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The influence of intervening on the pharmaceutical consultation targeting outpatients with advanced non-small cell lung cancer receiving erlotinib treatment

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Summary

Erlotinib is used to treat advanced non-small-cell lung cancer (NSCLC), the common serious adverse events are skin disorders. The dose intensity of erlotinib should be maintained as much as possible by an appropriate control of adverse events in order to maintain its efficacy. Therefore, the management of these adverse events related to skin disorders would enable a continuous erlotinib treatment without interruption and dose reduction. This study assessed the effect of pharmaceutical consultation in outpatients who received erlotinib. Participants included patients with NSCLC who received erlotinib therapy for more than 6 months between December 2007 and March 2019. The participants were divided into two groups: the intervention group that included patients who received pharmaceutical consultation targeting outpatients by a pharmacist and the nonintervention group that included patients who did not. We retrospectively investigated patient characteristics, treatment regimens, and treatment efficacy. We included a total of 33 patients (18 and 15 patients in the nonintervention and intervention groups, respectively) in this study. The intervention group had a significantly higher median relative dose intensity (RDI) of erlotinib than the nonintervention group (P = 0.0437). In addition, the pharmaceutical consultation targeting outpatients was identified as a factor contributing to the maintenance of RDI ≥ 90% (P = 0.0269). The present study indicated that there was improvement in RDI with pharmaceutical consultation targeting outpatients with advanced NSCLC.

Keywords: pharmaceutical consultation targeting outpatients, erlotinib, non-small-cell lung cancer, relative dose intensity, skin disorders
Introduction

Recently, treatment options for cancer chemotherapy have increased. Such an advancement, partially supported by the advent of oral anti-cancer drugs, allows patients to receive cancer chemotherapy in an outpatient setting without the need for hospitalization. Outpatients who receive cancer chemotherapy have more favorable quality of life (QOL) than inpatients\(^1\).

Erlotinib, which is used to treat advanced non-small-cell lung cancer (NSCLC), is an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor. A phase II clinical study conducted in Japan\(^2\) showed that the common adverse events associated with this drug include skin disorders, such as skin rash (82.5%), dry skin (79.6%), paronychia (67.0%), and pruritus (65.0%). Prophylactic treatment through supportive care attenuated the severity of skin disorders in patients who received panitumumab treatment\(^3\). This result suggested that an appropriate supportive care enables the management of adverse events associated with skin disorders. To manage the adverse events through collaboration with interprofessional teams, our hospital established the pharmaceutical consultation targeting outpatients to support physician’s medical care. The main reasons leading to erlotinib interruption/dose reduction are skin disorders\(^4\). The severity of skin rash associated with erlotinib treatment is correlated with survival\(^5\). Maintaining a sufficient blood concentration of erlotinib suppresses the central nervous system metastasis of NSCLC\(^6-7\). Therefore, an appropriate management of skin disorders would result in a continuous erlotinib treatment without dose reduction and thus help in maintaining the significant efficacy of this drug.

The frequent involvement of pharmacists in cancer chemotherapy enhances the quality of medical care and patient’s QOL\(^8-10\). As an effort of pharmacists to be
involved in outpatient cancer chemotherapy, the number of facilities establishing a “pharmaceutical consultation targeting outpatients” to perform pre-examination patient interview with pharmacists has increased. In June 2015, Fujita Health University Hospital established a pharmaceutical consultation mainly for outpatients taking oral anti-cancer drugs including erlotinib. The pharmaceutical consultation targeting outpatients in our hospital aims to increase the safety of anti-cancer drug treatment by performing the following procedures: explanation of treatment regimens and schedule; interviewing patients regarding adverse events associated with anti-cancer drugs to provide lifestyle guidance and appropriate use of these drugs as well as recommending supportive care; confirming of examination results on the same day; confirming of drug interactions; adjustment of prescription days according to the number of remaining drugs; recommendation for additional examination and of receiving concomitant treatment with another department; and proposal for changes and/or discontinuation in/of dose regimens of anti-cancer drugs. Interventions by a pharmacist are performed prior to a physician consult to present the patient’s information to doctors. The effect of pharmaceutical consultation targeting outpatients has been evaluated based on the intervention contents, the frequency of adverse events before and after interventions, the patient’s understanding level of drug therapy, and the questionnaires on medical professionals and patients. The results have shown that the interventions improve the understanding level and satisfaction of medical professionals and patients in addition to a reduced grade of adverse events\textsuperscript{10)-13). Moreover, the pharmaceutical consultation targeting outpatients exert favorable therapeutic effects. These include extending the duration of sorafenib administration\textsuperscript{14), improving the rate of continuous postoperative adjuvant chemotherapy with S-1\textsuperscript{15), and increasing the total dose of pazopanib,
extending the time to treatment discontinuation\textsuperscript{16}.

No study has evaluated whether pharmaceutical consultation targeting outpatients affect the treatment efficacy of erlotinib. Therefore, this study assessed the effect of pharmaceutical consultation in outpatients with NSCLC who received erlotinib.

**Material and methods**

**Patients**

The participants included patients with NSCLC who received erlotinib treatment for more than 6 months at the Department of Respiratory Medicine of Fujita Health University Hospital between December 2007 and March 2019. Patients were excluded if their EGFR mutation status was negative or unknown, their induction dose of erlotinib was other than 150 mg/day or they were introduced erlotinib at other hospitals.

**Investigation**

This was a nonrandomized controlled before- and after-study. Patients who received interventions by a pharmacist in outpatient consultation within 2 months after initiating erlotinib treatment were assigned to the intervention group and those who did not received interventions by a pharmacist were assigned to the nonintervention group. We retrospectively investigated the status of erlotinib treatment in both groups using electronic medical records. The period of investigation was between July 2015 and March 2019 for the intervention group and December 2007 and March 2019 for the nonintervention group. We investigated the sex, age at the time of erlotinib induction, types of mutation of EGFR genes, a history of previous treatments, and the presence/absence of brain metastasis. Moreover, we investigated the prescription date
dosage and days of erlotinib and other drugs that were administered during the erlotinib prescription period, along with the computed tomography and chest radiography results, proposals by pharmacists accepted physicians on the intervention group, medical records.

*Evaluation method*

RDI was represented as a percentage (calculated by dividing the actual dose [erlotinib prescriptions × erlotinib treatment days] by the standard dose [150 mg × erlotinib treatment days]).

Progression free survival (PFS) was defined as the time between the date of erlotinib induction and the date of first documented progressive disease (PD) or death from any causes, whichever occurred first. PD was defined as PD based on diagnostic imaging and clinical progression that is not confirmed by diagnostic imaging. The date when a physician confirmed PD based on diagnostic imaging or when he/she determined clinical deteriorations was regarded as the PD date. The definition of discontinuation was based on a phase III clinical trial conducted abroad\(^{17}\). Specifically, if a subsequent treatment and no PD were observed in the treatment, patients were withdrawn at the start date of the next treatment. If PD was confirmed in the next treatment, patients were withdrawn at the date of the last erlotinib assessment.

*Statistical analysis*

Software R (The R Foundation for Statistical Computing, Vienna, Austria version 3.5.2) was used for analysis. Non-normally distributed continuous variables were expressed as interquartile ranges. The Chi-square test and Fisher's exact test were used
to compare the rate of the two groups. The Mann-Whitney U test was used to compare medians in the two groups. Univariate and multivariate analyses were conducted using logistic regression analysis to identify factors contributing to maintaining RDI ≥ 90% with reference to previous studies\(^{18}\). The Kaplan-Meier methods, log-rank test, and Cox proportional hazards regression model were used to calculate the PFS curves, median PFS with 95% confidence interval (CI), and hazard ratio with 95% CI. \( P < 0.05 \) was considered as a significant difference.

**Ethical considerations**

This study was conducted after approval of Institutional Review Board of Fujita Health University. This study was recommended in accordance with the Declaration of Helsinki. Patient consent is obtained through opt-out informed consent.

**Results**

**Patient characteristics**

During the target period, 93 patients were introduced with erlotinib at Fujita Health University Hospital, and the exclusion resulted in 61 patients (36 and 25 patients in the nonintervention and intervention groups, respectively). By deviating from the conditions set to evaluate the pharmaceutical consultation targeting outpatients, we included a total of 33 patients (18 and 15 patients in the nonintervention and intervention groups, respectively) in this study (Figure 1). The intervention group (46.7%) had a significantly higher number of patients who received concomitant treatment with bevacizumab than the nonintervention group (5.6%) \( (P = 0.0120) \). No significant difference was observed in other characteristics (Table 1).
The effects of pharmaceutical consultation targeting outpatients

The erlotinib treatment periods were 360.5 (291.3–469.8) days and 378.0 (323.0–511.5) days in the nonintervention and intervention groups, respectively, with no significant difference observed between the groups (P = 0.651). The intervention group (97.6% [78.1–100.0]) had a significantly higher median RDI than the nonintervention group (71.4% [56.3–85.9]) (P = 0.0437) (Figure 2). For the purpose of searching for a factor contributing to the maintenance of RDI ≥ 90%, univariate analysis was performed on sex, age, EGFR mutation status, number of prior treatment regimens, presence of brain metastasis, concomitant treatment with bevacizumab and pharmaceutical consultation targeting outpatients. Multivariate analysis was performed on factors that number of prior treatment regimen and pharmaceutical consultation targeting outpatients P < 0.05 in univariate analysis. The analysis identified pharmaceutical consultation targeting outpatients (P = 0.0269) (Table 2).

The intervention group (547 [95% CI, 339–PFS was not reached] days) tended to be longer median PFS than the nonintervention group (305 [95% CI, 227–474] days), although no significant difference was observed (Figure 3). Sex, age ≥ 75 years, EGFR mutation status, number of prior treatment regimens ≥ 1, presence of brain metastasis, which are adjustment factors to confirm the effects of pharmaceutical consultation targeting outpatients, and concomitant treatment with bevacizumab, which showed a difference between the two groups at baseline had no effect on PFS (P = 0.600, P = 0.430, P = 0.418, P = 0.318, P = 0.983 and P = 0.356, respectively).

Physicians accepted 101 proposals by pharmacists as follows: prescription proposal associated with skin disorders (50 cases, 49.5%), gastrointestinal symptoms (21 cases,
20.8%), proposal related to examination results (15 cases, 14.9%), and other proposals (15 cases, 14.9%).

Discussion

This study investigated the efficacy of pharmaceutical consultation in the therapeutic effect of outpatients undergoing erlotinib treatment. The intervention group had a significantly higher RDI of erlotinib, indicating that pharmacist’s interventions were a factor contributing in maintaining RDI ≥ 90%. This suggests that pharmaceutical consultation targeting outpatients exert beneficial effects on maintaining the RDI of erlotinib. The proportion of patients who received erlotinib within 6 months due to adverse events was higher in the nonintervention group. Therefore, the criteria set in this study had not related to effects of pharmaceutical consultation targeting outpatients. Moreover, the erlotinib treatment tended to be extended PFS in the intervention group, suggesting that RDI maintenance contributes to improving the efficacy of this drug. This finding supports the results of previous studies\(^6\)-\(^7\). Patients who used erlotinib within second-line of treatment were 72.2% (nonintervention group) and 93.3% (intervention group). An improving tendency of PFS may be caused by use on the front line in the intervention group (i.e., fewer patients with advanced stages were included). However, the number of prior treatment regimens had no impact on PFS in our study. A previous study reported that the concomitant use of erlotinib and bevacizumab significantly improved PFS compared with erlotinib monotherapy\(^{19}\). In our study, more patients in the intervention group were concurrently treated with erlotinib and bevacizumab. Owing to this, PFS may show an improving tendency in this group. However, the concomitant use of erlotinib and bevacizumab had no impact on PFS in
our study; therefore, we failed to identify a factor for improving tendency of PFS in the intervention group. Unlike previously study, the reason why the concomitant treatment bevacizumab did not affect PFS may be due to the small number of cases. Although it is a report in a small number of cases, a previous study reported that partial response was achieved in 71.5% of patients who underwent a dose reduction of erlotinib (25 mg/day)\(^\text{20}\). Owing to this, in our study, RDI of erlotinib may not contribute to improved PFS. Therefore, a further detailed investigation would be warranted to clarify the relationship between the RDI of erlotinib and efficacy including PFS. A previous study demonstrated that pharmaceutical interventions maintained a high RDI and better therapeutic effects of sunitinib, resulting in a prolonged survival\(^\text{13}\). However, to the best of our knowledge, the previously reported is a comparison with other study, no study has been conducted to evaluate the effect of the pharmaceutical consultation targeting outpatients on RDI and survival by performing direct comparisons between the groups with or without interventions. With this background, our study indicated that pharmaceutical intervention is more effective for improvement in RDI than nonintervention.

Suggestions related to adverse events by the pharmaceutical consultation targeting outpatients. In our study, although it was not possible to investigate the reason why RDI improved with pharmaceutical intervention, inferring from the content of the proposal, that interviewing patients regarding adverse events and confirming of examination results to appropriate use of these drugs as well as recommending supportive care may have improved RDI.

This retrospective study has several limitations. First, background factors were not adjusted in this study. These included patient’s systemic conditions, study periods,
prescribing doctors, doctor’s experiences of treating erlotinib, and the prescription status of prophylactic supportive care drugs for erlotinib. Pharmacist’s interventions have been performed in almost all patients who received erlotinib treatment since the establishment of the pharmaceutical consultation targeting outpatients in our hospital. Therefore, a retrospective investigation is required when comparing the intervention and nonintervention groups. Owing to this, adjustments of background factors are challenging, which is another limitation of this study. In addition, since this study is an exploratory study and the number of cases is small, it is necessary to interpret the results carefully.

**Conclusions**

The present study indicated that there was improvement in RDI with pharmaceutical consultation targeting outpatients with advanced NSCLC; however, enough evidence was not provided about PFS.

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**Conflict of Interest**

The authors declare no conflict of interest.
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Figure 1  Patient Flow Chart
Figure 2  Influence of pharmaceutical consultation targeting outpatients on relative dose intensity (RDI) of erlotinib
Figure 3  Influence of pharmaceutical consultation targeting outpatients on progression free survival (PFS)
Table 1  Patient characteristics

|                        | Nonintervention group (n = 18) | Intervention group (n = 15) | p value |
|------------------------|--------------------------------|----------------------------|---------|
| Sex male/female (%)    | 50.0/50.0                      | 20.0/80.0                  | 0.155   |
| Age (years)            | 66.0 (59.5-68.0)               | 69.0 (61.0-76.5)           | 0.186   |
| Histology              |                                |                            | 1.000   |
| Adenocarcinoma (%)     | 94.6                           | 100.0                      |         |
| Adenocarcinoma + squamous cell carcinoma (%) | 5.6                 | 0                          |         |
| EGFR mutation status   |                                |                            | 0.131   |
| Exon 19 (%)            | 72.2                           | 40.0                       |         |
| Exon 21 (%)            | 27.8                           | 60.0                       |         |
| Number of prior treatment regimens |                    |                            | 0.578   |
| 0 (%)                  | 38.9                           | 60.0                       |         |
| 1 (%)                  | 33.3                           | 33.3                       |         |
| 2 (%)                  | 5.6                            | 6.7                        |         |
| 3 ≤ (%)                | 22.2                           | 0                          |         |
| Presence of brain metastasis (%) | 55.6                 | 33.3                       | 0.355   |
| Concomitant treatment with bevacizumab (%) | 5.6                        | 46.7                       | 0.0120  |
|                                      | Univariate analysis     |                        | Multivariate analysis     |                        |
|--------------------------------------|-------------------------|------------------------|---------------------------|------------------------|
|                                      | Odds ratio (95% CI)     | p value                | Odds ratio (95% CI)       | p value                |
| Sex (vs male)                        | 3.300 (0.692-15.700)    | 0.134                  | 4.970 (0.943-26.200)      | 0.0587                 |
| Age (vs <75)                         | 1.450 (0.247-8.580)     | 0.679                  |                           |                        |
| EGFR mutation status (vs Exon 19)    | 1.030 (0.255-4.170)     | 0.966                  |                           |                        |
| Number of prior treatment regimens   | 5.420 (1.200-24.500)    | 0.0283                 | 4.970 (0.943-26.200)      | 0.0587                 |
| (vs 1 ≤)                             |                         |                        |                           |                        |
| Presence of brain metastasis (vs     | 1.370 (0.343-5.510)     | 0.653                  |                           |                        |
| absence)                             |                         |                        |                           |                        |
| Concomitant treatment with bevacizumab| 2.960 (0.570-15.400)    | 0.196                  |                           |                        |
| (vs non-concomitant)                 |                         |                        |                           |                        |
| Pharmaceutical consultation          | 7.000 (1.490-32.800)    | 0.0136                 | 6.490 (1.240-34.000)      | 0.0269                 |
| targeting outpatients (vs non-       |                         |                        |                           |                        |
| intervention)                        |                         |                        |                           |                        |