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Original Article

The relationship between tyrosine kinase inhibitor therapy and overall survival in patients with non-small cell lung cancer carrying *EGFR* mutations

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Abstract

For patients with epidermal growth factor receptor (*EGFR*) mutation-positive lung cancer, the relationship between the dose or duration of treatment with tyrosine kinase inhibitor (TKI) and overall survival remains unclear. Here, we analyzed clinical data of 39 patients who were diagnosed with *EGFR* mutation-positive non-small cell lung cancer and treated with TKI, but subsequently died. Several parameters were measured in this study: overall survival; first, second, and overall TKI therapy durations; first TKI intensity (actual dose/normal dose); and TKI rate (overall TKI therapy duration/overall survival). The response rate to TKI therapy was 50%, and the median survival was 553 days. After TKI therapy failed, 38.5% patients were re-challenged with TKI. We observed a moderate relationship [r = 0.534, 95% confidential interval (CI) = 0.263 to 0.727, P < 0.001] between overall TKI therapy duration and overall survival. However, we found no relationship between overall survival and first TKI intensity (r = 0.073, 95% CI = –0.380 to 0.247, P = 0.657) or TKI rate (r = 0.0345, 95% CI = –0.284 to 0.346, P = 0.835). Non-small cell lung cancer patients with mutation-positive tumors remained on TKI therapy for, on average, 33% of the overall survival time. These findings suggest that patients with *EGFR* mutation-positive tumors should not stick to using TKIs.

Key words Tyrosine kinase inhibitor, gefitinib, erlotinib, non-small cell lung cancer, epidermal growth factor receptor mutation

Lung cancer is a leading cause of death worldwide. Epidermal growth factor receptor (*EGFR*) mutations of adenocarcinoma are seen in more than 30% of Asians. Molecular targeting therapy for these patients made dramatic impact in therapy. Patients with non–small cell lung cancer (NSCLC) with *EGFR* mutation showed superior progression-free survival by first-line tyrosine kinase inhibitor (TKI) treatment than by traditional platinum-doublet chemotherapy in several clinical trials[1-4]. Some study groups reported that TKI re-challenge was beneficial for patients who initially responded to TKI[5,6]. In a previous Japanese study, overall survival increased in patients with *EGFR* mutation–positive cancer after treatment with gefitinib[7]. However, to the best of our knowledge, the relationship between duration or dose of TKI (including dose reduction and re-challenge) and overall survival has not been investigated. Re-challenge of TKIs after cytotoxic agents or continuation of TKIs after disease progression is frequently seen in practical use. However, it remains unknown whether such administration for disease control benefits survival.

In this retrospective study, we sought to clarify the relationship between total TKI administration and overall survival in patients with *EGFR* mutation–positive NSCLC.

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Materials and Methods

Patients

We analyzed the medical records of 39 patients with *EGFR* mutation–positive NSCLC who were newly diagnosed at our institute between January 2003 and August 2010, underwent TKI therapy, and died before February 2012. This protocol was approved by the Ethics Committee of Osaka Prefectural Medical Center for Respiratory and Allergic Diseases.

Tumors from patients in this study harbored several *EGFR* mutations—exon 19 deletion, exon 21 point mutation (L858R), or exon 18 point mutation (G719C, G719S, and G719A)—as determined by direct sequencing or the PNA-LNA PCR Clamp method. Patients with *EGFR* exon 20 T790M mutation before treatment were excluded from this study. The TKI used in this study was gefitinib or erlotinib.

Parameters

The parameters measured in this study were overall survival; first, second, and overall TKI therapy duration; first TKI intensity; and TKI rate. Overall survival was measured from the date of diagnosis (or confirmed recurrence in postoperative cases) to the date of death. First TKI therapy duration was measured from the start to the end of TKI therapy, or to the switch to another TKI due to disease progression or toxicity. Second TKI therapy duration was calculated from the start of re-challenge to the end of therapy. Overall TKI therapy duration was defined as the first TKI therapy duration plus the second or more TKI therapy duration. First TKI intensity was defined as (actual dose of TKI)/(normal dose of TKI) during first TKI therapy. For example, for a patient who took gefitinib, 250 mg/day, for 100 days and then took it sequentially every other day over 100 days, the first TKI intensity is $(250 \times 100 + 250 \times 100 \times 0.5)/(250 \times 200) = 0.75$. Similarly, for a patient who took erlotinib, 150 mg/day, over 100 days followed by continuous low-dose erlotinib, 100 mg/day, over 100 days, the first TKI intensity is $(150 \times 100 + 100 \times 100)/(150 \times 200) = 0.83$. To evaluate the contribution of TKI to overall survival, TKI rate was defined as overall TKI therapy duration / overall survival. Response Evaluation Criteria in Solid Tumors [8] were used to evaluate treatment response.

Statistical analyses

We evaluated correlation coefficients between overall survival and overall TKI therapy duration, first TKI duration, first TKI intensity, and TKI rate. The correlation coefficients (r) were interpreted as follows: $-0.2 \leqslant r \leqslant 0.2$, no relationship; $0.2 < r \leqslant 0.4$ ($-0.4 \leqslant r < -0.2$), weak positive (or negative) linear relationship; $0.4 < r \leqslant 0.7$ ($-0.7 \leqslant r < -0.4$), moderate positive (or negative) linear relationship; and $0.7 < r \leqslant 1.0$ ($-1.0 \leqslant r < -0.7$), strong positive (or negative) linear relationship. The r values were analyzed using Pearson's correlation test. First TKI durations were compared between groups with and without cytotoxic treatment using the Mann-Whitney U test. Survival time from disease diagnosis to death was assessed by Kaplan-Meier survival analysis. P values less than 0.05 were considered significant. All statistical analyses were performed using software R [version 2.13.1, R Development Core Team (2011), R: a language and environment for statistical computing, R Foundation for Statistical Computing; Vienna, Austria].

Results

Of the 39 patients, 18 were males and 21 were females, with a median age of 66 years (Table 1). Of these, 33% received TKIs as first-line chemotherapy. More than three-quarters of the patients took gefitinib as the first TKI. After the first therapy failed, 38.5% patients were re-challenged with TKI. The response rate was 50%, although this objective group included 7 cases that could not be evaluated because toxicity or death reduced the therapeutic period. A variety of *EGFR* mutations were identified, including 19 exon 19 deletions, 17 exon 21 point mutations, and 3 exon 18 point mutations.

The median overall TKI therapy duration was 125 days. We found a moderate relationship [$r = 0.534$, 95% confidential interval (CI) = 0.263 to 0.727, $P < 0.001$] between overall survival and overall TKI therapy duration (Figure 1A). For first TKI intensity, the median was 0.928, the mean was 0.831, and the standard deviation was 0.2. Notably, one-third of patients (13/39) had TKI intensity less than 0.8. We found no relationship ($r = 0.073$, 95% CI = −0.380 to 0.247, $P = 0.657$) between first TKI intensity and overall survival (Figure 1B). The median first TKI duration was 79 days. As shown in Figure 1C, there was a weak relationship between overall survival and first TKI therapy duration ($r = 0.32$, 95% CI = −0.012 to 0.582, $P = 0.043$). There was no significant difference between first TKI duration and cytotoxic agent use duration (159 days vs. 174 days, $P = 0.93$). For TKI rate, the median was 0.266, the mean was 0.329, and the standard deviation was 0.268. We observed no relationship ($r = 0.0345$, 95% CI = −0.284 to 0.346, $P = 0.835$) between TKI rate and overall survival (Figure 1D). The estimated median survival time was 553 days (95% CI = 444 to 750 days).

Table 1. Baseline and treatment characteristics of 39 patients with non-small cell lung cancer

Category	Item	Number
Age (years; median, range)		66 (45–87)
Duration (days; median, range)	First TKI	79 (10–639)
	All TKI	125 (10–899)
Gender	Men	18
	Women	21
Active mutation	Exon 19	19
	Exon 21	17
	Exon 18	3
Stage	IIIB	8
	IV	23
	postoperative recurrence	8
Histopathology	Adenocarcinoma	36
	Adeno-squamous carcinoma	1
	Squamous cell carcinoma	2
First-line chemotherapy	Cytotoxic	26
	TKI	13
Response to first chemotherapy	PR	14
	SD	9
	PD	5
	(TKI alone)	(11)
First TKI	Gefitinib	30
	Erlotinib	9
First TKI response	PR	19
	PD	13
	NE	7
Re-challenge TKI	Yes	15
	No	24

TKI, tyrosine kinase inhibitor; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluated.

Discussion

This study showed that there is no obvious relationship between overall survival and first TKI intensity or TKI rate in *EGFR* mutation-positive NSCLC patients. These patients took TKI for one-third of the overall survival time in the mean. If the total duration of TKI therapy, including the time after first progression while on TKI, affects overall survival, physicians need to consider the use of TKI, even beyond disease progression. Many patients need dose reduction due to side effects during TKI therapy. For example, to reduce the dose of gefitinib, drug administration should be changed from everyday to once every 2 or 3 days. However, the effectiveness of such an approach has not yet been proven. If there is a clear relation between TKI dose intensity and overall survival, dose reduction can be accordingly monitored.

We found that overall survival increased as the overall TKI therapy duration increased, but there were insufficient data to determine a causal relationship between these parameters. In contrast, we observed no relationship between overall survival and first TKI intensity. In a post-hoc analysis of large phase III study, Satoh *et al*. [9] reported that low-dose gefitinib was superior to the usual dose of gefitinib. Likewise, low-dose erlotinib (25 mg/day) was found to be effective in cell lines and in clinical practice[10]. Our finding that TKI intensity and overall survival were not significantly related agreed that reduced doses of TKI did not directly affect overall survival.

The effect of *EGFR* mutations on patient response to cytotoxic agents remains controversial[11,12]. In this study, we found no relationship between overall survival and TKI rate. Anticancer agents, except for TKI, appear to increase the survival of cancer patients. We previously reported that long-term chemotherapy might extend survival in responders to first-line chemotherapy[13]. These

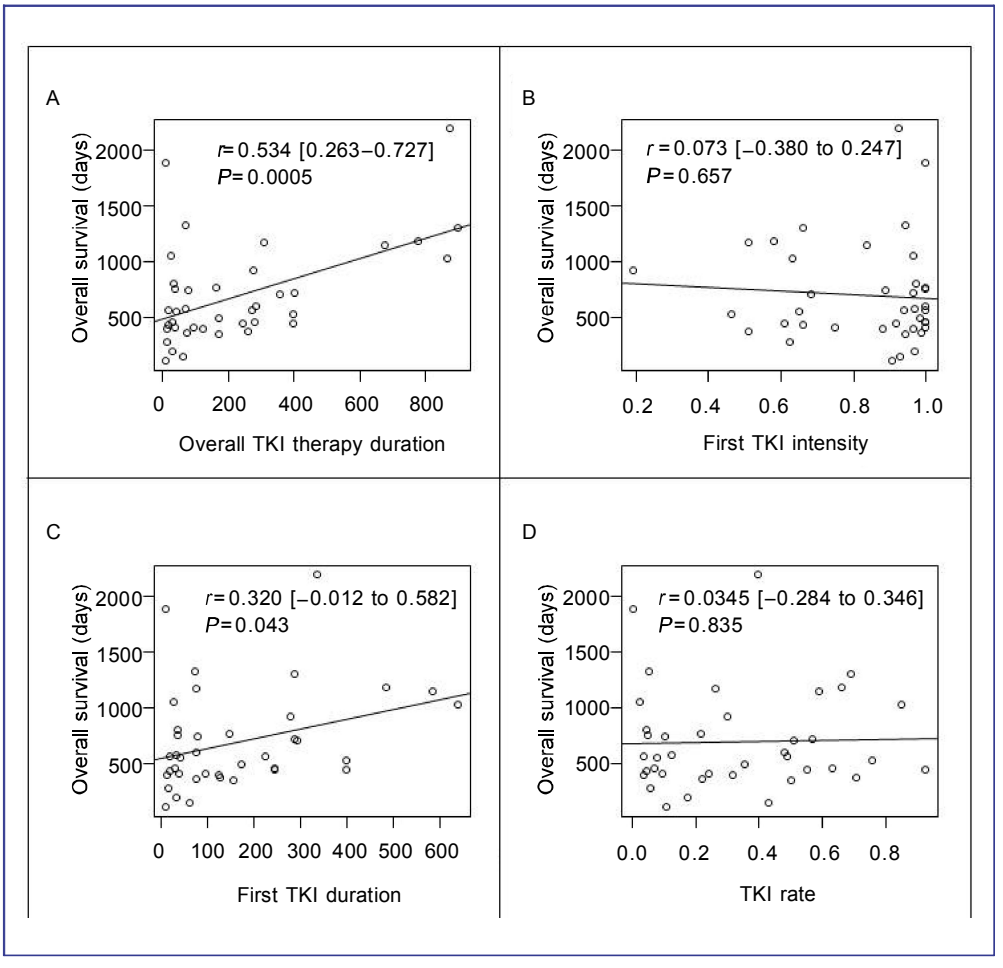

Figure 1. **The linear correlation between overall survival (OS) and parameters of tyrosine kinase inhibitor (TKI) therapy.** The values were analyzed by using the Pearson's correlation test. A, the relationship between OS and overall TKI therapy duration. B, the relationship between OS and first TKI intensity. One-third of patients had TKI intensity less than 0.8. C, the relationship between OS and the first TKI therapy duration. D, the relationship between OS and TKI rate. No significant relationship was found between OS and TKI rate. *r*: correlation coefficients [95% confidence interval].

data suggest *EGFR* mutation-positive patients should not stick to using TKIs.

Two prospective studies described the efficacy of TKI re-challenge. Asahina *et al.*[5] reported that the response rate and progression-free survival was 0% and 2.5 months, respectively, when gefinitib was re-administered after cytotoxic chemotherapy. They suggested that this was the most efficient treatment option. Koizumi *et al.*[6] reported that the response rate and progression-free survival was 15% and 2 months, respectively, after gefitinib readministration. In our study, 15 patients (38.5%) underwent TKI re-challenge, and we observed a moderate relationship between overall survival and overall TKI therapy duration. These results suggest that TKI re-challenge may contribute to survival in selected cases.

Our study has some limitations. First, it was retrospective and conducted on a small population at a single institution. *EGFR* mutation–positive patients who transferred to the palliative care unit or local hospitals were excluded from this study. Second, only patients who died were followed; long-term survivors were excluded. Third, the method of dose reduction was not unified. It remains unknown whether the two TKIs (gefitinib and erlotinib) showed the same clinical effect or whether their serum concentrations differed among mutation-positive patients. Hughes *et al.*[14] reported that the plasma concentrations of erlotinib were affected by smoking status. Thus, further investigation is needed to determine the relationship between overall survival and TKI administration.

In conclusion, we found no relationship between overall survival and first TKI intensity or TKI rate in the treatment of patients with *EGFR* mutation-positive NSCLC. *EGFR* mutation-positive patients should not stick to using TKIs. A prospective study to define the most effective duration of TKI therapy and to reduce adverse effects is needed.

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