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

Yuankai Shi[1], Yan Sun[1], Cuimin Ding[2], Ziping Wang[1], Changli Wang[3], Zheng Wang[4], Chong Bai[5], Chunxue Bai[6], Jifeng Feng[7], Xiaoqing Liu[8], Fang Li[9], Yue Yang[10], Yongqian Shu[11], Milu Wu[12], Jianxing He[13], Yiping Zhang[14], Shucai Zhang[15], Gongyan Chen[16], Honghe Luo[17], Rongcheng Luo[18], Caicun Zhou[19], Yanbin Zhou[17], Qingsong Pang[3], Hong Zhao[9], Qiong Zhao[20], Aiqin Gu[21], Yang Ling[22], Cheng Huang[23], Baohui Han[21], Shunchang Jiao[9], Hong Jiao[21]

[1]Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing Key Laboratory of Clinical Study on Anticancer Molecular Targeted Drugs, Beijing 100021, China; [2]Fourth Hospital of Hebei Medical University, Shijiazhuang 050000, China; [3]Tianjin Medical University Cancer Institute & Hospital, Tianjin 300070, China; [4]Shenzhen People's Hospital, Shenzhen 518020, China; [5]The Second Military Medical University Changhai Hospital, Shanghai 200433, China; [6]Fudan University Zhongshan Hospital, Shanghai 200032, China; [7]Jiangsu Cancer Hospital, Nanjing 210009, China; [8]The 307th Hospital of Chinese People's Liberation Army, Beijing 100071, China; [9]Chinese People's Liberation Army General Hospital, Beijing 100853, China; [10]Beijing Cancer Hospital, Beijing 100142, China; [11]Jiangsu Province Hospital, Nanjing 210029, China; [12]Qinghai University Affiliated Hospital, Xining 810000, China; [13]The First Affiliated Hospital of Guangzhou Medical University, Guangzhou 510000, China; [14]Zhejiang Cancer Hospital, Hangzhou 310022, China; [15]Beijing Chest Hospital, Capital Medical University, Beijing 101149, China; [16]Harbin Medical University Cancer Hospital, Harbin 150081, China; [17]The First Affiliated Hospital, Sun Yat-sen University, Guangzhou 510080, China; [18]Nanfang Medical University Nanfang Hospital, Guangzhou 510515, China; [19]Tongji University Affiliated Shanghai Pulmonary Hospital, Shanghai 200433, China; [20]The First Affiliated Hospital, Zhejiang University, Hangzhou 310003, China; [21]Shanghai Chest Hospital, Shanghai Jiaotong University, Shanghai 200030, China; [22]Changzhou Fourth People's Hospital, Changzhou 213001, China; [23]Fujian Cancer Hospital, Fuzhou 350014, China

This article is copublished in *Journal of Thoracic Disease*, *Annals of Translational Medicine*, and *Chinese Journal of Lung Cancer*.

Correspondence to: Yuankai Shi, MD. Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing Key Laboratory of Clinical Study on Anticancer Molecular Targeted Drugs, Beijing 100021, China. Email: syuankai@cicams.ac.cn.

Submitted Aug 15, 2015. Accepted for publication Oct 20, 2015.
doi: 10.3978/j.issn.2305-5839.2015.10.30
View this article at: http://dx.doi.org/10.3978/j.issn.2305-5839.2015.10.30

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 the lasted 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 CONVINCE 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.

Acknowledgements

Committee of experts Consultant: Yan Sun, Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing Key Laboratory of Clinical Study on Anticancer Molecular Targeted Drugs. Chairman of committee: Yuankai Shi, Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing Key Laboratory of Clinical Study on Anticancer Molecular Targeted Drug. Committee members: Cuimin Ding, Fourth Hospital of Hebei Medical University; Ziping WANG, Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing Key Laboratory of Clinical Study on Anticancer Molecular Targeted Drugs; Zheng WANG, Shenzhen People's Hospital; Changli Wang, Tianjin Medical University Cancer Institute & Hospital; Yuankai Shi, Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing Key Laboratory of Clinical Study on Anticancer Molecular Targeted Drugs; Chong Bai, The Second Military Medical University Changhai Hospital; Chunxue Bai, Fudan University Zhongshan Hospital, Jifeng FENG, Jiangsu Cancer Hospital; Xiaoqing Liu, The 307th Hospital of Chinese People's Liberation Army; Yan Sun, Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing Key Laboratory of Clinical Study on Anticancer Molecular Targeted Drugs; Fang Li, Chinese People's Liberation Army General Hospital; Yue Yang, Beijing Cancer Hospital; Yongqian Shu, Jiangsu Province Hospital; Milu Wu, Qinghai University Affiliated Hospital; Jianxing HE, The First Affiliated Hospital of Guangzhou Medical University; Yiping Zhang, Zhejiang Cancer Hospital; Shucai Zhang, Beijing Chest Hospital, Capital Medical University; Gongyan Chen, Harbin Medical University Cancer Hospital; Honghe Luo, The First Affiliated Hospital, Sun Yat-sen University; Rongcheng Luo, Nanfang Medical University Nanfang

Hospital; Caicun Zhou, Tongji University Affiliated Shanghai Pulmonary Hospital; Yanbin Zhou, The First Affiliated Hospital, Sun Yat-sen University; Qingsong Pang, Tianjin Medical University Cancer Institute & Hospital; Hong Zhao, Chinese People's Liberation Army General Hospital; Qiong Zhao, The First Affiliated Hospital, Zhejiang University; Aiqin Gu, Shanghai Chest Hospital, Shanghai Jiaotong University; Yang Ling, Changzhou Fourth People's Hospital; Cheng Huang, Fujian Cancer Hospital; Baohui Han, Shanghai Chest Hospital, Shanghai Jiaotong University; Shunchang Jiao, Chinese People's Liberation Army General Hospital; Hong Jian, Shanghai Chest Hospital, Shanghai Jiaotong University.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Chen W, Zheng R, Zeng H, et al. Annual report on status of cancer in China, 2011. Chin J Cancer Res 2015;27:2-12.
2. Kris MG, Johnson B, Berry L, et al. Treatment with therapies matched to oncogenic drivers improves survival in patients with lung cancers: results from the lung cancer mutation consortium (LCMC).15th World Conference on Lung Cancer (WCLC): Abstract PL0307. Presented October 29, 2013.
3. Shi Y, Au JS, Thongprasert S, et al. A prospective, molecular epidemiology study of EGFR mutations in Asian patients with advanced non-small-cell lung cancer of adenocarcinoma histology (PIONEER). J Thorac Oncol 2014;9:154-62.
4. Wu YL, Zhong WZ, Li LY, et al. Epidermal growth factor receptor mutations and their correlation with gefitinib therapy in patients with non-small cell lung cancer: a meta-analysis based on updated individual patient data from six medical centers in mainland China. J Thorac Oncol 2007;2:430-9.
5. China experts committee for non-small cell lung cancer patients with epidermal growth factor receptor gene mutation detection, Liang ZY. China experts committee consensus on non-small cell lung cancer patients with epidermal growth factor receptor gene mutation detection. Chinese Journal of Pathology 2011;40:700-2.
6. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med 2009;361:947-57.
7. Maemondo M, Inoue A, Kobayashi K, et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. N Engl J Med 2010;362:2380-8.
8. Mitsudomi T, Morita S, Yatabe Y, et al. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. Lancet Oncol 2010;11:121-8.
9. Zhou C, Wu YL, Chen G, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. Lancet Oncol 2011;12:735-42.
10. Rosell R, Carcereny E, Gervais R, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol 2012;13:239-46.
11. Sequist LV, Yang JC, Yamamoto N, et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. J Clin Oncol 2013;31:3327-34.
12. Wu YL, Zhou CC, Hu CP, et al. LUX-Lung6: A randomized, open label, phase III study of afatinib (A) versus gemcitabine/cisplatin (GC) as first line treatment for Asian patients with EGFR mutation positive advanced adenocarcinoma of the lung. J Clin Oncol 2013;31:abstr 8016.
13. Hu X, Han B, Gu A, et al. A single-arm, multicenter, safety-monitoring, phase IV study of icotinib in treating advanced non-small cell lung cancer (NSCLC). Lung Cancer 2014;86:207-12.
14. Li X, Yang XJ, Sun YF, et al. Clinical observation of icotinib hydrochloride for patients with advanced non-small cell lung cancer. Zhonghua Zhong Liu Za Zhi 2012;34:627-31.
15. Huang HP, Lin HY, editors. MIMS oncology guide. Hong Kong: UBM MEDICA PACIFIC LIMITED, 2014:12.
16. Zhi X, Shi Y, Yu J. Standards for the diagnosis and treatment of primary lung cancer (2015 version) in China. Zhonghua Zhong Liu Za Zhi 2015;37:67-78.
17. Zhang L, Ma S, Song X, et al. Gefitinib versus placebo as maintenance therapy in patients with locally advanced or metastatic non-small-cell lung cancer (INFORM; C-TONG 0804): a multicentre, double-blind randomised

phase 3 trial. Lancet Oncol 2012;13:466-75.
18. Takeda K, Hida T, Sato T, et al. Randomized phase III trial of platinum-doublet chemotherapy followed by gefitinib compared with continued platinum-doublet chemotherapy in Japanese patients with advanced non-small-cell lung cancer: results of a west Japan thoracic oncology group trial (WJTOG0203). J Clin Oncol 2010;28:753-60.
19. Cappuzzo F, Ciuleanu T, Stelmakh L, et al. Erlotinib as maintenance treatment in advanced non-small-cell lung cancer: a multicentre, randomised, placebo-controlled phase 3 study. Lancet Oncol 2010;11:521-9.
20. Thatcher N, Chang A, Parikh P, et al. Gefitinib plus best supportive care in previously treated patients with refractory advanced non-small-cell lung cancer: results from a randomised, placebo-controlled, multicentre study (Iressa Survival Evaluation in Lung Cancer). Lancet 2005;366:1527-37.
21. Kim ES, Hirsh V, Mok T, et al. Gefitinib versus docetaxel in previously treated non-small-cell lung cancer (INTEREST): a randomised phase III trial. Lancet 2008;372:1809-18.
22. Ciuleanu T, Stelmakh L, Cicenas S, et al. Efficacy and safety of erlotinib versus chemotherapy in second-line treatment of patients with advanced, non-small-cell lung cancer with poor prognosis (TITAN): a randomised multicentre, open-label, phase 3 study. Lancet Oncol 2012;13:300-8.
23. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al. Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med 2005;353:123-32.
24. Shepherd FA, Douillard J, Fulcuolca M, et al. Comparison of gefitinib and docetaxel in patients with pretreated advanced non-small cell lung cancer (NSCLC): Meta-analysis from four clinical trials. J Clin Oncol 2009;27:abstr 8011.
25. Shi Y, Zhang L, Liu X, et al. Icotinib versus gefitinib in previously treated advanced non-small-cell lung cancer (ICOGEN): a randomised, double-blind phase 3 non-inferiority trial. Lancet Oncol 2013;14:953-61.
26. Gu J, Shi YK, Sun Z, editors. Interpretation of Clinical Pathway and Therapeutic Drugs: the Oncology Volume (2014 version). Beijing: Peking Union Medical College Press, 2014:334.
27. Shi YK, Gu J, editors. Interpretation of Clinical Pathway: the Oncology Volume (2015 version). Beijing: Peking Union Medical College Press, 2015:1-38.
28. Chinese Association of Oncologists, Chinese Society for Clinical Cancer Chemotherapy, Chinese Association of Oncologists, et al. The diagnosis and treatment guideline of Chinese patients with EGFR gene active mutation and ALK fusion gene-positive non-small cell lung cancer (2014 version). Zhonghua Zhong Liu Za Zhi 2014;36:555-7.

Cite this article as: Shi Y, Sun Y, Ding C, Wang Z, Wang C, Wang Z, Bai C, Bai C, Feng J, Liu X, Li F, Yang Y, Shu Y, Wu M, He J, Zhang Y, Zhang S, Chen G, Luo H, Luo R, Zhou C, Zhou Y, Pang Q, Zhao H, Zhao Q, Gu A, Ling Y, Huang C, Han B, Jiao S, Jian H. China experts consensus on icotinib for non-small cell lung cancer treatment (2015 version). Ann Transl Med 2015;3(18):260. doi: 10.3978/j.issn.2305-5839.2015.10.30

