Number of metastatic organs negatively affects the treatment sequence in patients with EGFR-TKI failure

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Keywords
Chemotherapy; epidermal growth factor receptor (EGFR); non-small cell lung cancer; number of organs with metastasis; treatment sequence.

Abstract
Background: Several studies have previously demonstrated the survival benefit of both EGFR-TKI treatment and chemotherapy in patients with non-small cell lung cancer (NSCLC) harboring EGFR mutations. The aim of the present study was to clarify the factors influencing the treatment sequence after failure of EGFR-TKI therapy, focusing on the number of organs with metastasis (hereafter, metastatic organs).

Methods: Between January 2010 and December 2016, consecutive patients with EGFR-mutated NSCLC who were started on first-line EGFR-TKI were reviewed. The factors influencing withholding systemic chemotherapy and the post-progression survival (PPS) after failure of EGFR-TKI were investigated.

Results: A total of 393 patients were started on first-line EGFR-TKI during the study period. After excluding patients maintained on EGFR-TKI or who received osimertinib targeting secondary EGFR T790M, 297 patients were included in the analysis. Among these, 180 (60.6%) received chemotherapy after failure of EGFR-TKI (TKI-Ct group), while the remaining 117 (39.4%) received no chemotherapy (TKI-only group). Multivariate analysis identified older age (≥ 75 years: odds ratio [OR] = 0.25, 95% confidence interval [CI]: 0.11–0.43, P < 0.001), poor performance status (PS) (≥ 2: OR = 0.06, 95% CI: 0.03–0.15, P < 0.001), and three or more metastatic organs (OR = 0.42, 95% CI: 0.22–0.80, P = 0.008) as being significantly associated with withholding of chemotherapy after failure of EGFR-TKI.

Conclusion: A relatively large number of metastatic organs and a poor PS were associated with the withholding of subsequent chemotherapy after failure of EGFR-TKI in EGFR-mutated NSCLC patients. Further research for patients with such a poor prognosis should be investigated in the future.

Introduction
Epidermal growth factor receptor (EGFR) mutations as oncogenic driver mutations are encountered in 10% to 15% of non-small-cell lung carcinoma (NSCLC) patients in Western countries and approximately 50% of NSCLC patients in East-Asian countries.1–3 EGFR-tyrosine kinase inhibitor (EGFR-TKI) monotherapy has been demonstrated to yield better disease control rates and survival outcomes than conventional chemotherapy in EGFR-mutated NSCLC patients and has been the standard therapy for such patient population.4–7 EGFR-TKI therapy administered in combination with chemotherapy has been shown to yield a better prognosis than EGFR-TKI therapy or chemotherapy alone.8–10 While 60% to 90% of the patients who receive chemotherapy as first-line treatment receive subsequent EGFR-TKI therapy, half of the patients administered first-line EGFR-TKI therapy fail to receive subsequent chemotherapy.10–12 Few studies have been conducted to examine the reasons why patients given first-line...
EGFR-TKI therapy often fail to receive subsequent chemotherapy.\(^\text{11,12}\)

In a recent study, Nakamura et al. reported that the number of metastatic organs is a prognostic factor affecting the survival after failure of first-line EGFR-TKI therapy.\(^\text{13}\) They suggested that a lower number of metastatic organs may reflect a higher degree of tumor shrinkage and a lower tumor burden and lead to a better prognosis.

Here, we hypothesized that the number of metastatic organs would also affect the treatment sequence in addition to the prognosis, and examined the factors that influence the withholding of subsequent chemotherapy after failure of first-line EGFR-TKI therapy, focusing on the number of metastatic organs.

**Methods**

**Patient population**

The data of consecutive patients who were started on first-line EGFR-TKI therapy between January 2010 and December 2016 at the National Cancer Center Hospital (Tokyo, Japan) were retrospectively reviewed. Patient characteristics after failure of EGFR-TKI therapy were collected from the electronic medical records including the age, gender, Eastern Cooperative Oncology Group performance status (ECOG-PS), EGFR status at diagnosis, response to first-line EGFR-TKI therapy according to the RECIST criteria (ver. 1.1), number of metastatic organs after failure of first-line EGFR-TKI therapy, and the main reason for withholding subsequent chemotherapy. Positive lymph nodes were counted collectively as one metastatic organ. Disease progression was defined as PD according to RECIST, and progression after failure of TKI-Ct was defined as the start of TKI-only therapy.

We divided the patients into two groups: the TKI-chemotherapy (TKI-Ct) group and the TKI-only group. The TKI-Ct group consisted of patients who had received chemotherapy (platinum doublet or single-agent chemotherapy) after the failure of EGFR-TKI therapy, while the TKI-only group consisted of patients who did not receive any systemic treatment after the EGFR-TKI therapy. This study was conducted with the approval of the institutional ethical review board (2015-355).

**Systemic treatment**

Patients with brain metastasis tended to receive erlotinib or afatinib treatment after local therapies such as whole-brain radiotherapy or stereotactic radiotherapy for the brain metastasis. Patients without brain metastasis usually received gefitinib as the first-line treatment. Follow-up computed tomography for systemic lesions, including brain images, was performed every two to three months or when clinically indicated, to determine the disease status. After failure of EGFR-TKI therapy (PD according to RECIST), some patients were continued on EGFR-TKI therapy with the expectation of some clinical benefit. After discontinuation of the first-line EGFR-TKI therapy, many patients received systemic chemotherapy, including platinum-containing regimes, docetaxel, S-1 or immune checkpoint inhibitors.

**Statistical analysis**

The purpose of this study was to identify the factors influencing the withholding of subsequent cytotoxic chemotherapies and the prognosis after failure of first-line EGFR-TKI therapy in EGFR-mutated NSCLC patients. The post-progression survival (PPS) was defined as the time from the documentation of disease progression after the start of first-line EGFR-TKI therapy to death from any cause. We also conducted a subgroup analysis to compare the PPS depending on the number of metastatic organs.

We used the t-test or Mann-Whitney U test to compare continuous variables and the chi-square or Fisher’s exact test to compare categorical variables to detect the differences between the groups. Spearman rank correlation coefficients were used to examine the association between pairs of variables and the correlation ≥0.2 was defined as a meaningful correlation. The estimated survival was calculated using the Kaplan-Meier method, with determination of the 95% confidence intervals (CIs) and comparisons between the groups performed by the log-rank test. To detect the independent prognostic factors for determination of the treatment sequence and survival prognosis, a logistic regression model and Cox proportional hazards model were applied. All analyses were performed using the Statistical Package for the Social Sciences (SPSS v.21; SPSS, Inc., Chicago, IL, USA). Two-sided \(P < 0.05\) was considered to indicate a statistically significant difference.

**Results**

**Patient demographics**

In total, 393 EGFR-positive NSCLC patients were started on first-line EGFR-TKI therapy during the study period (Fig 1). At the data cutoff (30 June 2018), 330 patients experienced disease progression with first-line EGFR-TKI. A total of 265 patients progressed before approval of
Reasons for withholding subsequent chemotherapy

The causes of withholding of subsequent chemotherapy after failure of EGFR-TKI therapy are shown in Table 2. The most frequent reason was PS deterioration, mainly because of the presence of leptomeningitis or brain metastases, followed by older age, patient preference, and systemic progression without local symptoms. Approximately one half of the patients could not receive chemotherapy because of cancer-related regional complications, such as metastases in the central nervous system (CNS), pleura or bone.

We conducted univariate and multivariate logistic analyses to investigate the factors associated with withholding of chemotherapy after failure of EGFR-TKI treatment. A multivariate analysis with candidate prognostic factors in univariate analysis with P-value less than 0.05, identified older age (75 years or more: odds ratio (OR) = 0.21, 95% CI: 0.11–0.43, P = <0.001), poor ECOG-PS (two or more: OR = 0.06, 95% CI: 0.03–0.15, P < 0.001), and ≥3 metastatic organs (OR = 0.42, 95% CI: 0.22–0.80, P = 0.008) as being significantly associated with the withholding of chemotherapy after failure of first-line EGFR-TKI therapy (Table 3).
Factors associated with the administration of chemotherapy after EGFR-TKI treatment

| Factor                          | Univariate          | Multivariate         |
|---------------------------------|---------------------|----------------------|
| Age in years (≥75 vs. <75)      | 0.25 (0.14–0.43)    | 0.21 (0.11–0.43)     |
| Gender (male vs. female)        | 1.52 (0.92–2.49)    | 1.01                 |
| EGFR status (del 19 vs. L858R)  | 1.98 (1.23–3.19)    | 1.58 (0.85–2.93)     |
| Smoking status (ever smoker vs. | 1.65 (1.01–2.69)    | 0.98 (0.52–1.87)     |
| Best response to first-line TKI | 0.66 (0.41–1.07)    | —                    |
| ECOG-PS (≥2 vs. ≤1)             | 0.04 (0.18–0.81)    | 0.06 (0.03–0.15)     |
| Number of organs with metastasis (≥3 vs. ≤2) | 0.53 (0.33–0.85)    | 0.42 (0.22–0.80)     |

CI, confidence interval; CR, complete response; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; OR, odds ratio; PD, progressive disease; PR, partial response; PS, performance status; SD, stable disease; TKI, tyrosine kinase inhibitor.

Discussion

This study is the largest study until date conducted to examine the factors influencing the withholding of subsequent cytotoxic chemotherapy after failure of treatment with a first- or second-generation EGFR-TKI in consecutive EGFR-mutated NSCLC patients. We identified the number of metastatic organs and PS as independent factors associated with withholding of subsequent chemotherapy and a poor prognosis.

EGFR-TKI therapy has improved the survival and quality of life outcomes for NSCLC patients harboring EGFR mutations. Although several studies have shown that chemotherapy has an important role in improving the prognosis in EGFR-mutated NSCLC patients, a proportion of patients miss the opportunity to receive subsequent chemotherapy. In the present study, the initiation of subsequent chemotherapy after EGFR-TKI therapy contributed to a better prognosis, regardless of the number of metastatic organs. In particular, patients with a fewer number of metastatic organs after failure of EGFR-TKI therapy showed a median PPS of more than two years, despite the failure of EGFR-TKI therapy. This suggests that appropriate use of chemotherapy might yield a good prognosis in selected patients, and that the decrease in the number of metastatic organs after the initial therapy may contribute to the better prognosis, as shown by Nakamura et al. Recently, one randomized phase
### Table 4 Factors associated with post-progression survival after failure of EGFR-TKI

| Factor                                      | Univariate |    |    |    |    | Multivariate |    |    |    |    |
|---------------------------------------------|------------|--|----|--|----|---------------|--|--|----|--|----|
| Age in years (≥75 vs. <75)                  | 1.28       | 0.91–1.80 | 0.162 | — | — | —            | — | — | — | — |
| Gender (male vs. female)                    | 0.89       | 0.65–1.21 | 0.445 | — | — | —            | — | — | — | — |
| EGFR status (del 19 vs. L858R)              | 0.73       | 0.54–0.98 | 0.037 | 0.89 | 0.65–1.22 | 0.461 | — | — | — | — |
| Smoking status (ever smoker vs. never smoker) | 0.92       | 0.68–1.24 | 0.574 | — | — | —            | — | — | — | — |
| Best response to first-line TKI (CR/PR vs. SD/PD) | 1.20       | 0.89–1.62 | 0.091 | — | — | —            | — | — | — | — |
| ECOG-PS (≥2 vs. ≤1)                         | 4.53       | 3.13–6.56 | <0.001 | 3.90 | 2.63–5.78 | <0.001 | — | — | — | — |
| Number of organs with metastasis (≥3 vs. ≤2) | 2.33       | 1.73–3.15 | <0.001 | 2.55 | 1.85–3.50 | <0.001 | — | — | — | — |

CI, confidence interval; CNS, central nervous system; CR, complete response; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; HR, hazard ratio; PD, progressive disease; PR, partial response; PS, performance status; SD, stable disease; TKI, tyrosine kinase inhibitor.

**Figure 2** Kaplan-Meier survival analysis of PPS, from documentation of disease progression after EGFR-TKI therapy to death from any cause in the overall population. CI, confidence interval; EGFR, epidermal growth factor receptor; HR, hazard ratio; PD, progression disease; PPS, post-progression survival; TKI, tyrosine kinase inhibitor.

**Figure 3** Kaplan-Meier survival analysis of PPS, from documentation of disease progression after EGFR-TKI therapy to death from any cause in patients who received only EGFR-TKI treatment as their systemic treatment. CI, confidence interval; EGFR, epidermal growth factor receptor; HR, hazard ratio; PD, progression disease; PPS, post-progression survival; TKI, tyrosine kinase inhibitor.
II study conducted to evaluate the efficacy of local ablative therapy (LAT) for patients with a controlled primary solid tumor and one to five metastatic lesions was reported. This study showed a better survival after LAT for oligometastatic disease as compared to the standard of care, regardless of the increase of severe adverse events. LAT would also be a potential option for patients with a larger number of metastases if all the lesions were irradiable in parenchymal organs.

Kawaguchi et al. reported that the PS and patient preference could influence the treatment sequence in patients receiving first-line EGFR-TKI therapy. They also reviewed the initial recurrence site after failure of EGFR-TKI therapy and found CNS as the most frequent extrathoracic metastatic site. However, what causes the deterioration of the PS remains unknown. Therefore, we conducted an evaluation to understand, in detail, why patients could not make the transition to chemotherapy after failure of EGFR-TKI therapy and elucidated the cause; the analysis identified PS deterioration because of CNS metastasis, which mostly manifests as leptomeningitis, as the most frequent cause. As NSCLC patients with leptomeningitis or brain metastasis may also benefit from chemotherapy, close surveillance for the detection of CNS metastasis and a multidisciplinary approach for the CNS metastases may contribute to a better treatment sequence and prognosis.

Our study had several limitations. First, this was a retrospective study conducted at a single institution and the selection among the three first-line EGFR-TKI treatment agents available and the timing of change of treatment were left to the discretion of the attending physician and the patients’ preference. Although heterogeneous, 47% to 62% of patients in each EGFR-TKI treatment group received subsequent chemotherapy and the differences were not significant. Therefore, these patient cohorts could be considered as relatively uniform. Second, we excluded patients who were continued on the first-line EGFR-TKI treatment or received osimertinib; therefore, long responders tended to be excluded from the study and the PPS could have been underestimated. The present study focused on first- or second-generation EGFR-TKIs such as gefitinib, erlotinib or afatinib; therefore, further investigation is warranted to verify if the same results can be replicated for the third-generation EGFR-TKIs, for example, osimertinib. Third, the present study included patients treated with first- or second-generation EGFR-TKIs, so we should consider the T790M associated acquired resistance and subsequent osimertinib treatment. Because there was only 17% (67/393) of our study population who progressed after approval of osimertinib in Japan, the influence can be considered minimal. Fourth, there were differences in the patient background characteristics, including age, ECOG-PS, EGFR mutation status, and number of metastatic organs, between the groups. We adjusted this inter-subgroup heterogeneity using multivariate analyses and identified factors which significantly affected the outcomes.

In conclusion, a larger number of metastatic organs and PS deterioration are important factors for withholding subsequent chemotherapy after failure of EGFR-TKI therapy and poor prognosis in EGFR-mutated NSCLC patients. Particular attention should be given to the treatment of such patients with a poor prognosis and further studies should be carried out in the future.

**Disclosure**

H.H. reports personal fees from Chugai, Astra Zeneca. S.M. reports personal fees from Astra Zeneca, Chugai, Boehringer Ingelheim, Y.G. reports personal fees from...
Chugai, Boehringer Ingelheim, Pfizer, Astra Zeneca. S.K. reports personal fees from Astra Zeneca, Chugai. Y.F. reports personal fees from Astra Zeneca, Pfizer. NY reports personal fees from Chugai, Astra Zeneca. Y.O. reports grants from Astra Zeneca, Chugai, Boehringer Ingelheim. Y.O. reports personal fees from Pfizer, Astra Zeneca, Chugai. H.H. reports grants from Chugai, Astra Zeneca, Boehringer Ingelheim. Y.O. reports personal fees from Pfizer, Astra Zeneca, Chugai, Boehringer Ingelheim. Y.F. reports grants from Astra Zeneca, Chugai.

The authors report no conflicts of interest.

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