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ORIGINAL ARTICLE

The administration of gefitinib in patients with advanced non-small-cell lung cancer after the failure of erlotinib

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Abstract
Purpose Recent studies have demonstrated that erlotinib therapy may be considered an option for patients with advanced non-small-cell lung cancer who experienced disease progression after treatment with gefitinib, particularly in patients in whom the disease had been stabilized for a long time prior to gefitinib therapy. The aim of this study was to evaluate the disease control rate and toxicity of gefitinib in patients whose disease progressed after erlotinib therapy.
Methods From May 2005 to August 2006, 15 patients received a 250 mg/day dosage of gefitinib after having disease progression while taking erlotinib at a dose of 150 mg/day.
Results Among patients who received erlotinib, 1 (7%) achieved a partial response (PR), and 5 (33%) achieved stable disease (SD). Among patients who received gefitinib, none achieved a PR, and 6 achieved SD (40%). Five out of 6 patients who achieved PR/SD with erlotinib also achieved SD with gefitinib; 8 out of 9 patients who achieved a progressive disease (PD) with erlotinib also achieved a PD with gefitinib. The median time to progression (TTP) and overall survival (OS) were 2.3 and 3.5 months, respectively. The TTP and OS in SD patients were 3.7 and 7.4 months, respectively. The most common toxicities of gefitinib were dry skin (grade 1–2) in 27% of patients and acneiform rashes and rashes/desquamation in 20% of patients. Diarrhea (grade 1–2) occurred in 7% of patients.
Conclusions Our data suggest that patients who achieved PR/SD with erlotinib also benefit from taking gefitinib. Conversely, gefitinib is not recommended in patients whose disease progressed after taking erlotinib.

Keywords Non-small-cell lung cancer · Gefitinib · Erlotinib · EGFR-TKI toxicity · EGFR mutation · K-ras mutation

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Introduction

Erlotinib and gefitinib are reversible inhibitors of the kinase domain of EGFR (EGFR-TKIs). EGFR-TKIs compete with ATP in binding the catalytic pocket. These small molecules inhibit EGFR autophosphorylation, thereby inhibiting receptor dimerization and the downstream signaling that would otherwise stimulate cancer cell proliferation, angiogenesis, apoptotic mechanisms, invasion and metastasis [1, 2].

Gefitinib was the first oral EGFR-TKI to become commercially available. In the Iressa Survival Evaluation in

Lung Cancer (ISEL) study, gefitinib was shown to increase survival among patients in Asia and among patients who had never smoked. However, these benefits were not seen in the overall population [3]. Four randomized phase III trials of gefitinib have recently demonstrated that the drug provides patients with a superior progression-free survival (PFS) a higher objective response rate and a better quality of life compared with platinum-based chemotherapy in untreated advanced NSCLC harboring an EGFR mutation [4–7].

Erlotinib approval for second- and third-line treatment of advanced NSCLC was supported by the results of a phase III randomized double-blind, placebo-controlled trial (BR.21). This study assessed the efficacy of erlotinib in the treatment of patients with advanced and chemotherapy-refractory NSCLC. This study demonstrated that erlotinib not only prolongs survival in these patients (6.7 vs. 4.7 months; $P < 0.001$) but also improves their symptoms and quality of life [8, 9]. More recently, similar to the findings regarding the use of gefitinib, two randomized phase III studies demonstrated that erlotinib results in a better PFS and a higher response rate compared to chemotherapy when used as first-line treatment in patients with the EGFR mutation [10, 11].

Gefitinib and erlotinib have shown similar side effects, especially skin toxicity and diarrhea, although erlotinib seems to be associated with a higher toxicity and less tolerability than gefitinib [12].

This difference in toxicity is most likely a result of the clinical dose of gefitinib (250 mg/day) being only about one-fourth of its maximum tolerated dose, whereas erlotinib is used at its maximum tolerated dose (150 mg/day) [13, 14]. However, data from randomized trials comparing gefitinib with erlotinib are not available.

Several studies have reported a clinical benefit in NSCLC patients who took erlotinib after the failure of gefitinib treatment. These reports suggest that salvage treatment using erlotinib may be a valid option in patients who had achieved long-term disease stability on prior gefitinib therapy [15–26].

We conducted a phase II study to evaluate gefitinib as a potential therapy option in NSCLC patients whose disease progressed after treatment with erlotinib.

Patients and methods

Eligibility

Patients with histologically or cytologically confirmed advanced NSCLC (stage IIIB for pleural effusion or supraclavicular lymph nodes or stage IV) who had received no more than three prior chemotherapy regimens and who had a documented disease progression on erlotinib treatment, received in an expanded access program of erlotinib, were eligible for this study. To be included in the study, patients were required to have at least one unidimensionally measurable lesion, according to the Response Evaluation Criteria in Solid Tumor (RECIST) [27]; be at least 18 years of age; have an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; have adequate hematologic, hepatic and renal functioning; and have an estimated life expectancy of 12 weeks or more. Exclusion criteria included serious concomitant disorders, a significant ophthalmologic abnormality, untreated brain metastases and spinal cord compression, and any previous malignancies within the last 5 years (other than cervical carcinoma or skin cancer that was successfully treated).

Pretreatment evaluation and treatment

Eligible patients received gefitinib at a dose of 250 mg once daily. Therapy was continued until the disease began to progress, and there was an intolerable level of toxicity, death or withdrawal of consent. The administration of gefitinib could be interrupted for a maximum of 21 days in the event of a treatment-related adverse event. Baseline evaluations included a complete medical history, physical and radiologic examinations, a complete blood cell count and a biochemistry panel. Adverse events were recorded every 4 weeks based on clinical examination, a full blood count and a biochemistry panel and were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Event (version 3.0). In the event of grade 3 or 4 toxicities, the administration of gefitinib could be interrupted for a maximum of 14 days to allow the adverse events to resolve or decrease in severity.

It was also mandatory to record the toxicity levels of patients who had received previous erlotinib therapy.

Response assessment

Response assessments by computed tomography scan were carried out every 8 weeks according to the RECIST standards. Disease control was defined in terms of a complete response (CR), partial response (PR) or stable disease (SD). Time to progression (TTP) was defined as the period from the start of treatment to the date when disease progression or death was observed. Overall survival (OS) was defined as the period from the start of treatment to the date of death.

The study protocol required, in a non-mandatory manner, the collection of paraffin-embedded tumor samples for the assessment of biomarkers. Biomarker analyses were performed by GF at the University of Pisa, Italy, using automated sequencing of the kinase domain of EGFR (exons 18–21) and K-ras (exons 12–13).

Statistical considerations

The aim of the study was to assess the disease control rate (DCR; CR + PR + SD $\geq$ 90 days) of gefitinib therapy. The secondary purposes of the study were to evaluate the response rate (RR), OS, TTP and toxicity levels and to perform exploratory evaluations of tumor tissue for genomic profiles. Simon's two-stage MiniMax design was used to determine the sample size. A DCR of 45% in eligible patients indicated the potential usefulness of gefitinib, whereas a rate of 15% was set as the lower limit of interest with $\alpha = 0.05$ and $\beta = 0.2$. The estimated accrual number was 14 patients. The total number of successes (stage 1 and 2 combined) above which the study could be terminated was 4. This is the number at which the treatment required further evaluation and the number at which the treatment was determined to be abandoned when the total sample size was reached.

Patients eligible for the study received gefitinib via the expanded access program approved by the ethical committee of the National Institute for Cancer Research in Genoa, Italy.

Results

From May 2005 to August 2006, 15 patients were enrolled in the study. All were assessed for toxicity effects, and 12 were assessed for their response to gefitinib. Fourteen (93%) patients were men. The median patient age was 65 years (range: 50–85 years). Nine of 15 patients (60%) had the adenocarcinoma histologic subtype, 3 had squamous cell carcinoma (20%), 1 had bronchioloalveolar (7%), and 2 patients had unspecified NSCLC (13%). Three patients (20%) had a PS of 0, 9 patients (60%) had a PS of 1, and 3 patients (20%) had a PS of 2. The majority of patients were former smokers (67%), 4 patients (27%) had never smoked, and 1 was a current smoker. Before entering the study, the majority of the patients (87%) had received chemotherapy, 5 (33%) had received radiotherapy, and 4 (26%) had undergone surgery. All patients had received erlotinib. With regard to previous therapies, 4 patients (26%) had received 1 chemotherapy regimen, 7 (47%) had received 2 chemotherapy regimens, and 2 (13%) had received 3 chemotherapy regimens. Erlotinib was used as first-line treatment in 2 (13%) patients. Three patients (20%) received chemotherapy between the administration of erlotinib and gefitinib. One out of 15 patients (7%) exhibited PR with erlotinib, 5 patients (33%) exhibited SD, and 9 patients (60%) exhibited PD (Table 1).

After the administration of gefitinib, we observed SD in 6 (40%) patients and PD in 6 (40%) patients. Three patients (20%) were not evaluable for response (NE) because they died before the first treatment evaluation. The DCR $\geq$ 90 days was reached in 5 (33%) patients (Table 2). Five out of 6 patients who had achieved disease control with erlotinib also achieved SD with gefitinib. Eight out of 9 patients who experienced PD with erlotinib achieved PD or NE with gefitinib. One patient who achieved PD with gefitinib had SD with erlotinib, and one patient who achieved SD with gefitinib had PD with erlotinib (Table 3).

The median TTP and OS were 2.3 and 3.5 months, respectively. The TTP and OS in patients who achieved SD were 3.7 and 7.4 months, respectively.

The most common side effect was skin toxicity (grade 1–2 dry skin), which affected 27% of patients, and

Table 1 Patient characteristics ($N = 15$)

Characteristics	No.	%
Age, years		
Median	65	
Range	50–85	
Sex		
Female	1	7
Male	14	93
ECOG performance status		
0	3	20
1	9	60
2	3	20
Histology		
Adenocarcinoma	9	60
BAC	1	7
Squamous cell carcinoma	3	20
NOS NSCLC	2	13
Smoking history		
Current smokers	1	7
Former smokers	10	67
Never smokers	4	26
Prior therapy for NSCLC		
Chemotherapy	13	87
Surgery	4	26
Radiation therapy	5	33
N of prior CT regimens		
0	2	13
1	4	26
2	7	47
3	2	13
Response to erlotinib		
PR	1	7
SD	5	33
PD	9	60

BAC bronchioloalveolar carcinoma, *NOS* not otherwise specified, *NSCLC* non-small-cell lung cancer, *CT* chemotherapy, *PR* partial response, *SD* stable disease, *PD* progressive disease

Table 2 Response to gefitinib

Response	No.	%
CR/PR	0	0
SD	6	40
PD	6	40
NE	3	20
DCR (CR + PR + SD ≥ 90 days)	5	33

CR complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *NE* not evaluable, *DCR* disease control rate

acneiform rashes and rashes/desquamation, which affected 20% of patients. Diarrhea (grade 1–2) occurred in 7% of patients (Table 4).

Fourteen tumor tissue samples were available. None of the patients in our study had the EGFR mutation. K-ras mutations were detected in 2 patients but did not predict resistance to EGFR-TKI.

Discussion

To our knowledge, this is the first trial that has evaluated the role of gefitinib after disease progression in patients with advanced NSCLC who previously received erlotinib treatment. A single case report that described a striking response to gefitinib in a patient with leptomeningeal metastases and erlotinib-refractory lung adenocarcinoma was published in recent years [28]. In our study, 6 (40%) patients achieved SD, and 5 (33%) patients achieved a DCR ≥ 90 days with gefitinib treatment. Five out of 6 patients who benefited from gefitinib also benefited from erlotinib. These findings suggest that as a salvage treatment after the failure of erlotinib treatment, gefitinib should be carefully considered in a select subset of patients. However, gefitinib is not recommended in patients who had immediate disease progression after treatment with erlotinib. Our trial results are in line with previous trials and with the pooled analysis of the reports of erlotinib after failure of gefitinib published by Kaira et al. [29] that suggest a clinical benefit of the administration of erlotinib in patients who had shown SD with gefitinib therapy and in those who had a PFS of more than 6 months during gefitinib treatment. These results are surprising because both EGFR-TKIs share the same activity of the EGFR blockade. Several studies have suggested a possible explanation for the clinical benefit of EGFR-TKI retreatment. It is likely that tumors may possess both EGFR-TKI-sensitive and EGFR-TKI-resistant clones and that only EGFR-TKI-resistant clones can grow during gefitinib treatment. After the discontinuation of gefitinib treatment, sensitive clones may grow faster or survive better than do resistant clones [17]. Cytotoxic chemotherapies between gefitinib and erlotinib therapies could restore the sensitivity to EGFR-TKIs by killing erlotinib-/gefitinib-resistant cells or by inducing novel genetic mutations in EGFR or other unknown associated genes that regulate resistance to TKIs [30]. Nevertheless, other researchers have found no evidence that chemotherapy administered among two different EGFR-TKI treatments affects either PFS or OS in the second EGFR-TKI treatment [18, 23, 31]. Another hypothesis suggests that the presence of heterogeneous malignant clones with different EGFR mutation status may confer differential sensitivity to EGFR-TKIs [32].

However, we believe that another interpretation should be considered. Riely et al. [33] demonstrated that after restarting treatment with gefitinib or erlotinib, an improvement or stabilization of the disease occurred in the majority of patients. In this study, patients resumed treatment with the same drug (erlotinib or gefitinib) at the same dose they had received before treatment discontinuation. It is possible that the progression of the disease is very slow due to cell clones sensitive to EGFR-TKIs over a prolonged period of time. When the treatment was restarted with the same or a different EGFR-TKI, the best response is frequently disease stabilization due to a very slow progression rather than to a different EGFR-TKI. For this reason, our data and the previous results of gefitinib

Table 3 Characteristics of the six patients who achieved clinical benefit with gefitinib

Case	Histology	Sex	Smoking history	Number of prior chemotherapy regimens	Response to erlotinib	TTP to erlotinib (months)	Response to gefitinib	TTP to gefitinib (months)	EGFR mut	K-ras mut
1	NOS	M	FS	1	SD	8.2	SD	12.9	WT	WT
2	Ad	M	N	2	SD	4	SD	2.6	WT	WT
3	Ad	M	FS	2	SD	12.3	SD	3.5	WT	WT
4	Ad	M	N	2	PR	8	SD	4	WT	MUT
5	Ad	M	FS	1	PD	1.6	SD	3.5	WT	WT
6	Ad	M	S	1	SD	3.7	SD	28.7	WT	MUT

TTP time to progression, *Ad* adenocarcinoma, *M* male, *N* never smoked, *FS* former smoker, *S* smoker, *SD* stable disease, *PR* partial response, *WT* wild type, *MUT* mutation

Table 4 Comparison of toxicity results between erlotinib and gefitinib

Toxicity	Erlotinib		Gefitinib	
	All grades (%)	Grades 3–4 (%)	All grades (%)	Grades 3–4 (%)
Acneiform rash	93	27	20	0
Rash/desquamation	100	20	20	0
Pruritus	41	7	13	0
Dry skin	54	7	27	0
Paronychia	27	7	7	0
Diarrhea	53	0	7	0

treatment followed by erlotinib should be interpreted with caution. In our opinion, erlotinib or gefitinib should not be discontinued following disease progression in patients who have responded to treatment or who have had prolonged disease stabilization due to treatment with erlotinib or gefitinib. To confirm this hypothesis, randomized trials of continued treatment with erlotinib or gefitinib versus placebo or another line of chemotherapy are needed.

The intrapatient comparison between the toxicities of erlotinib and gefitinib was an interesting result of our trial. As reported in Table 4, gefitinib did not show grade 3–4 toxicities compared to those recorded for erlotinib. The grade 3–4 toxicities recorded for erlotinib included acneiform rash (27% of patients); rash/desquamation (20% of patients); and pruritus, dry skin and paronychia (7% of patients). Considering all grades of toxicities, almost all patients treated with erlotinib had acneiform rashes/desquamation, and half had diarrhea compared to 20% and 7% of patients treated with gefitinib, respectively. These data confirm previous suspicions about the higher levels of toxicities resulting from the treatment of erlotinib compared to those resulting from gefitinib.

Conclusion

In conclusion, our findings suggest that gefitinib may be an option for patients who have already benefited from prior erlotinib treatment. Conversely, gefitinib is not recommended in patients who experienced immediate disease progression after erlotinib treatment. The toxicity profile of gefitinib treatment appears to be more acceptable than that of erlotinib.

Conflict of interest Francesco Grossi received an honorarium to serve on scientific meetings of Roche and Astra-Zeneca. The other co-authors have not conflict of interest to declare.

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