# Impacts of Treatment Lines and Initiation Timing of Erlotinib for Advanced Non-small Cell Lung Cancer

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**Abstract.** *Aim: This study aimed to analyze whether or not the efficacy and safety of erlotinib are influenced by differences among treatment lines and initiation timing in advanced non-small cell lung cancer (NSCLC) patients. Patients and Methods: Stage III or IV NSCLC cases were retrospectively evaluated at three university hospitals. The primary outcome was progression-free survival (PFS). Results: Median PFSs of the second-, third- and fourth-line and over therapies were 138, 250 and 95 days; and median overall survivals (OSs) were 174, 260 and 270 days, respectively, with no significant differences. The response rates (RR) for the second-, third- and fourth-line and over therapies were 14%, 24% and 13%, respectively, with no significant differences. The toxicity profiles did not differ among the groups. The median PFSs and OSs according to initiation timing were not significantly different. Conclusion: Differences in treatment lines and initiation timing affected neither efficacy nor safety in patients with advanced NSCLC.*

Lung cancer has been the most common cancer worldwide since 1985, and remains the most common cause of death from cancer (1, 2). Many lines of evidence support the use of chemotherapy in patients with advanced non-small cell lung cancer (NSCLC) with good performance status (PS) as first-line therapy, since a landmark meta-analysis demonstrated that chemotherapy reduces the risk of death and increases 1-year survival (3). Platinum combinations of two cytotoxic drugs are the standard first-line therapy (4, 5). Docetaxel, erlotinib, gefitinib and pemetrexed are used as second-line therapies (4, 5).

The role of multiple-line chemotherapies following second-line chemotherapy has not yet been established (6, 7). There are presently no phase III data supporting routine use of cytotoxic chemotherapy in the third-line setting (4, 5). Massarelli *et al*. (8) reported that the response rate (RR) decreased with each line of treatment: first-line, 20.9%; second-line, 16.3%; third-line, 2.3% and fourth-line, 0%. The disease control rate (DCR), response plus stable disease (SD), also decreased dramatically from first- to fourth-line treatment. The role of targeted agents in multiple-line therapy also remains unknown. Erlotinib, an inhibitor of the epidermal growth factor receptor tyrosine kinase (EGFR-TKI), has clinical efficacy *versus* best supportive care (9) when administered as a second- or third-line therapy for advanced NSCLC. The efficacy and toxicity of erlotinib in fourth-line and over therapies have not, however, been demonstrated.

Development of effective therapies after initial platinum chemotherapy has raised questions about treatment duration and the optimal time to initiate second- or third-line therapy. The timing of second-line therapy initiation after completing first-line therapy is still controversial (10). A regimen delivering multiple lines of effective therapy without cumulative toxicity would be the most likely to improve survival. The current standard is to initiate second-line therapy at the time of disease progression (4). A recent phase III trial, however, revealed a statistically significant improvement in progression-free survival (PFS), although



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not in median overall survival (OS), with immediate initiation of second-line after first-line therapy (11). The RR to an EGFR-TKI targeting agent was not significantly altered by prior NSCLC treatments on gefitinib (12) or erlotinib (9, 13). A retrospective study demonstrated that a number of chemotherapeutic regimens prior to erlotinib influenced neither PFS nor OS (14). There are, however, no systematic analyses of RR, DCR, PFS, OS or AEs according to treatment lines and initiation time in patients receiving multiple-line treatments.

Lack of a rationale for multiple-line treatments and controversy regarding the most appropriate timing for initiating second- and third-line therapies is partly due to lack of an appropriate surveillance strategy for patients after completion of first-line therapy (15). Activities of second- and third-line treatments might, however, play a pivotal role in determining survival benefit. The efficacy and toxicity of erlotinib, as a molecular targeting agent, might differ from those of other cytotoxic agents in multiple-line treatment. Therefore, whether or not the efficacy and safety of erlotinib are influenced by differences in treatment lines and administration timing in advanced NSCLC patients was retrospectively evaluated.

## Patients and Methods

*Study design and treatment*. A total of 67 patients with advanced NSCLC registered for erlotinib treatment from December 2007 to March 2009 was retrospectively analyzed. The patients had been treated at Tokai University Hospital, Kitasato University Hospital and Saint Marianna Hospital in Kanagawa, Japan. The primary outcome of interest was PFS in relation to treatment lines and the timing of erlotinib initiation; secondary outcomes were OS, RR, DCR and adverse events (AEs). The retrospective protocol was approved by the institutional review board of each hospital. Prior to registration for erlotinib administration, all patients had undergone physical examination, baseline blood sampling, chest x-ray and computed tomography to determine PS, pulmonary fibrosis, liver and renal functions and infection status. All had histologically or cytologically proven stage III or IV NSCLC. Assessments of efficacy and safety were repeated every 3 to 7 days during hospitalization for 2 to 4 weeks after starting erlotinib. The patients were subsequently assessed at 1 to 4-week intervals.

*Assessments*. All medical data were assessed on December 15th, 2009. The extracted data included age, histology, smoking history, stage, Eastern Cooperative Oncology Group (ECOG) PS, AEs, previous treatments including gefitinib and the number of treatment lines. Responses were assessed using Response Evaluation Criteria in Solid Tumors (version 1.0) (16). Confirmation of a complete (CR) or partial response (PR) was required at least 4 weeks after initial documentation. SD was defined as disease control (i.e., absence of progression) maintained for at least 6 weeks. Toxicity was graded according to the National Cancer Institute's Common Toxicity Criteria for Adverse Events, version 3.0 (17). Erlotinib dose modification and post-erlotinib systemic therapy were decided by oncologists in each of the three participating hospitals.

*Statistical analysis*. PFS was defined as the time elapsed between the start of erlotinib therapy and the date of progressive disease (PD) or death. OS was defined as elapsed time between starting erlotinib and the date of death. The chi-square test or Fisher's exact test was used to test for statistically significant differences. PFS and OS differences between groups were analyzed by the Kaplan-Meier method and compared using the generalized Wilcoxon test. Differences were considered to be statistically significant at $p<0.05$.

## Results

*Patient characteristics*. The baseline characteristics of the patients are presented in Table I. Ten, 17, 3 and 1 patients received fourth-, fifth-, sixth- and seventh-line erlotinib treatment, respectively, within the fourth-line and over treatment group. One patient, a 78-year-old male smoker with adenocarcinoma, ECOG PS 4, stage IV disease was positive for the EGFR mutation, and was administered erlotinib as first-line therapy.

The median ages of those receiving second-, third- and fourth-line and over treatments were 65 (range, 41 to 83), 63 (range, 37 to 76) and 63 (range, 39 to 79) years, respectively. The proportions of patients previously given gefitinib (14%, 29% and 52%) tended to increase as more treatments were administered, although there were no significant differences between the groups.

According to the time elapsed since the first day of first-line treatment, the proportions of patients who had never smoked (29%, 29%, 44% and 71%) also significantly differed between the groups (Table I), the percentages given gefitinib as previous treatment (13%, 18%, 67% and 71%) were significantly different, rising with longer durations of previous treatments.

*Efficacy*. Details of the RRs and patient survival, at a median follow-up of 174 days (range, 9 to 610), are shown in Table II and Figures 1 and 2.

With erlotinib as second-line treatment the PFS rates were 41%, 27% and NR (not reached) and the OS rates were 45%, 45% and NR; with erlotinib as third-line treatment the PFS rates were 57%, 41% and 20% and the OS rates were 66%, 45% and 45% and with fourth-line and over treatment the PFS rates were 34%, 16% and NR and the OS rates were 55%, 39% and 29% all at 6, 12 and 18 months, respectively. There were no significant differences in PFS or OS rates among the treatment lines, nor in the RR or DCR, in relation to the line of erlotinib treatment.

In relation to the timing of erlotinib initiation (time since first day of first-line therapy), in those starting erlotinib at <1 year the PFS rates were 36.4%, 18.2% and NR and the OS rates were 42%, 28% and NR; in those starting erlotinib at 1-2 years the PFS rates were 59%, 37% and 19% and the OS rates were 82%, 67% and 67%; in those starting erlotinib at 2-3 years the PFS rates were 50%, NR and NR and the OS

Table I. *Patient demographics and clinical characteristics*.

| Characteristics | | | Erlotinib treatment line | | | | | | | | Time since first day of first-line therapy to erlotinib initiation | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | All (n=67) | | Second-line (n=14) | | Third-line (n=21) | | ≥Fourth-line (n=31) | | | | <1 year (n=24) | | 1-2 years (n=17) | | 2-3 years (n=9) | | >3 years (n=17) | | |
| | No. | (%) | No. | (%) | No. | (%) | No. | (%) | *p* | | No. | (%) | No. | (%) | No. | (%) | No. | (%) | *p* |
| Age | | | | | | | | | | | | | | | | | | | |
| <70 | 53 | (79) | 10 | (71) | 17 | (81) | 26 | (84) | 0.19 | | 17 | (71) | 15 | (88) | 7 | (78) | 14 | (82) | 0.58 |
| ≥70 | 14 | (21) | 4 | (29) | 4 | (19) | 5 | (16) | | | 7 | (29) | 2 | (12) | 2 | (22) | 3 | (18) | |
| Gender | | | | | | | | | | | | | | | | | | | |
| Male | 42 | (63) | 12 | (86) | 12 | (57) | 17 | (55) | 0.18 | | 19 | (79) | 11 | (65) | 4 | (44) | 8 | (47) | 0.12 |
| Female | 25 | (37) | 2 | (14) | 9 | (43) | 14 | (45) | | | 5 | (21) | 6 | (35) | 5 | (56) | 9 | (53) | |
| Smoking history | | | | | | | | | | | | | | | | | | | |
| Yes | 39 | (58) | 11 | (79) | 14 | (67) | 13 | (42) | 0.07 | | 17 | (71) | 12 | (71) | 5 | (56) | 5 | (29) | 0.04 |
| No | 28 | (42) | 3 | (21) | 7 | (33) | 18 | (58) | | | 7 | (29) | 5 | (29) | 4 | (44) | 12 | (71) | |
| Histology | | | | | | | | | | | | | | | | | | | |
| Adeno | 58 | (87) | 11 | (79) | 19 | (90) | 27 | (87) | 0.75 | | 21 | (88) | 15 | (88) | 7 | (78) | 15 | (88) | 0.87 |
| Non-adeno | 9 | (13) | 3 | (21) | 2 | (10) | 4 | (13) | | | 3 | (12) | 2 | (12) | 2 | (22) | 2 | (12) | |
| ECOG PS | | | | | | | | | | | | | | | | | | | |
| 0-1 | 43 | (64) | 8 | (57) | 13 | (62) | 22 | (71) | 0.43 | | 13 | (54) | 12 | (71) | 6 | (67) | 12 | (71) | 0.64 |
| ≥ 2 | 24 | (36) | 6 | (43) | 8 | (38) | 9 | (29) | | | 11 | (46) | 5 | (29) | 3 | (33) | 5 | (29) | |
| Disease stage | | | | | | | | | | | | | | | | | | | |
| IIIA or B | 16 | (24) | 7 | (50) | 3 | (14) | 6 | (19) | 0.07 | | 6 | (25) | 3 | (18) | 3 | (33) | 4 | (23) | 0.82 |
| IV | 51 | (76) | 7 | (50) | 18 | (86) | 25 | (81) | | | 18 | (75) | 14 | (82) | 6 | (67) | 13 | (77) | |
| Previous gefitinib Tx | | | | | | | | | | | | | | | | | | | |
| Yes | 24 | (36) | 2 | (14) | 6 | (29) | 16 | (52) | 0.07 | | 3 | (13) | 3 | (18) | 6 | (67) | 12 | (71) | 0.0001 |
| No | 43 | (64) | 12 | (86) | 15 | (71) | 15 | (48) | | | 21 | (87) | 14 | (82) | 3 | (33) | 5 | (29) | |

Adeno: Adenocarcinoma, ECOG: Eastern Cooperative Oncology Group, PS: performance status, Tx: treatment.

Table II. *Associations between efficacy and treatment lines*.

| Best response | | | Erlotinib treatment line | | | | | | | | Time since first day of first-line therapy to erlotinib initiation | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | All (n=67) | | Second-line (n=14) | | Third-line (n=21) | | ≥Fourth-line (n=31) | | | | <1 year (n=24) | | 1-2 years (n=17) | | 2-3 years (n=9) | | >3 years (n=17) | | |
| | No. | (%) | No. | (%) | No. | (%) | No. | (%) | *p* | | No. | (%) | No. | (%) | No. | (%) | No. | (%) | *p* |
| Complete response | 0 | (0) | 0 | (0) | 0 | (0) | 0 | (0) | 0.56 | | 0 | (0) | 0 | (0) | 0 | (0) | 0 | (0) | 0.57 |
| Partial response | 11 | (16) | 2 | (14) | 5 | (24) | 4 | (13) | | | 4 | (17) | 4 | (24) | 0 | (0) | 3 | (18) | |
| Stable disease | 23 | (34) | 4 | (29) | 8 | (38) | 10 | (32) | | | 5 | (21) | 6 | (35) | 5 | (56) | 7 | (41) | |
| Progressive disease | 30 | (45) | 6 | (43) | 8 | (38) | 16 | (52) | | | 13 | (54) | 6 | (35) | 4 | (44) | 7 | (41) | |
| Not evaluable | 3 | (5) | 2 | (14) | 0 | (0) | 1 | (3) | | | 2 | (8) | 1 | (6) | 0 | (0) | 0 | (0) | |
| Response rate | 11 | (16) | 2 | (14) | 5 | (24) | 4 | (13) | 0.48 | | 4 | (17) | 4 | (24) | 0 | (0) | 3 | (18) | 0.57 |
| Disease control rate | 34 | (51) | 6 | (43) | 13 | (62) | 14 | (45) | 0.37 | | 9 | (38) | 10 | (59) | 5 | (56) | 10 | (59) | 0.65 |
| Median PFS, days | 117 | | 138 | | 250 | | 95 | | 0.61 | | 62 | | 224 | | NR | | 105 | | 0.83 |
| 95% CI | 56 to 202 | | 25 to NR | | 41 to NR | | 44 to 198 | | | | 26 to 176 | | 14 to NR | | 9 to NR | | 41 to 235 | | |
| Median OS, days | 260 | | 174 | | 260 | | 270 | | 0.83 | | 170 | | NR | | NR | | 270 | | 0.14 |
| 95% CI | 148 to NR | | 53 to NR | | 78 to NR | | 130 to NR | | | | 54 to 241 | | 212 to NR | | 62 to NR | | 84 to 362 | | |

PFS: Progression-free survival, OS: overall survival, NR: not reached.

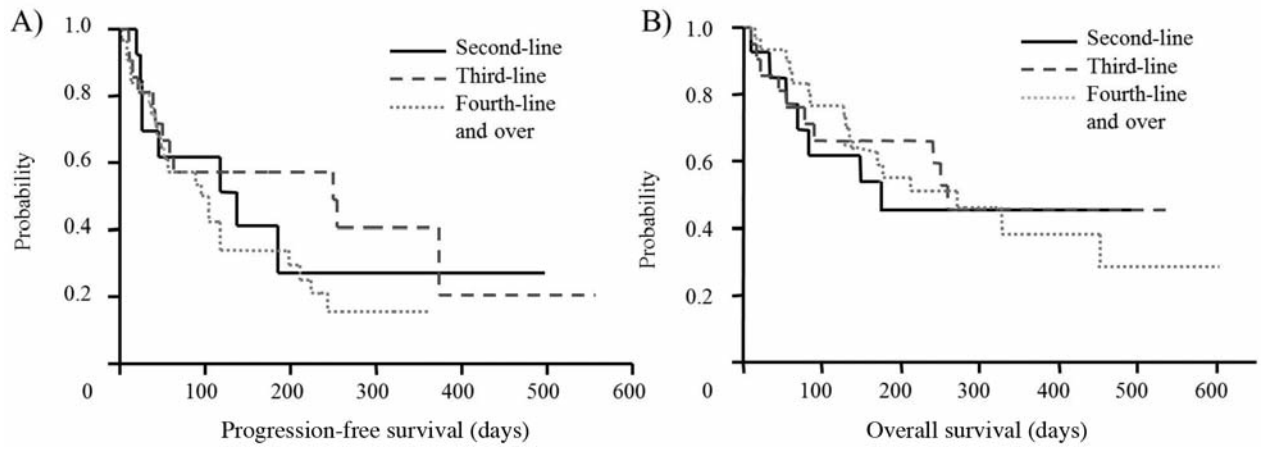


Figure 1. *Survival curves in relation to lines of erlotinib treatment.*

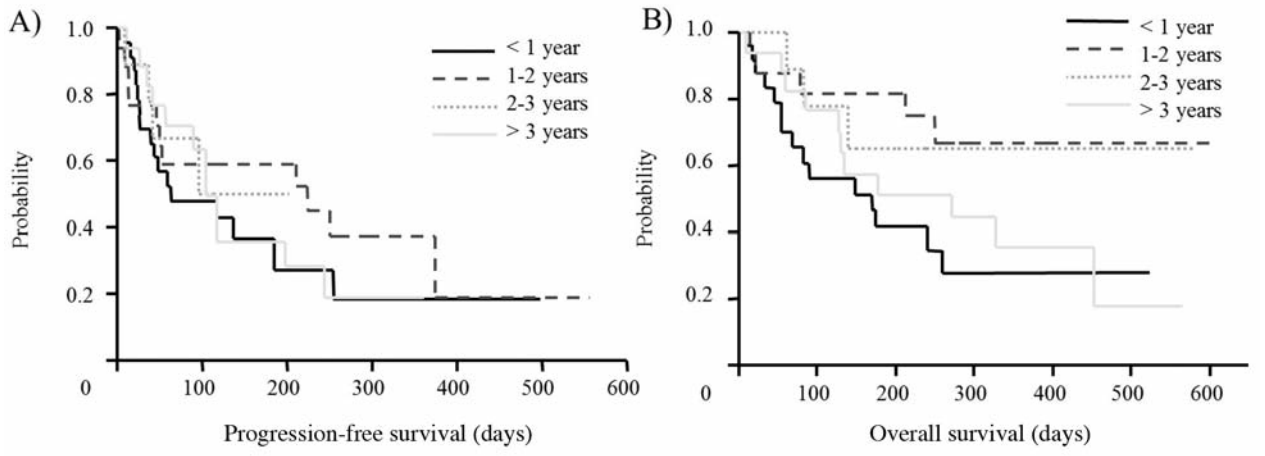


Figure 2. *Patient survival in relation to the time since first day of first-line therapy.*

rates were 65%, 65% and 65% and in those starting erlotinib at >3 years the PFS rates were 35%, 19% and NR and the OS rates were 51%, 36% and 18% all at 6, 12 and 18 months, respectively. There were no significant differences in median PFS or OS or in the RR or DCR among different times of erlotinib treatment-initiation (Table II).

*Safety*. There were no significant differences in adverce events (AE) overall or in the grade 3 and 4 AE profiles among the treatment lines (Table III). The rates of skin-related toxicities in all the patients were high and were appropriately treated or erlotinib was discontinued or the dose was reduced. No hematological AEs occurred. Other non-hematological AEs included 13 patients with diarrhea, grade 3 liver dysfunction (1 patient) and interstitial lung disease-like events (1 patient) and these toxicities were well managed. There were no treatment-related deaths.

The toxicity profiles according to timing of erlotinib initiation are also presented in Table III. There were no significant AE profile differences between the groups or in the grades 3 and 4 AE profiles according to the time elapsed since starting first-line therapy.

## Discussion

The present results indicate that erlotinib exhibits promising activity against NSCLC without intolerable toxicity, in patients receiving multiple-line therapies. Differences among the treatment lines and the timing of erlotinib initiation influenced neither the efficacy nor toxicity. Erlotinib has a

Table III. *Adverse events*.

| | All (n=67) | | Erlotinib treatment line: Second-line (n=14) | | Third-line (n=21) | | ≥Fourth-line (n=31) | | | Time since first day of first-line therapy to erlotinib initiation: <1 year (n=24) | | 1-2 years (n=17) | | 2-3 years (n=9) | | >3 years (n=17) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | No. | (%) | No. | (%) | No. | (%) | No. | (%) | *p* | No. | (%) | No. | (%) | No. | (%) | No. | (%) | *p* |
| All grades | | | | | | | | | | | | | | | | | | |
| Skin toxicity | 46 | (69) | 9 | (64) | 16 | (76) | 20 | (65) | 0.71 | 18 | (75) | 11 | (65) | 6 | (67) | 11 | (65) | 0.87 |
| Mucositis | 6 | (9) | 2 | (14) | 2 | (10) | 2 | (7) | 0.84 | 3 | (13) | 1 | (6) | 0 | (0) | 2 | (12) | 0.66 |
| Dry mouth | 1 | (2) | 0 | (0) | 0 | (0) | 1 | (3) | 0.76 | 0 | (0) | 1 | (6) | 0 | (0) | 0 | (0) | 0.39 |
| Diarrhea | 13 | (19) | 3 | (21) | 4 | (19) | 6 | (19) | 0.96 | 5 | (21) | 3 | (18) | 2 | (22) | 3 | (18) | 0.99 |
| Liver dysfunction | 2 | (3) | 0 | (0) | 0 | (0) | 2 | (7) | 0.50 | 0 | (0) | 1 | (6) | 1 | (11) | 0 | (0) | 0.28 |
| Renal dysfunction | 1 | (2) | 1 | (7) | 0 | (0) | 0 | (0) | 0.28 | 0 | (0) | 0 | (0) | 1 | (11) | 0 | (0) | 0.09 |
| ILD-like events | 2 | (3) | 0 | (0) | 0 | (0) | 2 | (7) | 0.50 | 0 | (0) | 1 | (6) | 0 | (0) | 1 | (6) | 0.57 |
| Cough | 1 | (2) | 0 | (0) | 1 | (5) | 0 | (0) | 0.53 | 1 | (4) | 0 | (0) | 0 | (0) | 0 | (0) | 0.61 |
| Pulmonary hemorrhage | 1 | (2) | 0 | (0) | 1 | (5) | 0 | (0) | 0.53 | 1 | (4) | 0 | (0) | 0 | (0) | 0 | (0) | 0.61 |
| Others | 2 | (3) | 0 | (0) | 0 | (0) | 2 | (7) | 0.50 | 1 | (4) | 0 | (0) | 0 | (0) | 1 | (6) | 0.70 |
| Grade 3 or 4 | | | | | | | | | | | | | | | | | | |
| Skin toxicity | 11 | (16) | 3 | (21) | 5 | (24) | 3 | (10) | 0.51 | 5 | (21) | 4 | (24) | 0 | (0) | 2 | (12) | 0.39 |
| Mucositis | 1 | (2) | 0 | (0) | 1 | (5) | 0 | (0) | 0.53 | 0 | (0) | 1 | (6) | 0 | (0) | 0 | (0) | 0.39 |
| Liver dysfunction | 1 | (2) | 0 | (0) | 0 | (0) | 1 | (3) | 0.76 | 0 | (0) | 0 | (0) | 1 | (11) | 0 | (0) | 0.09 |
| ILD-like events | 1 | (2) | 0 | (0) | 0 | (0) | 1 | (3) | 0.76 | 0 | (0) | 1 | (6) | 0 | (0) | 0 | (0) | 0.39 |

ILD: Interstitial lung disease.

consistent effect in all-lines of treatment and no cumulative toxicity with multiple-line therapies was observed. Furthermore, erlotinib showed beneficial effects even more than three years after the first day of first-line treatment.

Following two cytotoxic regimens, the survival advantage is thought to disappear because of drug resistance and/or lack of cytotoxic agents with clinically meaningful efficacy (8). After relapse following platinum-based chemotherapy, median OS for patients receiving best supportive care was reportedly only 4.5 to 5 months (3, 18-20), while OS for those receiving third- or fourth-line chemotherapies was 4 months from the start of the last treatment (8). In the present study, however, the median OSs were longer than 8 months for third- and fourth-line and over treatments with erlotinib and the response and survival data were comparable to those of a recent large, global, open-label, phase IV trial of erlotinib, in patients receiving mainly second- or third-line treatments (21).

The consistent effect and absence of cumulative toxicity of erlotinib in multiple-line therapies might be due to the difference in its mechanism of action *versus* conventional cytotoxic agents. Erlotinib is orally administered and targets the tyrosine kinase domain of the EGFR, a mechanism distinctly different than the DNA or tubulin targeting of cytotoxic agents (platinum, docetaxel, paclitaxel, *etc*.) (13, 22), which can produce different toxicity profiles. There were no hematological AEs with erlotinib in this study, and the major toxicity was skin rashes, which is a favorable clinical predictor for erlotinib (14, 23). Cytotoxic agents carry a risk of cumulative toxicity, which increases with multiple cycles, rendering continuous treatment impossible (24, 25).

Limitations of the present retrospective results, obtained in clinical settings, include the small number of patients, heterogeneity among the previous chemotherapy regimens and the lack of EGFR mutation determination in same cases. It is, however, extremely difficult to prospectively study third-line and over treatments (15). The limited life expectancies of patients also make it impossible to prospectively study outcomes of these treatments.

Another limitation is that the subpopulation of patients with advanced, recurrent NSCLC able to receive three or four chemotherapy regimens is considered to be a distinct group, not comparable to newly diagnosed patients enrolled in clinical trials (26). This subpopulation was found to be younger on average, generally had stage III disease at diagnosis, higher 1- and 2-year survival rates and prolonged median OS time, (from diagnosis, twice that of newly diagnosed patients with advanced NSCLC (8 to 10 months)) (26). In the present study, age, sex, smoking history, histology, ECOG PS and disease stage did not differ significantly among the second-, third- and over third-line treatment groups. According to erlotinib initiation timing, however, the percentages of non-smokers and patients

previously given gefitinib increased with longer prior treatment duration, suggesting that the percentages of patients with EGFR mutations might be increased in the groups in which erlotinib was initiated 2 years after the first day of first-line treatment. Thus, long-term survivors might have EGFR mutations, and EGFR-TKI could effectively prolong their survival (27).

Although erlotinib and gefitinib are both members of the EGFR-TKI family, the consistent effect regardless of treatment-line differences may be specific to erlotinib. Tumors with EGFR mutations showed high sensitivity to gefitinib and erlotinib in clinical studies (RR of approximately 75% and median PFS of 10-14 months) (28-34). In contrast, patients without EGFR mutations were unlikely to benefit from first-line gefitinib, showing RR of only 1.1% and median PFS <2 months (35). Despite this marked difference in sensitivity to gefitinib between NSCLC patients with *versus* without EGFR mutations, the survival impact of erlotinib monotherapy was confounded by mutation status in the recent sub-analyses of the BR.21 trial and the SATURN trial (36-39). Erlotinib is reportedly active even in NSCLC patients without EGFR mutations, achieving median OS and PFS of 9.2 and 2.1 months, respectively (40).

In conclusion, differences in treatment lines and erlotinib initiation timing affect neither efficacy nor safety in advanced NSCLC patients. Thus, in contrast to cytotoxic agents, erlotinib is potentially effective after fourth-line therapy regardless of the time elapsed since starting first-line treatment.

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