Effectiveness of Erlotinib in Advanced Non-Small Cell Lung Cancer in Cases of Gefitinib Resistance after Treatment of More Than 6 Months

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Keywords

Lung cancer · Lung adenocarcinoma · Gefitinib · Resistance · Erlotinib · Disease control rate

Summary

Background: There have been reports on the use of erlotinib in non-small cell lung cancer (NSCLC) patients after gefitinib resistance occurs, and it has been stated that erlotinib may be beneficial in patients with long stable disease (SD) previously treated with gefitinib. **Patients and Methods:** We retrospectively studied gefitinib-resistant NSCLC patients with favorable clinical features, who received erlotinib following disease progression after gefitinib treatment of more than 6 months. **Results:** A total of 21 patients with NSCLC were included. Partial response was seen in 2 cases (9%), SD in 6 cases (19%), and progressive disease (PD) in 13 cases (62%). Disease control (DC) was achieved with erlotinib in 8 cases (36%). The median survival time (MST) was 369 days in DC cases and 133 days in PD cases. There were no statistical differences between DC cases and PD cases in terms of MST relative to sex, smoking and skin rash. **Conclusion:** Subsequent erlotinib therapy is one of the therapeutic options in the treatment of gefitinib-resistant NSCLC in which prior gefitinib has shown long-term SD of more than 6 months.

Schlüsselwörter

Bronchialkarzinom · Adenokarzinom der Lunge · Gefitinib · Resistenz · Erlotinib · Kontrollrate

Zusammenfassung

Hintergrund: Vom Einsatz von Erlotinib bei Patienten mit nicht-kleinzelligem Bronchialkarzinom (NSCLC) nach Auftreten einer Gefitinib-Resistenz ist zuvor berichtet worden. Insbesondere bestehen Angaben dazu, dass mit Gefitinib vorbehandelte und langfristig krankheitsfreie Patienten von einer Behandlung mit Erlotinib profitieren könnten. **Patienten und Methoden:** Gefitinib-resistente NSCLC-Patienten mit günstigen klinischen Merkmalen, die im Anschluss an ein Krankheitsfortschreiten nach mehr als 6 Monaten Gefitinib-Therapie mit Erlotinib behandelt worden waren, wurden retrospektiv untersucht. **Ergebnisse:** Insgesamt wurden 21 NSCLC-Patienten in die Studie eingeschlossen. Ein partielles Ansprechen wurde in 2 Fällen beobachtet (9%), Krankheitsstabilisierung in 6 Fällen (19%) und Krankheitsfortschreiten (progressive disease, PD) in 13 Fällen (62%). Eine Krankheitskontrolle (disease control, DC) wurde in 8 Fällen (36%) erreicht. Das mediane Überleben war 369 Tage bei DC-Patienten und 133 Tage bei PD-Patienten. Hinsichtlich des medianen Überlebens in Bezug auf Geschlecht, Raucherstatus und Hautausschlag bestanden zwischen den DC- und PD-Patienten keine statistisch signifikanten Unterschiede. **Schlussfolgerung:** Erlotinib-Therapie ist eine therapeutische Option bei NSCLC-Patienten mit Gefitinib-Resistenz, bei denen mit Gefitinib eine langfristige Krankheitsstabilisierung von mehr als 6 Monaten erreicht werden konnte.

Introduction

Epidermal growth factor receptor (EGFR) should be considered as an option in the treatment of non-small cell lung cancer (NSCLC). The EGFR tyrosine kinase inhibitors

(TKIs) gefitinib and erlotinib are orally active and routinely used in the treatment of advanced NSCLC. These reversible EGFR TKIs block signal transduction pathways and inhibit cancer cell survival and proliferation [1]. Gefitinib was the first oral EGFR TKI to be made available. The ISEL study

indicated that gefitinib was more effective in treating Asian patients [2]. The BR.21 study indicated that erlotinib could prolong the survival in patients who had undergone chemotherapy pretreatment in this phase III study [3].

The biomarker analysis studies of BR.21, ISEL, INTEREST, IPASS, and SATURN [2–6] indicated that patients with EGFR mutations have a pronounced response to EGFR TKIs. However, while the initial response is positive, after about 6–18 months progression of the disease occurs, leaving no viable treatment options [7].

It has been suggested that because of similar structures and mechanisms, erlotinib and gefitinib should have similar effects. Both drugs have slightly different pharmacological properties. For example, erlotinib is less susceptible to metabolism by the cytochrome P450 pathway than gefitinib. Hence, with erlotinib there is a lower clearance rate blocking the activity of wild-type EGFR at lower concentrations than with gefitinib [8]. The maximum tolerated dosage of gefitinib is 700 mg/day, which is a considerably larger dose than the usual dose of 250 mg/day. The maximum dosage of erlotinib is 150 mg/day. It has been reported that these differences may account for the contrary results in both phase III studies in which only erlotinib was found to prolong survival [2, 3]. These data indicate treatment with erlotinib should be considered as a possible option in cases of gefitinib failure. There have been reports on the use of erlotinib in NSCLC patients after gefitinib resistance occurs [9–16]. There have also been reports on cases in which erlotinib was effective after failure of gefitinib. Kaira et al. [17] state that erlotinib may be beneficial in patients with long stable disease (SD), who have previously been on gefitinib [17].

We retrospectively studied gefitinib-resistant NSCLC patients treated with erlotinib after long periods of SD. Our primary aim was to assess the disease control (DC) rates of patients who received erlotinib after failure of long SD with gefitinib. Our secondary aim was to identify factors which would enable us to predict response to a transition to erlotinib.

Patients and Methods

Patients

A total of 21 patients who received both gefitinib and erlotinib from February 2008 to December 2009 at the Kanagawa Cancer Center were identified, and a retrospective review of their case files and radiographic records was undertaken. Patients included in the analysis had histologically or cytologically proven advanced NSCLC and received erlotinib following disease progression after long treatment with gefitinib of more than 6 months. We included those patients who had received the second TKI immediately after stopping the first TKI, without receiving cytotoxic chemotherapy between TKIs. Clinical data was collected retrospectively, including age, sex, performance status at diagnosis (Eastern Cooperative Oncology Group performance status (ECOG PS)), smoking history, EGFR mutation, systemic chemotherapy, best overall tumor response, erlotinib-related adverse events, and mortality rates, up until June 30th, 2010.

Response Evaluation

Our response assessment was made after reviewing patient records and radiographic evidence (chest X-ray and/or computed tomography (CT)) established during treatment with EGFR TKIs. The best overall tumor responses (complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD)) during the course of different treatment modalities were based on reviews of available medical records and imaging studies, according to RECIST criteria. DC was defined as a lack of PD and clinical improvement or stability, as assessed by the attending physicians. Treatment with EGFR TKIs would be stopped at the time of documented worsening of existing lesions or an emergence of new lesions which were regarded as PD. Overall survival rates were evaluated from the initiation of erlotinib therapy to the date of death or at the end of the study (June 30th, 2010).

Adverse Event Evaluation

The toxicity profile of erlotinib was assessed by reviewing medical records and included skin rashes, diarrhea, liver toxicity, and radiological evidence of interstitial pneumonitis. The severity of adverse reactions was determined according to dosage reduction or discontinuation of erlotinib.

Statistical Analysis

Continuous data were expressed as mean $\pm$ standard deviation, and categorical data were expressed as percentages. Comparisons between the 2 groups were performed with the Student's t-test for continuous variables and Fisher's exact test for categorical variables. Survival analysis was conducted with the Kaplan-Meier analysis and log rank test. A p value of less than 0.05 was considered significant. All statistical tests were conducted using the computer software SPSS version 16.0 (SPSS Inc., Chicago, IL, USA).

Table 1. Patient characteristics

Age, median (range), years	60 (47–80)
Gefitinib treatment, median (range), days	441 (183–1,571)
Patients, n	
Patients, total	21
Sex	
Male	9
Female	12
Histology	
Adenocarcinoma	19
Poorly differentiated carcinoma	2
Stage	
IIIB	3
IV	18
Performance status	
0	4
1	15
2	1
3	1
Smoking	
Yes	9
No	12
EGFR mutations	
Positive	12
Wild type	1
Unknown	8
Number of pretreatment regimens	
0	1
1	12
2	2
3	6

Fig 1. Kaplan-Meier curve of overall survival in all cases. Median survival time was 211 days.

Fig 2. Kaplan-Meier curve of overall survival in patients with partial response (PR), stable disease (SD), and progressive disease (PD). Median survival time was 357 days in SD cases and 133 days in PD cases ($p = 0.01$).

Fig 3. Kaplan-Meier curve of overall survival in disease control (DC) and progressive disease (PD) cases. Median survival time was 369 days in DC cases, and 133 days in PD cases ($p = 0.008$).

Results

Clinical and Epidemiological Characteristics

Patient characteristics are presented in table 1. A total of 35 NSCLC patients who received both gefitinib and erlotinib were screened. 21 Japanese patients (12 women, 9 men; mean age 60 years) received gefitinib as first EGFR TKI treatment and erlotinib as second TKI treatment, without cytotoxic chemotherapy between TKIs. 9 patients were smokers. Adenocarcinomas were diagnosed in 19 cases, and poorly differentiated carcinomas were found in 2 cases. Stage IV was found in 18 cases and stage III in 3 cases. EGFR mutations were evaluated in 16 patients, 12 of whom were positive for a point mutation in exon 21 (L858R), 1 patient was negative, and 2 patients were not evaluated. PR was achieved in 16 cases

Table 2. Treatment periods with erlotinib were significantly longer in disease control (DC) cases than in progressive disease (PD) cases; gefitinib pretreatment periods were not significantly different

	Treatment period, median (range), days		p
	DC (n = 8)	PD (n = 13)	
Erlotinib	259 (71–524)	28 (13–159)	0.005
Gefitinib	686 (183–1,571)	420 (193–1,612)	0.57

using gefitinib, and SD in 5 cases. At the time of initiation of erlotinib treatment, most of the patients had a good PS (ECOG 0: 4 patients; ECOG 1: 15 patients; ECOG 2: 1 patient; ECOG 3: 1 patient). Gefitinib was prescribed at standard dosages of 250 mg daily and erlotinib at 150 mg daily. Erlotinib was used as second-line treatment in 1 patient, as third-line treatment in 12 patients, as fourth-line treatment in 2 patients, and as fifth-line treatment in 6 patients. Erlotinib was used immediately after failure of gefitinib. The median period of gefitinib treatment was 441 days (range: 183–1,571).

Efficacy of Erlotinib

The median period of erlotinib treatment was 55 days (range 16–524). PR was achieved in 2 cases (9%), SD in 6 cases (19%), and PD in 13 cases (62%). DC was achieved in 8 patients with erlotinib. The median survival time (MST) in all patients was 211 days (fig. 1). There were no statistical differences in sex, smoking, and skin rash between the DC cases and the PD cases. MST was 369 days in DC cases and 133 days in PD cases (figs. 2 and 3). There were no significant differences between treatment periods with gefitinib, but there were differences between treatment periods with erlotinib (table 2). Fig. 4 shows the efficacy of erlotinib. There were no

Fig. 4. A case showing positive results after erlotinib therapy.

significant differences between the effects of erlotinib in PR cases and SD cases. There were no significant differences between the positive and negative EGFR mutation cases.

Adverse Events

The development of skin rashes during erlotinib treatment was experienced in 11 cases (52%), with grade 1 in 4 cases, grade 2 in 5 cases, and grade 3 in 2 cases. Diarrhea occurred in 19% of cases (grade 1 in 3 cases, grade 2 in 1 case). Loss of appetite was reported in 24% of the patients (grade 1 in 5 cases, grade 2 in 2 cases). Other events included grade 1 oral mucositis in 1 case, grade 3 neuropathy in 1 case, grade 1 increased creatinine levels in 1 case, and grade 3 abdominal distension in 1 case.

Discussion

Several researchers have reported on cases in which erlotinib was effective after failure of gefitinib. The response rate ranged from 4.3 to 25%, and the DC rate was relatively high at 8.7–75% [9–16]. These researchers reported that erlotinib was effective in specific cases. In our study, MST was 211 days which was longer than that previously reported (fig. 1). Our study also demonstrated that erlotinib is effective in specific cases. Wong et al. [16] reported that erlotinib was effective in DC cases in which gefitinib was also effective. They suggested that patients who responded to gefitinib may also respond to erlotinib. Kaira et al. [17] reported that when cases showed an SD period of more than 6 months using gefitinib, erlotinib would be effective.

We studied specific patients who had been treated with gefitinib for more than 6 months. In our study, the MST of

DC cases was 369 days which was longer than that previously reported [9, 15, 16]. While this long MST might be due to erlotinib [9], it is difficult to clarify the mechanisms behind the effectiveness of erlotinib in DC cases. In fact, both EGFR TKIs share the same mechanism of EGFR blockade and are considered to be cross-resistant. Furthermore, the acquisition of resistance mutations such as T790M implies a potential loss of sensitivity to both TKIs. In our opinion, this might be due to the fact that the accepted dosages of gefitinib (250 mg/day) and erlotinib (150 mg/day) are not equivalent [7]. Erlotinib was administered at its maximum dosage, whereas gefitinib was administered at only one third to one sixth of its maximum dosage [18].

Another reason for differences in tumor sensitivity, especially in wild-type EGFR tumors, might be related to the relative concentration of EGFR TKIs. The half maximal inhibitory concentration (IC₅₀) value of erlotinib is much lower than that of gefitinib [9]. Additionally, a tumor's biological characteristics might contribute to a longer MST. There have been reports about slow growth lung cancer. For example Kojima et al. [19] reported on slow growth lung cancer in cases where the positive rates of EGFR mutations were more than 60%. Kalikaki et al. [20] reported that the EGFR mutation status is useful in predicting responses to cytotoxic chemotherapy. Sae-Won et al. [21] reported that the EGFR mutation status is related to a better prognosis with gefitinib. There are reports which claim that the EGFR mutation status is related to a good prognosis, and is not dependent on the efficacy of chemotherapy [22]. One of our patients (fig. 4) tested positive for a point mutation in exon 21, and we noted that the tumor grew slowly and was sensitive to various cytotoxic agents, including docetaxel and pemetrexed, after failure of erlotinib. Some reports have suggested that the EGFR

mutation status is not related to the efficacy of erlotinib after gefitinib failure. Among our 21 cases, the EGFR mutation status was examined in 16 cases (12 tested positive, 1 tested wild, 3 tested unknown). There were no significant statistical differences in survival rates between the positive and negative/unknown EGFR mutation cases.

Several researchers have stated that most patients who did not respond to prior gefitinib therapy, experienced rapid tumor growth on subsequent erlotinib therapy. However, patients who responded to prior gefitinib therapy responded positively to subsequent erlotinib therapy. Hence, response to prior gefitinib therapy may be a predictive maker for subsequent erlotinib therapy [9, 11, 14]. In our study, subsequent erlotinib therapy was effective in 38% of cases and ineffective in 62%. More importantly, MST of PD cases were very short with only 133 days. We know that erlotinib is not effective in every SD case, but we do know that it is effective in some cases. We could not predict which long-term SD cases would respond positively to erlotinib therapy. There were no significant differences in the treatment periods for patients who had undergone prior gefitinib therapy (table 2). We must, there-

fore, evaluate the effectiveness of erlotinib therapy after treatment.

The effectiveness of subsequent erlotinib is limited. Our results indicate that erlotinib can produce clinical benefits in patients displaying long-term SD of more than 6 months, who have undergone gefitinib therapy. Further research is required to determine in which cases erlotinib will be effective after onset of gefitinib resistance. At present, several EGFR/HER2-targeted agents and pan-HER inhibitors are being tested in clinical trials. Irreversible TKIs are an emerging class of agents that may have the potential to overcome and prevent the emergence of acquired resistance which occurs with reversible EGFR-TKIs [23]. The results from ongoing phase II and III trials of these agents in patients with NSCLC, particularly in patients who are resistant to reversible EGFR-TKIs, are eagerly awaited.

Disclosure Statement

The authors declare no conflict of interest.

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