Differential efficacy of docetaxel according to non-small cell lung cancer histology and the therapeutic effect of epidermal growth factor receptor tyrosine kinase inhibitors

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Abstract. The active mutation of epidermal growth factor receptor (EGFR) and clinical characteristics are significant biomarkers for chemotherapy selection in non-small cell lung cancer (NSCLC). Although docetaxel is a key agent in second-line therapy for NSCLC, predictive biomarkers for assessing its efficacy have yet to be determined. To assess the clinical efficacy of docetaxel in second-line therapy for NSCLC according to NSCLC histology and the therapeutic effect of EGFR-tyrosine kinase inhibitors (EGFR-TKIs), we retrospectively reviewed 454 NSCLC patients treated with docetaxel between April 2002 and April 2009. In total, 239 patients with advanced NSCLC treated with docetaxel as second-line therapy following failure of platinum-based chemotherapy were analyzed in this study. A total of 59 (25%) patients had squamous cell carcinoma. The overall response rate and median progression-free survival time in the squamous cell group were significantly inferior to those in the non-squamous cell group (p=0.031 and p=0.005, respectively). Following the failure of docetaxel, 91 non-squamous patients were treated with EGFR-TKIs. The patients that achieved clinical benefit from EGFR-TKIs (n=32) demonstrated a significantly better response rate and longer progression-free survival compared to the other group (p<0.001 and p=0.027, respectively). In the univariate and multivariate analysis, the favorable therapeutic effect of EGFR-TKIs had an independent effect on progression-free survival (HR 1.484, p=0.0464). In conclusion, this retrospective study suggests that non-squamous histology and favorable therapeutic effect from EGFR-TKIs are useful markers for predicting the efficacy of docetaxel in second-line therapy for NSCLC.

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Introduction

Lung cancer is the leading cause of mortality worldwide, and non-small cell lung cancer (NSCLC) accounts for approximately 80% of all cases of lung cancer (1). The majority of NSCLC patients present with advanced disease at the time of diagnosis, and treatment of these patients with intensive chemotherapy does not prevent recurrence. Therefore, most NSCLC patients become candidates for palliative chemotherapy or radiotherapy.

Advances in chemotherapeutic agents led to new chemotherapy strategies for NSCLC. Pemetrexed, a multitargeted antifolate, revealed both efficacy and tolerability as an active therapeutic agent for NSCLC patients in two Phase III trials (2,3). Integration analysis of the two Phase III trials indicated that the survival benefit of pemetrexed therapy was observed only in non-squamous histology (4). This outcome revealed a new treatment strategy of selecting the chemotherapeutic agent in accordance with the histology.

Epidermal growth factor receptor (EGFR) is a promising target for anticancer therapy in various tumors. In NSCLC, newly developed EGFR-targeted anticancer agents include EGFR-tyrosine kinase inhibitors (EGFR-TKIs), such as gefitinib and erlotinib. EGFR-TKIs inhibit intracellular signals for the proliferation and survival of cancer cells and have shown efficacy in clinical practice. In 2004, two pivotal reports demonstrated that sensitivity to EGFR-TKI therapy is significantly associated with somatic mutations in the tyrosine kinase domain of the EGFR gene at exons 19 and 21 (5,6). These active EGFR mutations and clinical characteristics, including female gender, Asian ethnicity, adenocarcinoma histology, and never or light smoker, are now established as useful biomarkers for predicting the efficacy of EGFR-TKIs (7-9).

Docetaxel is well established as the first agent selected for previously treated advanced NSCLC patients. FDA approval of docetaxel was based on two Phase III trials, TAX317 and

Table I. Patient characteristics at administration of docetaxel therapy.

		Histology			Therapeutic effect of EGFR-TKIs		
	Total	Sq	Non-sq		EGFR-R	EGFR-OTH	
	(n=239) No. (%)	(n=59) No. (%)	(n=180) No. (%)	p-value	(n=32) No. (%)	(n=207) No. (%)	p-value
Gender							
Male	193 (81)	51 (56)	142 (79)	0.201	18 (56)	175 (85)	<0.001
Female	46 (19)	8 (14)	38 (21)		14 (44)	32 (15)	
Age							
Median (range)	63 (23-82)	63 (23-82)	63.5 (45-77)	0.391	64 (23-79)	60.5 (45-82)	0.233
ECOG performance status							
0	67 (28)	18 (30)	49 (27)	0.177	8 (25)	59 (28)	0.157
1	142 (59)	30 (51)	112 (62)		23 (72)	119 (58)	
2	30 (13)	11 (19)	19 (11)		1 (3)	29 (14)	
Stage							
IIIB	34 (14)	7 (12)	27 (15)	0.549	1 (3)	33 (16)	0.057
VI	205 (86)	52 (88)	153 (85)		31 (97)	174 (84)	
Histology							
Adenocarcinoma	163 (68)	0 (0)	163 (91)	<0.001	29 (91)	134 (65)	0.002
Squamous	59 (25)	59 (100)	0 (0)		1 (3)	58 (28)	
Lar	9 (4)	0 (0)	9 (5)		0 (0)	9 (4)	
Other	8 (3)	0 (0)	8 (4)		2 (6)	6 (3)	
Smoking history (smoker >10 pack/year)	199 (83)	133 (82)	66 (87)	0.311	19 (53)	180 (89)	<0.001

EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; EGFR-R, responder to EGFR-TKIs; OTH, other; SQ, squamous; Lar, large cell carcinoma.

TAX320 (10,11). These pivotal studies demonstrated favorable survival rates compared with best supportive care alone or other single-agent therapies. No chemotherapeutic agents have shown a survival benefit comparable to docetaxel for unselected NSCLC recurrence patients. Biomarkers, such as Class III β-tubulin expression and mRNA, are suggested to predict the efficacy of docetaxel. However, these methods are not used in the clinic (12,13).

To identify biomarkers that may actually be used to predict the efficacy of docetaxel, we investigated the potential of NSCLC histology and the favorable therapeutic effect of EGFR-TKIs as predictive markers for second-line docetaxel therapy in our institution.

Patients and methods

Patients. A total of 454 consecutive NSCLC patients treated with docetaxel at the Shizuoka Cancer Center, Japan, between April 2002 and April 2009 were retrospectively reviewed. The patients included in this study were 193 males (81%) and 46 females (19%), with a median age of 63 years. The study included patients with histologically or cytologically proven NSCLC who had previously been treated with docetaxel monotherapy, following a previous regimen of platinum doublet therapy. The study protocol was reviewed and approved by the Institutional Review Board of the Shizuoka Cancer Center.

Collection of data and response evaluation. Demographic data were collected from the patients with regard to gender, age, ECOG performance status (PS), clinical stage, histology, and history of smoking as of the date that docetaxel therapy started. Docetaxel was administered every 3 weeks as a 1-h intravenous infusion of 60 mg/m^2. Tumor response was assessed as complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD) in accordance with the World Health Organization criteria (14). The data cut-off date was March 30, 2010.

Subgroup classification. Subgroup analyses were performed according to histology and the clinical benefit of EGFR-TKIs following docetaxel therapy. The histological subtypes were classified into a squamous cell carcinoma group and a non-squamous cell carcinoma group, which included adenocarcinoma, large-cell carcinoma and other NSCLCs not otherwise specified. Moreover, to assess the relativity of the EGFR mutation status and the efficacy of docetaxel therapy, we collected data on the EGFR gene mutation status. However, only a small number of patients could be assessed for EGFR gene mutation. It was previously reported that the clinical benefit of EGFR-TKIs is a useful marker for predicting active EGFR mutations (15). We considered the clinical benefit of EGFR-TKIs as a surrogate marker of active EGFR mutations for assessing the EGFR mutation status in practical data, and performed an analysis.

Table II. Summary of efficacy of docetaxel therapy according to histology or therapeutic effect of EGFR-TKIs.

		Histology			Therapeutic effect of EGFR-TKIs		
	Total (n=239)	Sq (n=59)	Non-sq (n=180)	p-value	EGFR-R (n=32)	EGFR-OTH (n=207)	p-value
Number of cycles, median (range)	2 (1-31)	2 (1-31)	2 (1-8)	0.064	4 (1-15)	2 (1-31)	<0.001
Response to docetaxel therapy, no. (%)							
CR	0 (0)	0 (0)	0 (0)	0.084	0 (0)	0 (0)	<0.001
PR	21 (8.8)	1 (1.7)	20 (11.1)		10 (31.2)	11 (5.3)	
SD	89 (37.2)	22 (37.3)	67 (37.2)		15 (46.9)	74 (35.7)	
PD	120 (50.2)	32 (54.2)	88 (48.9)		7 (21.9)	113 (54.6)	
NE	9 (3.8)	4 (6.8)	5 (2.8)		0 (0)	9 (4.4)	
Response rate (95% CI)	8.8 (5.8-13.0)	1.7 (0.3-9.0)	11.1 (7.3-16.5)	0.031	31.2 (17.9-48.5)	5.3 (3.0-9.3)	<0.001
Median PFS, weeks (95% CI)	7.8 (6.7-9.0)	7.1 (5.7-8.8)	8.0 (6.7-12.1)	0.005	21.0 (12.1-27.8)	7.1 (6.4-7.8)	0.027
MST, months (95% CI)	9.1 (7.6-10.8)	8.7 (6.9-10.2)	9.3 (7.6-11.9)	0.019	31.0 (25.2-42.9)	7.6 (6.4-8.9)	<0.001
One year survival, %	39.8	28.5	43.2		87.5	31.6	

EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; EGFR-R, responder to EGFR-TKIs; OTH, other; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable; PFS, progression-free survival; MST, median survival time; CI, confidence interval.

The objective clinical benefit from treatment with EGFR-TKIs was defined as: documented PR or CR, or durable (>180 days) clinical benefit with SD after initiation of EGFR-TKIs (15). The patients were classified into two groups according to the clinical benefit of EGFR-TKIs after docetaxel therapy: patients who achieved clinical benefit from EGFR-TKIs were classified as the responder group (EGFR-R group) and patients who did not achieve clinical benefit from EGFR-TKIs or who were not administered EGFR-TKIs were classified as the other group (EGFR-OTH group).

Statistical analysis. The comparison of clinical characteri stics and response rate was performed using Pearson's χ^2 test, two-sided Fisher's exact test and Wilcoxon's test, as appropriate. Overall survival time was calculated as the number of months from the date of docetaxel administration until the date the patient succumbed. The progression-free survival (PFS) time was the period from the date of docetaxel administration until the date of progression or death, whichever occurred first. The Kaplan-Meier method was used to calculate the median duration of overall survival and PFS, and the log-rank test was used to compare the two curves. The Cox proportional hazard regression test was used to determine univariate and multivariate hazard ratios of PFS and overall survival for docetaxel therapy. The prespecified prognostic factors (gender, age, performance status and clinical stage) were included in the multivariate analysis. Two-sided p-values of <0.05 were considered to be statistically significant. Data were analyzed using JMP 8 statistical software for Windows (SAS Institute Inc., Cary, NC, USA).

Results

Patient demographics and clinical characteristics. In total, 239 patients with advanced NSCLC were treated with docetaxel as a second-line therapy following the failure of platinum-based chemotherapy in our institute. The patient characteristics are shown in Table I. Among the patients, 193 were male (81%) and 46 were female (19%). The median age was 63 years, and 13 patients (13%) had a performance status of 2. Fifty-nine (25%) patients had squamous cell carcinoma histology and 180 (75%) had non-squamous histology. The majority of eligible patients were current or former smokers (83%). When classified according to histology, no significant difference was found among the characteristics in each group. Of the 239 patients, 96 (40%) received EGFR-TKIs after docetaxel therapy and 32 (13%) achieved clinical benefit from EGFR-TKIs. When classified according to the therapeutic effect of EGFR-TKIs, a significantly lower rate of male individuals and current or former smokers was observed in the EGFR-R group.

Efficacy of docetaxel according to histological type. A summary of the efficacy data for docetaxel therapy is shown in Table II. The median number of cycles of docetaxel in all patients was 2, and ranged from 1 to 31. The objective response to docetaxel was obtained in 21 of the 239 patients [8.8%;

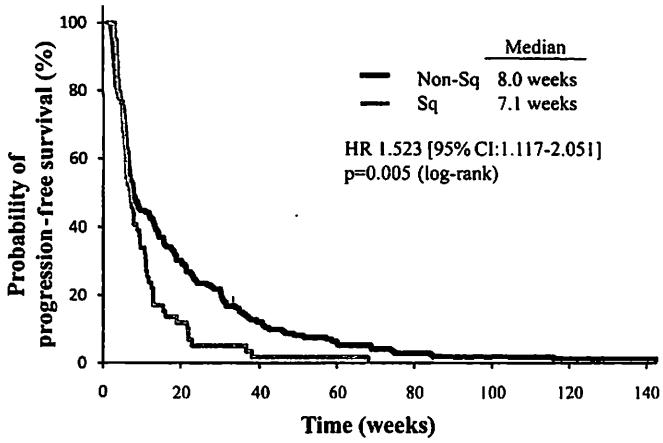

Figure 1. Kaplan-Meier curve comparing progression-free survival between squamous cell carcinoma patients and non-squamous cell carcinoma patients. HR, hazard ratio; CI, confidence interval.

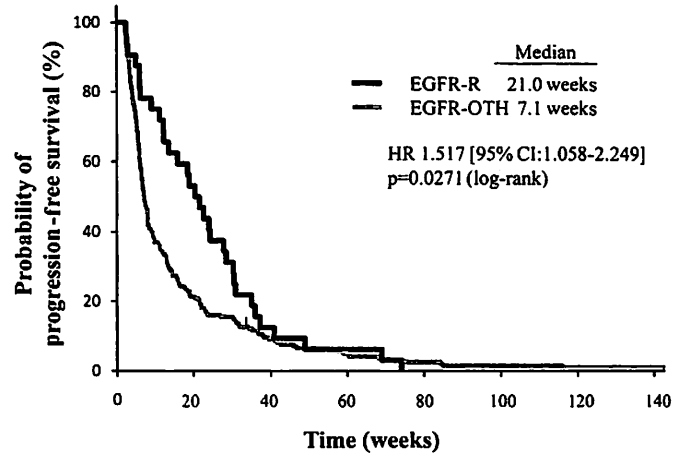

Figure 2. Kaplan-Meier curve comparing EGFR responder patients (EGFR-R) and other patients (EGFR-OTH). HR, hazard ratio; CI, confidence interval.

95% confidence interval (CI): 5.8-13.0%]. The median PFS, median overall survival time (MST) and one-year survival rate of all patients were 7.8 weeks, 9.1 months and 39.8%, respectively. In the category of histological grouping, a significantly higher response rate was achieved in the non-squamous group compared to the squamous group (11.1 vs. 1.7%, respectively; p=0.031). The median PFS was significantly shorter in the squamous group compared with the non-squamous group: 7.1 vs. 8.0 weeks (HR, 1.523; 95% CI, 1.117-2.051; p=0.005) (Fig. 1). Similarly, survival time was significantly shorter in the squamous group than the non-squamous group; the MST and one-year survival rate were 8.7 months and 28.5% vs. 9.3 months and 43.2%, respectively (HR, 1.463; 95% CI, 1.053-2.003; p=0.019).

Evaluation of association between EGFR-TKI therapeutic effect and docetaxel efficacy. After the failure of docetaxel therapy, 91 non-squamous patients were treated with EGFR-TKIs. Twenty-eight patients (30%) demonstrated a partial response and 4 patients (4%) achieved clinical benefit with long-term disease stabilization. These 32 patients were included in the EGFR-R group. Sixty patients (66%) did not respond to EGFR-TKIs and 4 patients were not evaluable, and along with the patients who were not administered EGFR-TKIs, the 207 patients were included in the EGFR-OTH group. The EGFR-R group was compared with the EGFR-OTH group for differences in efficacy of docetaxel therapy. The response rate of second-line docetaxel therapy in the EGFR-R group was significantly superior to that in the EGFR-OTH group (31.2 vs. 5.3%, respectively; p<0.001) (Table II). In addition, the median PFS in the EGFR-R group was significantly longer than that in the EGFR-OTH group (21.0 vs. 7.1 weeks, respectively; p=0.027) (Fig. 2). Overall survival time was markedly prolonged in the EGFR-R group compared to the EGFR-OTH group (31.0 vs. 7.6 months, respectively; p<0.001).

Univariate and multivariate analysis of progression-free survival in second-line docetaxel therapy. The results of the univariate and multivariate analysis for determining the predictive factor for PFS of second-line docetaxel therapy are shown in Table III. The univariate analysis revealed that histology, PS and clinical efficacy of EGFR-TKIs were significant predictive factors. In previously reported multivariate analyses using other prognostic covariates, the clinical efficacy of EGFR-TKIs remained a significant predictive factor for PFS of second-line docetaxel therapy (HR 1.484, 95% CI, 1.006-2.252; p=0.0464) (Table III).

Discussion

This is the first report to demonstrate the efficacy of docetaxel therapy for previously treated NSCLC patients according to NSCLC histology and the therapeutic effect of EGFR-TKIs. In the non-squamous patient group, the response rate and survival benefit of docetaxel therapy were significantly superior compared to those in the squamous group. This result is similar to the previously reported difference in efficacy of pemetrexed therapy according to histology. Another finding of our analysis was that the efficacy of docetaxel is associated with sensitivity to EGFR-TKIs following docetaxel administration. Patients who achieved a clinical benefit from EGFR-TKIs revealed a significantly higher response rate and longer progression-free survival time with second-line docetaxel therapy. These results suggest that the efficacy of docetaxel therapy may be predicted by patient characteristics, including histology and the therapeutic effect of EGFR-TKIs.

Docetaxel is the most frequently investigated agent for previously treated NSCLC patients, but the difference in its efficacy according to histology was not observed in earlier large randomized studies. In this study, the efficacy of docetaxel was found to be significantly superior for patients with non-squamous cell carcinoma histology. This discrepancy may simply be attributed to the retrospective analysis in a single institution. Another possible explanation is that the administration dose for docetaxel is lower in Japan compared to that in the USA and Europe. In Japan, the recommended dose for docetaxel was determined as 60 mg/m^2 every three weeks due to the similar efficacy shown with this dose in two Phase II studies (16,17).

Another noteworthy finding is the relationship between the therapeutic effect of EGFR-TKIs and docetaxel efficacy

Table III. Univariate and multivariate analysis for progression-free survival in second-line docetaxel therapy (n=239).

Factors			Univariate			Multivariate		
	Total	PFS (weeks)	HR	95% CI	p-value	HR	95% CI	p-value
Gender								
Female	193	7.2	0.901	0.658-1.260	0.5351	0.789	0.563-1.127	0.1893
Male	46	8.0						
Age								
<70	176	7.2	0.816	0.605-1.086	0.1660	0.912	0.669-1.229	0.5538
>70	63	8.0						
Histology								
Non-squamous	180	8.0	1.523	1.117-2.051	0.0084	1.377	0.995-1.882	0.0533
Squamous	59	7.1						
PS								
0-1	209	8.0	1.739	1.157-2.522	0.0088	1.482	0.968-2.198	0.0688
2	30	6.0						
Stage								
IIIB	37	11.8	1.314	0.933-1.905	0.1206	1.264	0.884-1.855	0.2027
IV	202	7.0						
EGFR-TKI therapy								
Responder	32	21.0	1.517	1.058-2.249	0.0222	1.484	1.006-2.252	0.0464
Other	207	7.1						

PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; PS, ECOG performance status; EGFR-TKI, epidermal growth factor receptor tyrosine kinase inhibitor.

in the second-line setting. A number of large Phase III trials and retrospective analyses suggested that patients with active EGFR mutations are sensitive to cytotoxic agents. In the V15-32 trial, the response to docetaxel differed significantly by EGFR mutation status (active mutation vs. wild-type; 46 vs. 0%, respectively) in a small subset analysis (18). The IPASS study also showed similar indications in first-line chemotherapy; the combination therapy of carboplatin plus paclitaxel had relatively favorable efficacy for patients with the active EGFR mutation compared to EGFR wild-type patients (active mutation vs. wild type; 47.3 vs. 23.5%, respectively). In addition, three retrospective analyses reported that the efficacy of chemotherapy by cytotoxic agents tended to be high in patients with active EGFR mutations (19-21). These data suggest that the EGFR gene mutation would be a useful predictive biomarker for treatment with cytotoxic agents. The clinical benefit of EGFR-TKIs suggests that it is a useful method for predicting active EGFR mutations (15). Therefore, the results of our analysis suggest that active EGFR mutation is a predictive factor for the efficacy of docetaxel treatment. The EGFR gene mutation is one of the major causes of oncogenic addiction. If the biological features of cancer cells are significantly affected by the addicted oncogene, there is a possibility that the effectiveness of chemotherapy may differ according to the EGFR gene mutation. However, basic data for explaining this hypothesis are not currently available, and further molecular biological studies are required.

In the univariate and multivariate analysis, sensitivity to EGFR-TKIs was extracted as a predictive factor for the efficacy of docetaxel. On the other hand, histological type was extracted as a significant factor in the univariate analysis; however, it did not remain a significant factor in the multivariate analysis with other covariates. A global Phase III study revealed that the efficacy of EGFR-TKI is high for adenocarcinoma histology. Adenocarcinoma histology and sensitivity to EGFR-TKIs are strong confounding factors, which is why it was not extracted as an independent predictive factor in the multivariate analysis. In contrast, results of this study showed that the efficacy of docetaxel is markedly high in patients with clinical benefit from EGFR-TKIs. There is a possibility that sensitivity to docetaxel in adenocarcinoma patients depends on the sensitivity to docetaxel in the EGFR-R group. It is well known that there are differences in the frequency of active EGFR mutations among different ethnic groups, i.e., this frequency is extremely high in Asian patients with lung adenocarcinoma compared with American patients (22). This fact may be another reason for the difference in efficacy of docetaxel according to histology not being observed in the large randomized Phase III study in the USA, which was observed in this analysis of patients in a Japanese institute.

The major limitation of the present study is that it is based on a retrospective analysis of patients in a single institute, thus there may be a potential bias with regard to patient selection and follow-up procedure. Furthermore, the analysis of EGFR status is based solely on the therapeutic effect of EGFR-TKI. We were able to examine the EGFR gene mutation status for only 21 patients; active EGFR mutation was observed in 6 cases and

wild-type in 15 cases. No association was determined between the efficacy of docetaxel and active EGFR mutations due to lack of computing power for the statistical analysis (data not shown). There are two reasons for the difficulty experienced in examining a sufficient number of EGFR gene mutations for statistical analysis. First, the EGFR gene mutation had not been examined in clinical practice for most of the target period. Second, assessment of the EGFR gene mutation by polymerase chain reaction and direct sequencing methods requires proper preservation of tumor tissue. Hindrances in the assessment of patient EGFR mutation status are often experienced due to economic constraints or difficulty in collecting tumor specimens in clinical practice. Therefore, we frequently use the patient's background data such as smoking history and adenocarcinoma histology as predictive factors for EGFR-TKI efficacy; the so-called IPASS population. Further analysis is necessary to show the association of the EGFR mutation status and the efficacy of docetaxel therapy, such as through prospective trials based on EGFR mutation status. However, our results support the significant hypothesis that the effectiveness of chemotherapy differs according to the EGFR gene mutation status. Therefore, EGFR gene mutation status, which has already been established as a predictive marker for chemotherapy by cytotoxic agents, may be useful for predicting the efficacy of docetaxel.

In this analysis, we presented two major results. First, the efficacy of docetaxel is superior in non-squamous patients; and second, it produces favorable results in patients who achieved clinical benefit from EGFR-TKIs. This retrospective analysis is the first to suggest that the efficacy of docetaxel differs according to the histology and therapeutic effect of EGFR-TKIs. These findings provide physicians with a crucial basis for selecting agents for second-line therapy.

In conclusion, this retrospective study suggests that non-squamous histology and the favorable therapeutic effect of EGFR-TKIs are useful markers for predicting the efficacy of docetaxel as a second-line therapy for NSCLC. Confirmation of these observations requires further investigation through prospective clinical trials and basic molecular biology analyses.

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