Clinical Review of Iressa for the Treatment of NSCLC

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ABSTRACT Following development of basic science and the advancement of tumor molecular biology, molecular-target therapy has evolved as a new field for cancer treatment. The agents used act at specific target points such as receptors, kinases and signal transduction systems which are related to tumor growth. These actions result in inhibting proliferation, metastasis, vascularization, and promoting tumor apoptosis. Iressa (gefitinib) which is used for the treatment of NSCLC is a small molecular weight agent acting by inhibition of epidermal growth factor receptor-tyrosine kinase. Iressa was the first approved agent for target therapy for the treatment of NSCLC. This article focuses on the results from clinical trials and the potential of Iressa for the treatment of NSCLC.

KEYWORDS: target therapy, NSCLC; iressa (gefitinib).

As the most common malignant tumor, the incidence of lung cancer is gradually increasing in the world. Almost 1 million new cases are diagnosed each year and lung cancer incidence ranks second in the U.S. just after prostatic cancer. In China, especially in big cities, lung cancer is the most common cancer. Almost 80% are non-small-cell lung cancers (NSCLC) of which 70% are in stage III-IV at the time of diagnosis. Therefore the majority of cases are beyond a chance for radical surgery. One-third of the patients in an early stage eventually recur even after radical surgery.

Systemic chemotherapy is the only way to treat both an advanced stage and a recurring NSCLC to extend survival and improve quality of life. With the appearance of new chemotheraputic agents over the past decade, the efficacy of NSCLC chemotherapy has gradually improved, but only slowly. Several phase III randomized trials showed the response rates to be 20% ~40% with combinations of new platin-based regimen for advanced NSCLC, producing in recent years, one-year survival rates of 35%~45%.[1,2] Without a specific mode of action on tumor cells, intolerable severe side effects may occur, which made the patients weak. Because of these circumstances, as well as the development of basic research, molecular-target therapy has begun to play a role in the treatment of NSCLC. The mechanism by which these agents attack a target in tumor cells is different from cytotoxic agents. They act selectively on tumor-specific structures or receptors, kinases, proteins or factors related to tumor signal-transduction pathways and thereby block tumor growth. Iressa, which was the first approved target agent for the treatment of NSCLC, is used in more then 20 countries. In this article we have reviewed clinical research and development of this agent for the treatment of NSCLC.

Clinical Research

Iressa is a small molecular weight target agent given orally. As an epi-

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dermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI), it blocks the tumor signal-transduction pathway by inhibiting EGFR-TK resulting in decreased tumor proliferation and promoted tumor apoptosis. Because EGFR-TK and the signal-transduction pathway are critical in both the development and the progression of NSCLC, inhibiting TK is very selective and important. EGFR-TK, which is expressed in 40~80% of NSCLS, is a transmemberance protein which includes both an extracellular receptor and intracellular tyrosine kinase composed of 1186 amino-acids.

Four phase I clinical trials have been conducted with Iressa, the dosage ranging from 50~1000 mg/d. The dose had to be limited due to development of diarrhea. Ten of 100 patients with NSCLC developed a response, using an effective dosage of 150 mg~700 mg/d. The dosage needed to be adjusted in patients receiving more than 600 mg/d due to adverse effects. There was no obvious myelosuppression during the trials.[3-6] Two phase II clinical trials, Ideal (Iressa Dose Evaluation in Advanced Lung Cancer)1 and Ideal 2 all started to use either 250 mg or 500 mg i.e. two different dosages for the treatment of advanced or metastatic NSCLC as the second or third line treatment for patients who had failed to respond to platin-based chemotherapy, The results showed the response rates were 18.4% and 11.8% with a disease-control rate of 54.4% and 42.2%, respectively. Improvement of symptoms was 40.3% and 43.1% respectively. Median survival for those patients reached to 7.6 and 6.5 months. Both of these trials have not just confirmed the efficacy of Iressa for the treatment of NSCLC but also limited Iressa side effects as well. The most common side effects were grade I-II diarrhea and skin rash. Only 1%-2% of the patients had interstitial pneumonia and there was almost no myelosuppressive toxicity.[7,8] No significant differences were observed between the groups receiving 250 mg and 500 mg of Iressa in both Ideal 1 and Ideal 2, but the higher dose showed more toxicity. A subgroup analysis also showed that the response rate in Japanese patients was better than in Westerners, namely, 27.5% versus 10.4% in the Ideal 1 trial which included 50% Japanese. The response rate in females (19%) was better than did in males (5%). The adenocarcinoma response rate was 13% versus 4% for other types in Ideal 2. Further analysis also revealed the response rate was better in non-smoking patients. There was no relation based on efficacy between 157 patients with EGFR expression and others in the trials. The same results were reported by Cohen et al.[9] in a FDA analysis with response rates of 29% versus 5% between non-smoking and smoking patients. Ochs et al.[10] also confirmed that efficacy in females and Orientals was greater during an expanded access program (EAP) that included 21,064 patients. The phase II clinical trials defined both the efficacy of Iressa for the patients who failed to the chemotherapy and some related factors.

Two phase III clinical trials, Intact 1 (Iressa Non-small-cell lung cancer Trial Assessing Combination Treatment) and Intact 2 were conducted. The subjects had not been treated previously with chemotherapy and had advanced or metastatic NSCLC. The purpose was to see whether a combination of Iressa and other chemotherapeutic agents could provide more clinical benefit over other chemotherapeutic agents alone in a first-line setting. Unfortunately both trial results showed there were no differentces in the response rates, time for progression, median survival no matter if Iressa was used in combination with gemcitabine and cisplatin or paclitaxel and carboplatin compared to chemotherapy alone.[11,12] The conclusion from the 2 phase III clinical trials was that Iressa, in combination with other chemotherapy, did not improve efficacy (compared to chemotherapy alone).

Is it possible for Iressa to prolong patient survival time? So another phase III clinical trial, ISEL (Iressa Survival Evaluation in Lung Cancer) involved 1,692 patients with advanced or metastatic NSCLC patients. This trial was conducted to assess if there was any differentce in survival between an Iressa-treated group and a control group after chemotherapeutic failure. The results from that trial showed median survival of 5.6 months for the Iressa group and 5.1 months for the control group (P=0.11), with no differentce between the 2 groups. However subgroup analysis showed an median survival of 6.3 months for adenocarcinoma patients and 5.4 months for other cases (P=0.07), although there still was no statistical difference. The results trended to show a benefit for the Iressa group with adenocarcinoma; but the Iressa treated group among Oriental and non-smoking patients was statistically different from the control group. This trial tended to confirm that Iressa showed survival advantage for subgroups of patients with NSCLC, but the number of patients in this trial was too small, so the total response rate of 8.2% could not translated to survival benefit.

Kim et al.[13] reported the results of Iressa on the treatment of NSCLS patients who failed chemotherapy in South Korea. The response rates and disease control rates were 25% and 47.5% respectively in treating 80

patients who could be assessed, but the response rates for cases of adenocarcinoma, never smokers and females were 41%,58.8% and 42.1%. Takano et al.[14] also reported the results of treating 112 NSCLC patients with Iressa in Japan. The overall response rate was 33%, but for adenocarcinoma cases, non-smokers and females were 38%, 63% and 53% respectively. A report from a China clinical trial showed a response rate of 27% in 159 patients with NSCLC after chemotherapy failure, which was similar to the response rate of 26.4% of the EAP in China. Miller et al.[15]reported a response rate of only 15% in treating 139 patients from the Memorial Sloan-Kettering Cancer Center, but adenocarcinoma patients and never smokers reached to 19% and 36% respectively. All those reports have confirmed Iressa's efficacy in some subgroups of patients with NSCLC, especially in Orientals, never smokers, females and adenocarcinoma cases.

Development of basic research

Why are there differences among NSCLC patients treated with Iressa? With some patients Iressa was very effective, but with others there is no effect. Lynch and Paez et al.[16,17] have published their results in both *the New England Journal of Medicine* and *Science*. Lynch et al.[16] have searched for mutations in the EGFR gene in primary tumors from patients with NSCLC who had responded to Iressa, in those who had no response, and in those who had not been exposed to Iressa. They found mutations in the tyrosine kinase domain of the EGFR gene in 8 of 9 patients with an Iressa response, mutations were either in-frame deletions or amino acid substitutions. But none of the 7 patients with no response to Iressa had those mutations. Mutations were also found in tumors from 2 of 25 (8%) patients with primary NSCLC who had not been exposed to Iressa. Paez's [17] research showed differences between nationalities. Mutations of the EGFR gene were found in 15 of 58 Japanese (26%) patients, but only 1of 61 USA (1.6%) patients. Mutations were also high in adenocarcinomas.

Huang et al.[18] also found EGFR gene mutations among patients with NSCLC in Taiwan. Similar mutations were found in 7 of 9 patients who had a response to Iressa, but in just 1 of 7 who showed no response. Mutations in the EGFR gene were also identified in 39 of 101 patients with NSCLC (69 adenocarcinoma, 24 squamous carcinoma, 8 other types) who had not been exposed to Iressa. Mutation rates were 38% in all of the adenocarcinomas but in only one adenosquamous carcinoma. All mutations in the EGFR gene were in the exons 18 to 21.

Mitsudomi et al.[19] reported that the mutations in the EGFR gene were found in 33 of 59 (56%) patients with NSCLC in Japan, which accounted for 56% of all patients. Of these patients, 50 were assessed and 24 of 29 patients with EGFR mutations responded to Iressa and only 2 of 21 patients without EGFR mutations showed a response. Studies from South Korea [13] showed that of 8 patients with NSCLC who responded to Iressa, 6 of them had EGFR mutations and all patients with EGFR mutations had a response to Iressa.

Tokumo et al. [20] reported on the relationship between EGFR mutations and tumor types, smoking status and gender in Japan. EGFR mutations were identified in 38 of 120 patients with NSCLC. The incidence of mutations was significantly higher in adenocarcinomas, never smokers and females compared to controls, with *P*-values of <0.0001, <0.0001, and 0.0001 respectively. Mutations were more common in exon 19 for males and exon 21 for females. Pao et al.[21] studies also showed that of 10 patients who responded to Iressa, 7 had EGFR mutations, whereas of 8 patients who did not respond to Iressa none had EGFR mutations. Seven of 15 patients with adenocarcinoma who had not been exposed to Iressa and had never smoked had EGFR mutations compared to 4 of 81 smokers.

Based on all of the above results from the literature, efficacy varied with different nationalities, tumor types, gender and smoking status. It is more effective for Orientals, adenocarcinoma or bronchoalverlar carcinoma, females and people who never smoked. The response rates have reached to 25%~35% for Oriental patients and 8% ~15% for Western patients with NSCLC. Further research found selective responses from patients that had EGFR gene mutations. The majority of responders had EGFR gene mutations, the response rates being 80% ~100% in patients with NSCLC who did have EGFR gene mutations. This rate was much higher than those patients who did not have EGFR gene mutations. [13,16,18,21] There were less than 10% of EGFR gene mutations for Westerners compared to 26%, 32%, and 38% of Orientals respectively in reports from Paez, Tokumo and Huang. The mutation rates were very similar to the response rates in Oriental patients which probably could partially explain why the response rates are higher in Orientals compared to in Westernerns. Further research has confirmed high EGFR gene mutations for patients with adenocarcinoma, females and never-smokers in Japan. The relationship between gene mutations and the efficacy of Iressa therapy revealed that gene mutations are

critical in both tumorigenesis and proliferation in a subgroup of NSCLC patients which differ from other NSCLCs.

Summary

Molecular target therapy is a new field for the treatment of tumors which evolved with the development of basic research. The major goal is to identify molecular biological features of tumor cells which differ from normal tissue. The agents can act on specific targets such as receptors, kinases, signal-transduction systems of the tumor cells to block or inhibit tumor growth with high efficacy but low toxicity due to their selective action.

Because EGFR is expressed in 40% ~80% of NSCLC, and because its expression is correlated to the development and prognosis of NSCLC, Iressa, as a molecular agent which can block activation of EGFR-TK and kill tumor cells, has been approved for the treatment of metastatic NSCLC in more than 20 countries including China. But the mechanism of tumorigenesis and development is both complex and comprehensive. Therefore the etiology could be different, even in same type of tumor. Iressa has shown to be effective only for subgroups of patients with NSCLC. We have found high response rates in Orientals, adenocarcinoma patients, females, and never-smokers, but it is still difficult to identify and predict those patients who will or will not respond to Iressa. Although there was a significant relationship between EGFR gene mutation and efficacy, there were still some NSCLC patients who did not have EGFR gene mutations and yet responded to Iressa. An explaination for this is not clear.

The use of gene mutations as a predictable factor for clinical practice is not feasible. It is probably more important to find an easier and more practical way to predict responsive patients. Because target agents produce less side effects, combinations or a sequence of different target agents or combinations with cytotoxic agents should be studied to expand efficacy in the near future.

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