

INVITED REVIEW

Clinical experiences with molecular targeted therapy in lung cancer in China

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Introduction

Undoubtedly, with their distinct mechanisms of action and toxicity, molecular targeted agents have tremendously changed the therapy for advanced non-small cell lung cancer (NSCLC). An improved understanding of the gene mutations responsible for tumor growth and proliferation has challenged the traditional model of cancer treatment. Targeted therapy has expanded the concept of individually tailored cancer treatment. The epidermal growth factor receptor (EGFR) gene mutation rate among patients of Asian origin is significantly higher than that of European and American populations.^{1,2} The higher mutation rate, which is known as “a gift for Asians from God,” has led to a larger population in China benefiting from tyrosine kinase inhibitor (TKI) therapy than in Caucasian populations (as TKI is commercially available in China, the median survival time of advanced NSCLC patients has been significantly prolonged, 35 vs. 14 months, $p < 0.001$).³

Research and development in China of foreign licensed molecular targeted agents

Chinese oncologists initially gained clinical experience of targeted agents from participation in a variety of international

Abstract

In the past decade, a dramatic shift has been witnessed in cancer therapy in China. Although traditional cytotoxic chemotherapy still remains the treatment of choice for many malignancies, targeted therapies are now a component of treatment for many types of cancer, including lung cancer. As molecular target agents are widely used in clinical practice and relevant studies have been conducted, we have accumulated valuable experience in the treatment strategy for advanced non-small cell lung cancer. On this basis we have successfully developed our Class-I new drug through independent research, which significantly accelerates the clinical development of targeted therapy for lung cancer. This article summarizes the clinical practice and relevant studies of current targeted therapies for lung cancer in China.

clinical trials related to targeted drugs for lung cancer. Gefitinib (Iressa, AstraZeneca Pharmaceuticals LP, Macclesfield, Cheshire, UK), a small molecule tyrosine kinase inhibitor, was the first molecular targeted drug introduced in China. A registry study, conducted in 2003, demonstrated the miraculous effect of targeted therapy.⁴ However, the ISEL study comparing gefitinib with a placebo in the treatment of advanced NSCLC yielded negative results.⁵ Fortunately, the international multi-center phase-III clinical study, INTEREST, involving five research centers with the largest number and fastest pace of patient enrollment, was the first head-to-head comparison between TKI and chemotherapy and yielded favorable results, especially for Asian patients.⁶ As a result, gefitinib was successfully launched in the Chinese market. From the INTEREST study, Chinese clinicians gained first-hand experience of the differences between targeted and cytotoxic drugs in terms of response and toxicity and summarized the prevention and treatment methods for skin rash with Chinese characteristics.^{7–10} Although gefitinib was not launched in the United States (US) market, increasing clinical evidence of Chinese patients markedly benefiting from gefitinib treatment led to the inclusion of gefitinib in the Chinese version of the National Comprehensive Cancer Network guidelines. Gefitinib has been established as a

second-line option for NSCLC treatment. Since then, similar drugs including erlotinib (Tarceva, OSI Pharmaceuticals, LLC, Northbrook, IL, USA) were also launched to the market successfully. They are widely applied in clinical practice, providing Chinese researchers with more material and a deeper insight into the drugs and their treatment strategy for NSCLC.

Initially, China followed the pace of researchers in Europe, the US, Japan, South Korea, and Taiwan, and participated in a number of international multi-center clinical studies investigating the targeted treatment of NSCLC, including a head-to-head first-line study of gefitinib versus carboplatin/paclitaxel (Taxol, Bristol-Myers Squibb Company, Princeton, NJ, USA; Paraplatin, Biomedical Engineering Company Ltd., Toyama, Japan) in clinically selected patients (non-smokers with lung adenocarcinoma; IPASS), as well as two clinical trials comparing the multi-targeted drug sorafenib (Nexavar, Onyx Pharmaceuticals Inc. and Bayer HealthCare Pharmaceuticals Inc., Berlin, Germany) in combination with chemotherapy (paclitaxel+carboplatin or gemcitabine+cisplatin [Gemzar, Lilly France, Fegersheim, France]) versus chemotherapy alone as the first-line treatment for advanced NSCLC.^{11–13} Furthermore, we have accumulated experience with the antitumor efficacy of TKI therapy for specific populations, such as patients with brain metastases, the elderly, and men, attempting to detect factors that could predict efficacy.^{14–21} Before confirming that EGFR gene mutation is the most important predictor for the efficacy of TKI, we established a model suggesting that patients with adenocarcinoma have higher response rates to TKI, which was actually the result of the higher EGFR gene mutation rate of adenocarcinoma.²² Subsequently, foreign scholars have found that lung cancer bearing anaplastic lymphoma kinase mutations are a special type, and crizotinib (Xalkori, Pfizer Ireland Pharmaceuticals, Dublin, Ireland) was then designed for this disease. During this period, China participated in international multicenter studies 1005 and 1007.

In international studies in which Chinese doctors have participated, Chinese enrollment is typically completed before that of any other country and Chinese subjects account for 15–20% of all study samples. Moreover, the US Food and Drug Administration, among other companies, have inspected Chinese data and declared it credible. China has also made improvements through our defects and gradually standardized procedures of clinical trials, which have paved the way for future domestic clinical research. Through these studies, we have found that China has an advantage over other countries when studying lung cancer, as there are an abundance of patients with NSCLC in China. Furthermore, China promises to be a leader in the research of therapy for EGFR mutation-positive tumors, on the basis of the fact that Asian patients harboring the EGFR gene mutation in lung

cancer account for 30–40%, among which non-smokers with lung adenocarcinoma make up 50–60%, a mutation rate much higher than that of Europeans and Americans.^{1,2} At the same time, our researchers are gradually becoming experienced and aware of the importance of clinical research. They have started to design independent clinical trials under the guidance of good clinical practice, such as the OPTIMAL study comparing the near-term and long-term efficacy of chemotherapy with that of erlotinib in patients bearing EGFR mutations; the study of maintenance therapy of gefitinib investigating the antitumor efficacy of second-line chemotherapy versus TKI therapy in wild-type patients, which suggested that patients with EGFR mutations benefited most from TKI therapy, whether as first-line, maintenance or second-line therapy, while wild-type patients only gained very limited benefits; and the FASTACT-2 study, suggesting that alternating EGFR-TKIs and chemotherapy can improve the objective response rate, progression-free survival (PFS), and overall survival of advanced NSCLC patients with EGFR mutations and in advanced NSCLC patients with unknown mutations.^{23–26}

Drug resistance is an unavoidable topic when investigating anti-tumor therapy. Although there has been some exploration as to the mechanism, the focus has been on how to deal with the problem of drug resistance.^{27,28} It is believed that secondary T790M and c-met mutations are the main reasons for acquired resistance, and new drugs targeting these mutations are still being developed. Therefore, most researchers in China conduct retrospective analyses on the clinical characteristics of patients presenting with drug resistance and the problem of whether to switch to chemotherapy or another TKI therapy after drug resistance. Prospective randomized controlled studies according to different drug resistance patterns have been designed to answer these questions.^{29–32}

Clinical studies on anti-angiogenic drugs, including bevacizumab (Avastin, Genentech Inc., San Francisco, CA, USA) are very interesting; however there have not been as many studies on bevacizumab as on TKIs. Given the different efficacy of TKIs among different ethnic groups, the Chinese registered clinical study, BEYOND, which was designed exactly the same as ECOG4599, showed a higher response rate and longer PFS in Chinese patients compared with past data (54% vs. 35% and 9.2 vs. 6.2 months).³³ The most interesting finding of the study was that patients with or without EGFR gene mutations could benefit from bevacizumab therapy. In addition, the study found that gemcitabine and carboplatin (GC) in combination with bevacizumab reduced the two-year cumulative incidence of brain metastases in comparison with GC alone (14% vs. 31%).³⁴ Compared with cisplatin alone, bevacizumab in combination with cisplatin significantly improved the pleural effusion control rate (85% vs. 50%).³⁵

Individualized treatment relies mainly on molecular biological testing methods. With the recognition of EGFR gene mutation in predicting efficacy, a number of centers in China also began to try various testing methods and gradually standardized them. After being tested by international counterparts, gene mutation testing was gradually put into practice in China. Meanwhile, various multinational pharmaceutical companies are competing to establish central clinical laboratories in China to conduct multi-center clinical trials, which presents an important opportunity for China to integrate globally in the field of targeted therapies. Many phase-III international multi-center clinical studies have also commenced in China.

Apart from the difference in sensitivity of different testing methods, EGFR mutation abundance is also closely related to clinical efficacy, which explains why TKI therapy is also effective for some wild-type patients.²⁵ Not all medical institutions can be included in testing because of the imbalance of medical resources; currently only 20–30% of Chinese medical institutions participate in studies.³⁶ Therefore we need to look for more convenient and reliable samples for further improvement. A study paired and tested the EGFR gene mutation of tissues and peripheral blood, and the resulting correlation was above 70%.³⁷ Circulating tumor cell detection and droplet digital polymerase chain reaction technology enable qualitative and quantitative testing, with the possibility of realizing continuous testing to meet the demand of clinical practice, which can provide more accurate information for monitoring the efficacy of targeted drugs and judging prognosis.

Self-developed new anti-tumor drugs

As is universally known, China's investment in drug research and development (R&D) is minor in comparison to Europe and the US; therefore China lags far behind in the field of independent R&D of new drugs. Typically, foreign R&D companies invite China to participate in phase III multi-center clinical studies on drugs after phase I and II clinical trial screening. However, as more and more foreign visitors commence their pioneering work in China, the development of Chinese anti-tumor drugs has begun. We take great pride in that TKI targeted drugs, such as icotinib (Beta Pharma, Hangzhou, China) and anti-angiogenic drugs endostatin (YH-16, Endostar, Medgenn, Simcere Pharmaceutical, Nanjing, China) and the Shenyi Capsule (Jilin Yatai Pharmaceutical, Changchun, China) have achieved success through rigorous randomized controlled clinical trials.

The recombinant human endostatin (Endostar), produced in China, is the first endogenous angiogenesis inhibitor put into global clinical trial.³⁸ A large number of preclinical studies show that endostatin has a broad-spectrum anti-tumor effect but mild toxicity, without drug resistance.³⁹ A

phase III multi-center, double-blind comparison study of inoperable NSCLC patients researched endostatin (YH-16) in combination with vinorelbine (Navelbine, Pierre Fabre Pharmaceuticals Inc., Paris, France) cisplatin (NP) versus NP therapy alone, and the result showed that effective rates of the NP+YH-16 and NP groups were 35.40% and 19.51% respectively ($P < 0.01$; median time to progression 6.25 and 3.59 months, respectively; $P < 0.001$; 1-year survival rate 62.8% and 31.4%; median survival time 14.4 and 9.9 months, respectively.) These results indicate that YH-16 has a synergistic effect with NP therapy without increasing the adverse effects of NP; therefore, adding YH-16 to NP is a safe and effective therapy for advanced NSCLC. It has also been suggested that YH-16 may improve the relapse-free survival of patients with NSCLC after surgery (phase Ib-IIIa). Note, however, that the time to progression was longer in patients with lower levels of peripheral circulating endothelial progenitor cells ($<0.35\%$) before chemotherapy or endostatin treatment ($P < 0.001$).⁴⁰ Furthermore, domestic scholars have conducted studies on injecting recombinant human endostatin into the thoracic cavity in combination with chemotherapy in malignant and refractory pleural effusion. The main chemotherapy drugs in these studies were cisplatin and 5-fluorouracil and results indicated that the effective rate of combined intracavitary drug usage was 45–80%; therefore, this strategy is another option for treating refractory pleural effusion in lung cancer.^{41,42}

Another Chinese-developed drug is icotinib, another EGFR-TKI, which is different from gefitinib and erlotinib both in structure and in pharmacokinetics.⁴³ The results of preclinical, phase I and II clinical trials indicated that icotinib is a good prospect.^{44,45} The ICOGEN trial, a national multi-center phase III randomized controlled clinical trial, compared the antitumor efficacy of icotinib with gefitinib in NSCLC refractory to chemotherapy.⁴⁶ The results showed that icotinib efficacy was not inferior to gefitinib, and in terms of safety, the incidence of drug-related adverse reactions was lower than when using gefitinib. This result was published in *Lancet Oncology*, indicating that drug R&D and clinical research in China have reached the international advanced level. We are expecting to set in motion a Chinese-style wave of independent R&D of anti-tumor drugs, that is, a type of R&D with lower costs and higher speed.

The quintessence of Chinese culture, namely traditional Chinese medicine, also now focuses on anti-tumor therapy. The Shenyi Capsule contains an effective monomer extracted from ginseng, with the codename Rg3. It has been proven that the Shenyi Capsule can inhibit tumor angiogenesis, restrain the expression of matrix metalloproteinases, interfere with the interaction between endothelial cells and extracellular matrix, prevent the formation of tumor vascular network, and downregulate the expression of vascular endothelial growth factor in tumor tissues. A multi-center, double-blind

phase III study researching the Shenyi Capsule in combination with NP (combination group) versus NP chemotherapy alone (control group) in treating advanced NSCLC concluded that the effective rate of the combination group (33.4%, 17/51) was significantly higher than the control (14.5%, 8/55). The median survival time of the combination group was 15.3 months, significantly better than 9.7 months for the control, and the quality of life of patients in the combination group was improved to some extent.⁴⁷

Discussion

The same molecular events are present in different tumors and the same tumors show different molecular events, which is a perfect embodiment of “treating the same kind of diseases with different methods and treating different diseases with the same method” in traditional Chinese medicine. The incidence of lung cancer in China is so high that prevention is a very serious social problem. Chinese oncologists work to determine the mechanism of tumor pathogenesis and clinical treatment despite disadvantages, such as a shortage of funding for clinical research, poor compliance of subjects, and loopholes in policy and regulatory systems. An individualized standard operating procedure for lung cancer treatment based on molecular events must be established, and might as well realize the human-machine interaction model by understanding the characteristics of targeted drugs, combining various clinical issues (such as the treatment of intracranial lesions, the strategy after drug resistance, and the status of targeted drugs in neoadjuvant and adjuvant fields), and through appropriate and reliable monitoring methods (the advantage of blood samples and continuous sampling). The ideal for tumor treatment is a human-machine interaction model.

Conclusion

In conclusion, over the past decade, oncologists in China have made great contributions to the development of clinical oncology. Among the top 10 studies awarded the 2013 China Clinical Oncology Annual Progress Appraisal, three were related to NSCLC.^{27,46,48} Numerous clinical studies have objectively shown the diversity of drug efficacy and toxicity among different ethnic groups. Clinical studies on the R&D of new drugs, represented by icotinib and endostatin, also suggest a bright future in China of the development of clinical oncology and the further improvement of the cure rate in patients with advanced NSCLC. Chinese scholars participate in international multi-center clinical studies and are taking the lead in clinical studies of China and the Asia-Pacific region, independently developing anti-tumor drugs, and moving from following the trend to independent innovation. We expect that more and more Chinese researchers will have a voice in

the international arena, and lead the trend in the field of individually tailored treatment for lung cancer worldwide.

Disclosure

No authors report any conflict of interest.

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