Evidence for Disease Control with Erlotinib after Gefitinib Failure in Typical Gefitinib-Sensitive Asian Patients with Non-small Cell Lung Cancer

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Introduction: The epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) gefitinib and erlotinib are gaining an increasing role in the management of advanced non-small cell lung cancer (NSCLC). There is mounting interest in the benefit of administering a second TKI after failure of the first TKI, especially in Asian patients, in whom they are expected to be more efficacious.
Methods: We did a retrospective analysis of patients receiving both gefitinib and erlotinib in our institution during a 2-year period. Patients were to have received the second TKI after progressive disease on the first TKI. EGFR gene mutation analysis was done on patient tumor samples.
Results: Fourteen patients were included in the analysis, all of whom received erlotinib after progression on gefitinib. Chinese race, females, never-smokers, and adenocarcinoma subtype were predominant in their respective categories. Disease control rate was 64.3% (9 of 14) for gefitinib. Disease control rate for erlotinib administered after progression on gefitinib was 35.7% (5 of 14). All patients who achieved disease control with erlotinib after progression on gefitinib were never-smokers with adenocarcinoma subtype, who had prior disease control on gefitinib. Presence of EGFR mutations predicted for disease control with gefitinib, and for disease control with erlotinib after gefitinib failure.
Conclusion: A significant proportion of typical gefitinib-sensitive Asian NSCLC patients can have disease control with erlotinib after gefitinib failure. The role of subsequent administration of a second EGFR TKI after failure of the first TKI in advanced NSCLC should be further pursued.

Key Words: Gefitinib, Erlotinib, Non-small cell lung cancer, Asian.

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The epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) gefitinib and erlotinib are routinely used for the treatment of advanced non-small cell lung cancer (NSCLC). Erlotinib was shown to prolong survival in chemotherapy pretreated patients in the phase III BR.21 trial,[1] whereas gefitinib did the same for the Asian patient subgroup in the ISEL study.[2] Gefitinib has also been used in the first-line setting in Japanese and Korean patients with impressive results.[3,4] The EGFR TKIs are known to have higher response rates in Asian NSCLC patients, females, nonsmokers, and those with adenocarcinoma histologic subtype.[5–7] Responses were also found to be correlated with the presence of somatic mutations in the kinase domain of the EGFR gene,[8,9] which are found to occur with greater frequency in Asian patients.[7] Despite the excellent initial response, disease progression usually occurs after a median time of 4 to 6 months, after which no good treatment options exist for these patients.

It would be therefore be desirable if there was a role for the subsequent use of a second TKI after failure of the first TKI in the management of this difficult disease. As small molecule oral agents, their attractiveness lies not only in the ease of administration but also in their tolerability compared with conventional chemotherapy. There were anecdotal reports of clinical activity seen with the second TKI after failure of the first TKI,[10,11] although others suggested no role for this.[12] A retrospective study was conducted with the primary objective of assessing the disease control rate of the second TKI after failure of the first. Secondary objectives were to characterize the clinical, pathologic, and molecular features of patients benefiting from a second TKI.

PATIENTS AND METHODS

Patients

After institutional approval, patients at the National University Hospital who received both gefitinib and erlotinib from January 2005 to December 2006 were identified through the electronic pharmacy record system, and a retrospective review of case files and radiographic records was undertaken. Patients included in the analysis had histologically or cytologically proven advanced NSCLC who received erlotinib following disease progression on gefitinib. We included patients who received the second TKI immediately after stop-

ping the first TKI, as well as those who received the second TKI any length of time after stopping the first TKI, with or without conventional chemotherapy being administered between TKIs. Patients excluded were those who received the second EGFR TKI for reasons other than disease progression on the first TKI, such as toxicity or financial reasons or those who received erlotinib before gefitinib. Response assessment was from review of patient records and radiographic studies including chest roentgenograms and computed tomographic scans. Disease control was defined as radiographic evidence of improvement or stability, associated with clinical alleviation or stability of symptoms as assessed by the treating physician, and continuation of drug treatment. Progression was defined as a radiographic worsening of existing lesions or the appearance of new lesions. As patients with peripheral adenocarcinoma often have a large or even predominant component of nonmeasurable disease (subcentimeter miliary nodules, reticulonodular infiltrates, or pneumonic pattern) on imaging,[13] the use of conventional response criteria such as RECIST[14] was considered unsuitable in such patients.[15]

EGFR Mutation Analysis

Formalin-fixed, paraffin-embedded tumor samples of the cases were obtained from the Departments of Pathology, National University Hospital and Tan Tock Seng Hospital, Singapore. DNA was extracted from 5 μm sections of each sample as described previously.[16] Mutations in the tyrosine kinase domain (exons, 18–21) of EGFR were detected using partially denaturing high-performance liquid chromatography as described previously.[17]

Statistical Analysis

Duration of disease control was defined as the number of days that the patient received the respective TKI up to the point of documented disease progression. Survival was calculated from the time of diagnosis to death or the last follow-up date. Disease control rates were compared between variables of interest using Fisher exact test.

RESULTS

We identified 18 patients with advanced NSCLC who received both gefitinib and erlotinib in the course of their treatment. Four patients were excluded from further analysis, because three patients did not receive the second EGFR TKI for progressive disease on the first TKI and one patient received erlotinib prior to gefitinib. The remaining 14 patients who received erlotinib after prior progression on gefitinib were analyzed (Figure 1). The median age was 56 years, and there was a majority of Chinese, females, and nonsmokers.

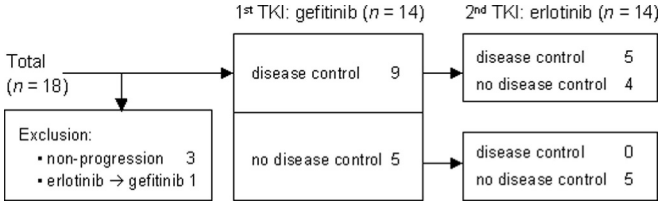

FIGURE 1. Analysis of treatment results.

Eight of 14 patients had adenocarcinoma histologic subtype, 1 had squamous-cell carcinoma, 2 had bronchioloalveolar carcinoma (on tissue diagnosis), and 3 patients were NSCLC not otherwise specified. The majority of patients had florid lung metastases in the form of subcentimeter nodules, often in a miliary pattern, reticulonodular infiltrates, or pneumonic shadows (Table 1).

Gefitinib was used as first-line systemic treatment in 9 of 14 patients whereas erlotinib was used later in the course of the disease, with 9 of 14 patients receiving it as fourth-line treatment and beyond (Table 2). The dose of gefitinib was 250 mg daily, and that of erlotinib was 150 mg daily, in all patients. Thirteen patients also received conventional cytotoxic chemotherapy, with a median of two lines administered (range, 1–5).

Disease control for gefitinib was seen in 9 of 14 patients (64.3%). In the 9 patients who received gefitinib as first-line treatment, disease control was seen in 6 (66.7%). Overall disease control rate for erlotinib as second TKI was seen in 5 of 14 patients (35.7%). Of the 9 patients who achieved prior disease control with gefitinib, 5 (55.6%) subsequently also achieved disease control with erlotinib (Figure 1). Of the 5 patients who did not achieve prior disease control with gefitinib, none achieved disease control with subsequent erlotinib ($p = 0.09$).

We analyzed the other baseline and treatment characteristics of the 5 patients who showed benefit from receiving

TABLE 1. Patient Characteristics

Characteristic	*n*	Percent
Total patients	14	100.0
Median age, yr	56	
Range, yr	40–73	
Sex		
Male	4	28.6
Female	10	71.4
Race		
Chinese	12	85.7
Malay	1	7.1
Indian	1	7.1
Smoking status		
Never/nonsmoker	13	92.9
Exsmoker	1	7.1
Histology		
Adenocarcinoma	8	57.1
BAC	2	14.3
Squamous	1	7.1
Non-small cell unspecified	3	21.4
Metastases sites at presentation		
Thoracic-only	7	50.0
Extrathoracic	7	50.0
Bones	4	28.6
Liver	3	21.4
Brain	1	7.1
Abdominal lymph nodes	2	14.3

BAC, bronchioloalveolar carcinoma.

TABLE 2. Treatment Characteristics

Treatment	*n*	Percent
Gefitinib		
1st-line	9	64.3
2nd-line	2	14.3
3rd-line	2	14.3
≥4th-line	1	7.1
Erlotinib		
1st-line	0	0.0
2nd-line	4	28.9
3rd-line	1	7.1
≥4th-line	9	64.3
Conventional chemotherapy	13	92.9
Median no. of lines	2	
Range	1–5	

erlotinib after gefitinib failure (Tables 3 and 4). All patients were never-smokers who had adenocarcinoma subtype. All had responded to prior gefitinib. Three of the 5 patients had dramatic radiographic responses to gefitinib, including significant improvements in nonmeasurable disease. Median duration of disease control in these 5 patients for gefitinib was 227 days (range, 197–537), and subsequently to erlotinib was 97 days (range, 50–238). Dramatic radiographic improvement to erlotinib was seen in two patients, which we illustrate in Figure 2. One patient had no change in 2-monthly computed tomographic scans of lung lesions previously progressing on gefitinib, until 8 months later. Disease control was associated with symptomatic improvement or stability in all patients. All five patients ultimately had progressive disease on erlotinib. Four of the five patients had conventional chemotherapy (one or 2 lines) in between the different TKI treatments, with a "TKI-free interval" of between 89 to 388 days.

Chemotherapy was administered in between first and second TKI treatments in 8 of 14 patients. Five patients received two different regimens, 2 patients received one regimen, and 1 patient received three different regimens of conventional chemotherapy in the interval between gefitinib cessation and erlotinib commencement. The regimens were carboplatin plus gemcitabine (4 patients), pemetrexed (4 patients), docetaxel (4 patients), carboplatin plus vinorelbine (1 patient), S-1 (1 patient), and irinotecan plus capecitabine (1 patient). The median number of chemotherapy cycles administered in these patients between gefitinib cessation and erlotinib commencement was 6 (range, 2–9). Disease control was achieved by at least one regimen of chemotherapy in 5 of these 8 patients. We did not find any association between disease control with chemotherapy during the "TKI-free interval" and disease control with the second TKI, in both the entire group as well as in the subgroup achieving disease control with the first TKI.

EGFR mutations were detected in 8 of 14 patients (57.1%). The mutations in 7 of 8 patients included previously described sensitizing EGFR mutations, such as exon 19 deletions and the L858R substitution. Four patients had deletions, three patients had substitutions (including 1 patient with 2 substitutions) and one patient had both deletion and substitution. EGFR mutations predicted for disease control with gefitinib. Eight of eight patients (100.0%) with EGFR mutations achieved disease control versus 1 of 6 patients (16.7%) with wild-type EGFR ($p = 0.003$). EGFR mutations were also associated with disease control with erlotinib. Five of eight patients (62.5%) with EGFR mutations achieved

TABLE 3. Baseline Characteristics of Patients Benefiting from a Second EGFR TKI

Patient No.	Age	Sex	Smoking Status	Race	Histology	EGFR Mutation
1	40	M	Never	Chinese	Adenocarcinoma	747:del 21bp (del L747-A755, +S)
2	50	F	Never	Chinese	Adenocarcinoma	746:del 15bp (del E746-A750)
3	70	F	Never	Chinese	Adenocarcinoma	833:TTG>GTG (L833V), 858:CTG>CGG (L858R)
4	68	M	Never	Indian	Adenocarcinoma	868:GAG>GTG (E868V)
5	62	F	Never	Chinese	Adenocarcinoma	746:del 15bp (del E746-A750), 851:GTC>GTT(V851V)

EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; M, male; F, female.

TABLE 4. Treatment Characteristics of Patients Benefiting from a Second EGFR TKI

		Gefitinib			Erlotinib					
Patient No.	TKI Sequence	Line of Treatment	DC	Duration of DC (d)	Line of Treatment	DC	Duration of DC (d)	Conventional Chemotherapy No. of Lines	TKI-free Interval (d)	Survival from Diagnosis (d)
1	G before E	2nd	Yes	197	5th	Yes	50	5	105	690 (DOD)
2	G before E	2nd	Yes	354	4th	Yes	50	2	92	690 (DOD)
3	G before E	1st	Yes	227	2nd	Yes	238	2	0	911 (AWD)
4	G before E	1st	Yes	226	3rd	Yes	97	2	89	674 (DOD)
5	G before E	1st	Yes	537	4th	Yes	198	2	388	1276 (AWD)

EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; G, gefitinib; E, erlotinib; DC, disease control; DOD, died of disease; AWD, alive with disease.

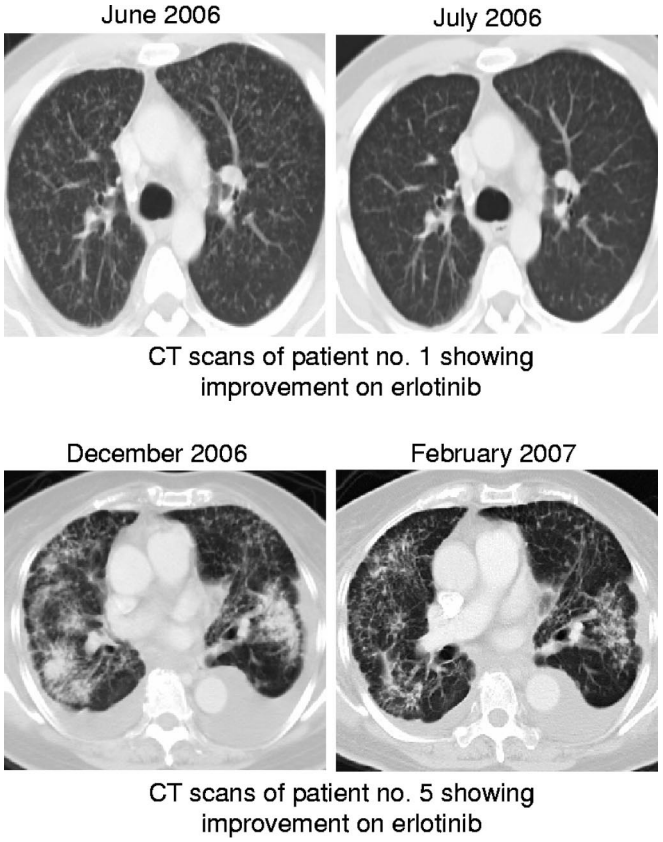

FIGURE 2. Computed tomographic scans of two patients (nos. 1 and 5—see Tables 3 and 4) demonstrating dramatic responses of miliary and reticulonodular lung disease with erlotinib. Both patients had prior progression on gefitinib with new subcentimeter lung nodules.

disease control with erlotinib after gefitinib failure, compared with 0 of 6 patients (0.0%) with wild-type EGFR ($p = 0.03$).

DISCUSSION

Both gefitinib and erlotinib have been in routine use in Asian patients with NSCLC for the several years, but little is known about the efficacy of a second reversible EGFR TKI after disease progression on the first. A case report by Garfield[10] showed response to erlotinib after gefitinib failure in a male smoker with squamous-cell carcinoma, whereas Choong[11] reported response to gefitinib after erlotinib failure in a never-smoker female with adenocarcinoma. However, Viswanathan[12] suggested that there was no role for the subsequent usage of erlotinib after gefitinib failure in five patients which included four females with prolonged responses to gefitinib.

Although EGFR sensitizing mutations and clinical responses to EGFR TKIs are known to occur more frequently in Asian patients,[7] there has not been any conclusive bench or clinical evidence to suggest that use of erlotinib after progressive disease on gefitinib or vice versa would be beneficial in this group of patients. In fact, both EGFR TKIs share the same mechanism of EGFR blockade and are hence thought to be cross resistant.[18,19] Furthermore, the acquisition of resistance mutations such as T790M implied a potential loss of sensitivity to both TKIs.[20–22]

A recent publication of a phase II trial by Cho and colleagues[22] showed a disease control rate of 29.6% in NSCLC patients treated with erlotinb after gefitinib failure. It was reported that higher disease control and response rates with subsequent erlotinib were associated with patients who lacked EGFR mutations and achieved stable disease on gefitinib. It was proposed that patients who responded initially to gefitinib and subsequently progressed were less likely to benefit from erlotinib due to the acquisition of secondary mutations, in particular T790M, which would confer resistance on both drugs. However, there may be a concern if the RECIST[14] criteria was applied to patients in whom a large or predominant component of disease was nonmeasurable.[13,15] Hotta et al.[23] found that disease stability as assessed by conventional criteria, was associated with survival benefit in patients on gefitinib, whereas Comis[18] commented on the lack of correlation of response rates with survival. The dramatic responses seen in Figure 2 illustrate the inadequacy of RECIST criteria in assessing the predominant nonmeasurable components in these patients.

In the current study, evidence for clinical benefit in a number of Asian NSCLC patients treated with erlotinib after progression on gefitinib was seen. All five cases in our study were patients who had responded to prior gefitinib, and all had the characteristics of never-smoker, adenocarcinoma subtype, and EGFR gene mutations. Two of the patients showed dramatic responses on imaging (Figure 2), lasting for durations of 50 and 198 days. The disease control rate of erlotinib after gefitinib failure was similar to that in Cho's study.[22] However, we found that the patients who had disease control with erlotinib were typical gefitinib-sensitive NSCLC patients with most of them harboring classic sensitizing EGFR mutations.

There could be several explanations for this finding. Noncross-resistance of EGFR tyrosine kinase to gefitinib and erlotinib is the first possibility. It has been proposed that the different survival outcomes in the BR.21[1] and ISEL[2] studies attest to the qualitative differences between gefitinib and erlotinib. The potential for cross-resistance conferred by acquired secondary mutations like T790M could be abrogated by other unknown mutations conferring differential sensitivity. An example of differential sensitivity to erlotinib and gefitinib was shown in a case report by the discovery of the novel E884K mutation on exon 22.[11] The mechanism of acquired resistance has also not been explained by the T790M mutation in all cases,[24] hence nonoverlapping susceptibility of gefitinib and erlotinib to acquired resistance is a consideration.

It is possible heterogenous malignant clones within the same patient could harbor different mutation status and EGFR TKI-sensitivity.[25] A patient may benefit from a second EGFR TKI if the progressive component on the first EGFR TKI at a different site (e.g., brain metastases) was controlled by radiotherapy, whereas the original EGFR TKI-sensitive clone remained sensitive and continued to respond on EGFR TKI resumption.[26] However, this was not the situation in any of the

five patients in our study. All five patients had disease control with erlotinib in the lungs, which was the same site that showed disease progression on gefitinib.

Another possibility is the loss of acquired-resistance after a "TKI-free interval."[26] Conventional chemotherapy given after first-TKI failure may also result in reduction of TKI-resistant clones, leaving the TKI-sensitive ones to be further controlled by a second TKI "rechallenge" subsequently.[26] Four of the five patients in our series received conventional chemotherapy during "TKI-free intervals" of between 89 and 388 days. However, we could not demonstrate an association between disease control with chemotherapy during the "TKI-free interval" and disease control with the second TKI in our small group of patients.

There is a possibility that erlotinib can salvage gefitinib failures by sheer difference in drug potency, since erlotinib (150 mg) is administered at its maximum-tolerated dose whereas gefitinib (250 mg) is administered at about one third its maximum-tolerated dose.[18] However, this mechanism is not borne out by the lack of difference in clinical efficacy between 250 and 500 mg daily dosing for gefitinib in previous studies.[5,6] Furthermore, responses to gefitinib 250 mg daily dosing after disease progression on erlotinib 150 mg daily dosing have also been reported.[11,27]

In conclusion, we found evidence for disease control with erlotinib after gefitinib failure in a significant proportion of typical gefitinib-sensitive Asian patients with NSCLC. We think our results may apply to other non-Asian patients who harbor typical mutations for EGFR TKI response. The role of administering a second EGFR TKI after failure of the first TKI in advanced NSCLC warrants further development.

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