

China experts consensus on icotinib for non-small cell lung cancer treatment (2015 version)

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Introduction

According to *Chinese Cancer Registry Annual Report* in 2011, the incidence rate of lung cancer was 48.32/100,000 and the mortality rate was 39.27/100,000 in China in 2011, being the highest among all cancers (1). Most patients with non-small cell lung cancer (NSCLC) which accounts for 85% of all lung cancers have entered the advanced stage at the first visit to hospital and thus missed the opportunity for surgery. As the main treatment for advanced NSCLC, chemotherapy has reached a plateau in its efficacy and has been restricted in clinical application due to adverse reactions. In recent years, epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs), thanks to their definite efficacy, mild adverse reaction and convenience for oral use, have broken the bottleneck of traditional chemotherapeutic

drugs and become an essential treatment for advanced NSCLC.

Commercially available EGFR-TKIs include icotinib, gefitinib and erlotinib in China. Icotinib (trade name: Conmana) is the first EGFR-TKI with proprietary intellectual property rights in China and the third commercially available EGFR-TKI in the globe. Since it was available in the market in China on June 7, 2011, icotinib has been used to treat more than 50,000 patients with NSCLC in clinical practice. To further standardize the use of icotinib by clinicians and provide better service for lung cancer patients, Chinese Association for Clinical Oncologists and the Council of Cancer Chemotherapy of the Chinese Anti-Cancer Association called on experts from across China to formulate this Experts Consensus on the

basis of previous Chinese guidelines on the diagnosis and treatment of lung cancer.

First-line treatment for advanced stage NSCLC patients with *EGFR* gene active mutation

As shown by many studies, *EGFR* mutation status is the most important efficacy predictor of advanced NSCLC and the molecular marker for treatment selection. Mutation is most commonly seen in exons 18-21, with exon 19 deletion and exon 21 point mutation being the most frequently observed *EGFR* gene active mutations. According to the latest research on Lung Cancer Mutation Consortium (LCMC), advanced stage NSCLC patients with *EGFR* gene active mutations can have up to 4 years of median survival after receiving EGFR-TKIs (2). Several other studies also showed that the rate of *EGFR* gene active mutation was about 30% in unselected Chinese NSCLC patients, 50% in patients with lung adenocarcinoma (3), 60-70% in non-smoking patients with lung adenocarcinoma and 10% in patients with squamous cell lung carcinoma (4,5). Therefore, for patients who have been pathologically confirmed with advanced NSCLC and cannot receive surgery, *EGFR* gene mutation should be detected before treatment. As revealed by several randomized, phase III clinical trials of first-line treatment (including IPASS, NEJ002, WJTOG3405, OPTIMAL, EURTAC, LUXLUNG3, LUXLUNG6) (6-12), EGFR-TKIs as first line treatment for advanced NSCLC patients with *EGFR* gene active mutations could achieve 9.5-13.7 months of progression free survival (PFS) compared to 4.6-6.9 months with traditional first line chemotherapy. The overall effective rate of EGFR-TKIs was also higher than that of traditional chemotherapy (58-84% vs. 15-47%). Moreover, it has been demonstrated by all studies that EGFR-TKIs showed mild adverse reactions, particularly in hematological toxicity, better tolerability and improved quality of life compared to traditional chemotherapy. In a post-marketing phase IV study of icotinib (13), 6,087 patients with advanced NSCLC were enrolled from August 2011 to August 2012 to receive icotinib, among whom 989 patients received *EGFR* mutation detection. The objective response rate (ORR) and disease control rate (DCR) of 738 patients with sensitive *EGFR* mutations was 49.2% and 92.3%, respectively. A total of 144 patients received icotinib as first line treatment. The ORR and DCR for them were 56.3% and 95.1%, respectively. Another retrospective study (14), which analyzed the efficacy of icotinib in 59 patients with advanced NSCLC admitted to

Beijing Chest Hospital, Capital Medical University from March 2009 to January 2012, showed that among 20 patients who received icotinib as first line treatment, 8 were in partial response (PR), 7 were in stable disease (SD) and 5 were in progressive disease (PD). Among those 20 patients, 8 had *EGFR* gene active mutations, 5 of these 8 patients had exon 19 deletion and all reached PR. The remaining 3 patients had exon 21 point mutation, with 1 in PR, 1 in SD and 1 in PD. As a result, *MIMS Oncology Guide* (2013 and 2014 versions) (15) and *Standards for the Diagnosis and Treatment of Primary Lung Cancer in China (2015 version)* (16) recommend icotinib as the first line treatment in advanced stage NSCLC patients with *EGFR* gene active mutations. There are several currently ongoing clinical trials of icotinib as the first line treatment in advanced stage NSCLC patients with *EGFR* gene active mutations, including registered clinical trial CONVINCENCE comparing first-line icotinib and chemotherapy (NCT01719536), BRAIN Study of first-line icotinib in patients with brain metastasis (NCT01724801) and the study of first-line icotinib in elderly patients with *EGFR* gene active mutations (NCT01646450). On November 13, 2014, icotinib was approved by China Food and Drug Administration (CFDA) as the first line treatment of advanced stage NSCLC patients with *EGFR* gene active mutations (Approval No.: 2014B02155) and became the second EGFR-TKI in China after gefitinib.

Maintenance therapy for advanced NSCLC

As shown by several studies of first-line chemotherapy followed by maintenance therapy with EGFR-TKIs, advanced stage NSCLC patients with *EGFR* gene active mutations can benefit from EGFR-TKI maintenance treatment (17-19). In a retrospective study which analyzed 59 patients with advanced NSCLC who were admitted to Beijing Chest Hospital, Capital Medical University from March 2009 to January 2012 and received icotinib (14), 2 patients with *EGFR* gene active mutation received icotinib as maintenance therapy after first-line chemotherapy and reached PR. Prospective study of icotinib as maintenance therapy is hopeful in the future.

Second- and third-line treatment for advanced NSCLC

According to ISEL, INTEREST, TITAN and BR21 as well as meta-analysis (20-24), for unselected Asian patients with recurrent advanced NSCLC, EGFR-TKIs can significantly

reduce the risk of disease progression, improve ORR and is well tolerated by patients even though it is comparable to standard second-line chemotherapy in overall efficacy. Thus, EGFR-TKIs play a very important role in second- and third-line treatment of advanced NSCLC. ICOGEN study (25) is a non-inferiority, phase III clinical trial conducted in China to compare the efficacy and safety of icotinib and gefitinib as second- and third-line treatment of unselected patients with advanced NSCLC.

This is the first phase III head-to-head clinical study which compared two EGFR-TKIs in the globe. The results of this study showed that icotinib was non-inferior to gefitinib in efficacy and the primary endpoint PFS was 4.6 months in icotinib group and 3.4 months in gefitinib group; the incidence of drug-related adverse events was 61% in icotinib group and 70% in gefitinib group ($P=0.046$); the incidence of diarrhea, the commonly seen adverse event, was significantly lower in icotinib group than in gefitinib group (19% vs. 28%, $P=0.033$). The detection of *EGFR* gene active mutation status in patients with available lung cancer biopsy specimens during the study showed that there was no differences in PFS and OS between icotinib and gefitinib, regardless of *EGFR* gene active mutation or wild-type patients. PFS was 7.8 months in icotinib group and 5.3 months in gefitinib group; OS was 20.9 months in icotinib group and 20.2 months in gefitinib group. PFS and OS of icotinib and gefitinib in patients with *EGFR* gene active mutation were superior to that in wild type patients ($P<0.001$). Based on the results of ICOGEN study, icotinib was approved for marketing purposes by CFDA on June 7, 2011. According to *MIMS Oncology Guide* (2013 and 2014 versions) (15), *Interpretation of Clinical Pathway and Therapeutic Drugs the Oncology Volume (2014 version)* (26), *Interpretation of Clinical Pathway the Oncology Volume (2015 version)* (27), *Diagnosis and Treatment Guideline of Chinese Patients with EGFR Gene Active Mutation and ALK Fusion Gene-Positive Non-Small Cell Lung Cancer (2014 version)* (28) and *Standards for the Diagnosis and Treatment of Primary Lung Cancer in China (2015 version)* (16), icotinib is recommended as second- and third-line treatment for patients with advanced NSCLC.

Neoadjuvant and adjuvant therapy with EGFR-TKIs

No definite conclusion has been made concerning EGFR-TKIs as neoadjuvant and adjuvant therapy. Several studies of icotinib are currently ongoing (NCT02125240, NCT01929200, NCT01843647). The

results of these studies will tell us whether stage II-IIIa lung adenocarcinoma patients with *EGFR* gene active mutations can benefit from the treatment with icotinib.

Conclusions

In conclusion, China's homemade EGFR-TKI, icotinib has provided a new choice for NSCLC patients. The committee of experts will update this Experts Consensus with the emergence of new study results.

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Footnote

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