gene family members are demonstrated to be widely expressed in various human cancers, including breast, head and neck, NSCLC and ovarian cancers (Jemal et al., 2011). On this background, gefitinib become a specific EGFR kinase inhibitor (EGFR TKIS). It was suggested that clinical characteristics, eg., Asian ethnicity, female sex, non-smoking status, and adenocarcinoma were associated with a higher likelihood of response by previous analysis of trials evaluating EGFR TKIS. Therefore, these characteristics were considered useful in clinical trials to enrich patients who could benefit from these medications. However, it is now clear that the population of patients who derive the greatest benefit from EGFR TKIS are patients with tumours harbouring activating mutations of the EGFR gene. Nevertheless, the available data still support a more modest benefit from

EGFR TKIS in unselected populations of NSCLC patients.

Icotinib is a small-molecule EGFR TKIS, with a similar chemical structure and active mechanism to gefitinib (Tan et al., 2012), and was recently approved by the State Food and Drug Administration of China (<http://app1.sfda.gov.cn/datasearch/face3/base.jsptatement.>).

Previous study was conducted to retrospectively evaluate the safety and efficacy of icotinib in patients with advanced NSCLC across China at Beijing Key Laboratory of Clinical Study on Anticancer Molecular Targeted Drugs of Chinese Academy of Medical Sciences & Peking Union Medical College (Hu et al., 2014). In this study, they registered 6087 advanced NSCLC patients, of which 5549 were evaluable for safety and tumor response. And in this study, The median age of patients was 63 years, and 1571 (28.3%) patients were over the age of 70 years. The majority of patients were non-smokers, and had adenocarcinoma and stage IV disease. This study revealed that Crizotinib treatment was associated with an ORR and DCR of 30.0% and 80.6%, respectively, for the overall population, and 33.4% and 81.2%, 30.3% and 80.3%, and 30.4% and 89.3%, for first-line, second-line, and third-line or multiple line subsets, respectively. In 665 EGFR-mutated patients who were evaluable for tumor response, the ORR and DCR were 49.2% (327/665) and 92.3% (614/665), respectively (Hu et al., 2014). The most common ADRs included rash (17.4%) and diarrhea (8.5%), and three patients experienced interstitial lung disease (ILD) (Hu et al., 2014). In conclusion, Hu et al.suggested that Icotinib demonstrated a favorable toxicity profile and efficacy in a routine clinical setting (Wu et al., 2015). In a retrospective study by Zheng et al., they analyzed 42 Chinese patients with lung adenocarcinoma, including 35 females and 7 males, (Zheng et al., 2014). All 42 patients received oral Icotinib 125 mg three times a day. In this study, the overall response rate and disease control rates were 33.3 and 85.7%, respectively. The median survival time was 13.0 months (95%CI, 5.6-20.4), The median progression-free survival time was 7.0 months, and the 1-year survival rate was 71.4%. A total of 79% of patients had an improved PS following icotinib treatment. Grade 1 to 2 rashes and diarrhea were the most frequent side effects. One patient succumbed during the study due to interstitial pneumonia. (Zheng et al., 2014). In conclusion, In conclusion, this study indicated that patients with lung adenocarcinoma and poor PS may benefit from first-line icotinib therapy, but should be cautious of the occurrence of interstitial lungdisease ( Zheng et al., 2014). In a study by Zheng Y. et al., they enrolled 38 patients with advanced NSCLC (Zheng Y. et al., 2014). In their results, they suggested that the response rates to pemetrexed and icotinib were 21.1% and 42.1%, respectively. The median overall survival was 27.0 months (95%CI, 19.7-34.2 months). The 12-month overall survival probability was 68.4%. The most common toxicities observed in icotinib phase were rashes, diarrheas, and elevated aminotransferase. Subgroup analysis indicated that the overall survival is correlated with response to icotinib (Zheng Y. et al., 2014). Thus in conclusion, Zheng Y.suggested that The sequence of first-line pemetrexed-based chemotherapy

followed by icotinib treatment is a promising option for advanced lung adenocarcinoma with unknown EGFR gene status in China (Zheng Y. et al., 2014). In another study by Chen et al., they enrolled 82 patients with advanced NSCLC (Chen et al., 2014). In their results, they suggested that median progression-free survival was 4.0 months and overall survival was 11.0 months for this cohort of patients. Median progression-free survival for first and second/third line were 7.0 and 3.0 months, respectively. Median overall survival for first and second/third line were 13.0 and 10.0 months, respectively. In patients with EGFR mutation, icotinib significantly reduced the risk of progression (HR 0.36, 95%CI 0.18-0.70, p=0.003) and death (HR 0.10, 95%CI 0.02-0.42, p=0.002) compared with those EGFR status unknown (Chen et al., 2014). Therefore, in their conclusion, they indicated that Icotinib is active in treating patients with NSCLC both in first or second/third line, especially in those patients harbouring EGFR mutations, with an acceptable adverse event profile.

Our current study was designed to evaluate the efficacy and safety of icotinib based regimen in treating patients with NSCLC. Our results demonstrated that when icotinib based regimens was used as a palliative treatment, the pooled reponse rate was 30.1% (1803/5985). Mild skin itching, rash, and diarrhea were the main side effects. No grade III or IV renal or liver toxicity were observed. No treatment related death occurred in patients with icotinib based regimens. In conclusion, our current systemic analysis suggests that icotinib based regimens are associated with mild response rate and accepted toxicities for treating patients with NSCLC.

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