Re-administration of Chemotherapy in Patients with Advanced Non-small Cell Lung Cancer Who Recovered from Chemotherapy-induced Interstitial Lung Disease

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Abstract. *We reported that epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor re-administration (TKI-R) might be salvage therapy in patients with advanced non-small cell lung cancer after recovery from EGFR-TKI-induced interstitial lung disease (ILD). Here we retrospectively evaluated whether chemotherapy re-administration (CT-R) was effective in patients after chemotherapy-induced ILD. After providing their informed consent due to the risk of severe ILD, five patients received CT-R and six received TKI-R with oral administration of 0.5 mg/kg prednisolone. The overall survival (OS) from the occurrence of drug-induced ILD was shorter in CT-R cases than that in TKI-R cases (7.3 months vs. 25.4 months, $p=0.003$). The median duration of OS, however, was 7.3 months in cases with CT-R and 1.9 months in cases without CT-R. Multivariate analysis showed that CT-R as well as TKI-R tended to reduce the risk of mortality. CT-R might be salvage therapy in such patients, although the benefit of CT-R was smaller than that of TKI-R.*

In general, drug re-administration is contraindicated in patients who have developed serious drug-induced interstitial lung disease (ILD). Some patients with non-small cell lung cancer (NSCLC) with active epidermal growth factor receptor (EGFR) mutations, however, desire re-administration of EGFR tyrosine kinase inhibitor (TKI) because they experienced a good response to EGFR-TKI and know that EGFR-TKI is more effective and less toxic than chemotherapy (CT). There are several case reports of

successful EGFR-TKI re-administration (TKI-R) after recovery from EGFR-TKI-induced ILD (1-10). We already reported that TKI-R with concurrent prednisolone therapy might be salvage therapy in patients with advanced NSCLC with active EGFR mutations after recovery from TKI-induced ILD (11).

On the other hand, drug-induced ILD also occurs in patients receiving CT with cytotoxic anticancer agents, with an incidence of 0.1-3.6% (12-14). The pathogenesis of CT-induced ILD is poorly understood, but is thought to result from the following types of direct cytotoxicity: direct injury to pneumocytes or the alveolar capillary endothelium with subsequent release of cytokines and recruitment of inflammatory cells, endothelial dysfunction, capillary leak syndrome and non-cardiogenic lung edema caused by the systemic release of cytokines, cell-mediated lung injury due to activation of lymphocytes and alveolar macrophages, or oxidative injury from free oxygen radicals (13, 15). Unlike TKI-R after recovery from TKI-induced ILD, it is logically possible to perform CT re-administration (CT-R) with other cytotoxic anticancer agents, the mechanism of lung toxicity of which is different from that of the suspected drug, when patients have an improved performance status (PS) after recovery from CT-induced ILD. Nonetheless, it is unclear whether CT-R is feasible and effective in those patients. Therefore, we retrospectively investigated the efficacy and tolerability of CT-R in patients with advanced NSCLC who had recovered from CT-induced ILD and evaluated the difference in the duration of overall survival (OS) between patients with treated with CT-R and those treated with TKI-R.

Patients and Methods

This retrospective study was approved by the Institutional Review Board of Kumamoto Regional Medical Center (approval date, September 22, 2017; approval number, 17-021). The data of 42 patients with advanced NSCLC or postoperative recurrence who had developed drug-induced ILD (21 cases with CT-induced ILD and 21 cases with TKI-induced ILD) were retrospectively retrieved from the database of electronic medical record during the 7-year period

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Key Words: Drug-induced interstitial lung disease, re-administration, chemotherapy, EGFR-TKI, corticosteroid.

Table I. Patient and disease characteristics in cases treated with chemotherapy- (CT) or epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI)-induced interstitial lung disease (ILD).

Characteristic	CT-induced ILD N=21	TKI-induced ILD N=21	p-Value
Median age (range), years	70 (50-84)	74 (39-89)	-
Male gender, n (%)	19 (90)	10 (48)	0.006
Smokers or ex-smokers, n (%)	21 (100)	4 (19)	<0.001
Pathological type of lung cancer, n (%)			
Adenocarcinoma	14 (67)	21 (100)	0.008
Squamous cell carcinoma	7 (33)	0	0.008
EGFR mutation, n (%)	1 (5)	21 (100)	<0.001
Clinical stage IIB or IV at diagnosis, n (%)	19 (90)	15 (71)	0.237
Postoperative recurrence, n (%)	2 (10)	6 (29)	0.237
Median (range) no. of previous regimens	1 (0-5)	0 (0-7)	-
Median time (range) to drug-induced ILD, months	1.1 (0.1-6.8)	1.2 (0.1-43.4)	-
Suspected ILD-inducing drug, n			
DTX/PEM/PTX/other	11/4/3/3	-	-
GEF/ERL/AFA	14/5/2	-	-
Tumor response to suspected drug, n (%)			
Partial response	1 (5)	7 (33)	0.044
Stable disease	6 (29)	3 (14)	0.453
Progressive disease	2 (10)	2 (10)	0.999
Not evaluated	12 (56)	9 (43)	0.537
DAD pattern ILD on HRCT, n (%)	6 (29)	6 (29)	0.999
Clinical course after drug-induced ILD			
Treatment-related death	4 (19)	7 (33)	0.484
Best supportive care alone	12 (57)	8 (38)	0.354
Re-administration	5 (24)	6 (29)	0.999

AFA, Afatinib; DAD, diffuse alveolar damage; DTX, docetaxel; ERL, erlotinib; GEF, gefitinib; HRCT, high-resolution computed tomography; PEM, pemetrexed; PSL, prednisolone; PTX, paclitaxel.

from April 1, 2010 to March 31, 2017. Seventeen of 21 cases with TKI-induced ILD were included in previously published data (11). These patients were diagnosed as having NSCLC using bronchoscopy with/without percutaneous needle biopsy at our Institute and their disease was staged according to the guidelines of the Union for International Cancer Control TNM Classification of Malignant Tumors (16).

The diagnosis of drug-induced ILD was based on the following criteria: (i) a history of drug exposure with correct identification of the drug, (ii) clinical imaging or histopathological patterns of ILD consistent with earlier observations for the same drug, (iii) exclusion of other pulmonary disease, (iv) improvement following discontinuation of the suspected drug, (v) recurrence of symptoms on rechallenge [but rechallenge can be hazardous (17, 18)].

The high-resolution computed tomographic (HRCT) images of drug-induced ILD were evaluated independently by both a radiologist and a respirologist and were classified into two categories: diffuse alveolar damage (DAD) pattern and non-DAD pattern. As DAD is observed in acute interstitial pneumonia or acute exacerbation of idiopathic interstitial pneumonia, DAD pattern ILD was clinically diagnosed when patients satisfied all three of the following conditions: acute or subacute dry cough and hypoxemia; new bilateral pulmonary infiltrates, often with consolidation of the dependent lung on chest HRCT scan; and the absence of infection, heart failure or pulmonary embolism (19, 20). Non-DAD pattern ILD was diagnosed by HRCT scan and consisted of hypersensitivity pneumonitis

(bilateral ground-glass opacities with poorly defined centrilobular nodules), organizing pneumonia (consolidations with predominantly peripheral or peribronchial distributions), eosinophilic pneumonia (consolidations with peripheral or upper lobe distributions) and nonspecific interstitial pneumonia (patchy or diffuse ground-glass opacities, sometimes with traction bronchiectasis) (19).

CT-R or TKI-R was performed in 11 patients who satisfied all of the following conditions: PS score of 0 to 2 after recovery from drug-induced ILD (peripheral oxygen saturation >90% in room air, and improvement of respiratory symptoms and pulmonary infiltrates); desire to receive CT-R or TKI-R; and patients and their family recognized the risk of the recurrence of severe, occasionally fatal, ILD and gave their signed informed consent to receive CT-R or TKI-R. An oral administration of 0.5 mg/kg prednisolone was concurrently added during the re-administration (19). Any adverse events were evaluated according to the National Cancer Institute-Common Terminology Criteria for Adverse Events, version 4.0 (20). Treatment-related death was defined as death occurring within 4 weeks of the completion of treatment without clear evidence of any other cause of death or death obviously caused by treatment toxicity.

The statistical analysis was performed using the Stat View J 5.0 statistical program (SAS, Institute Inc., Berkeley, CA, USA). Differences in clinical data between two independent samples were tested using the Mann-Whitney *U*-test. The analysis of categorical data was performed using the chi-squared test or Fisher's exact probability test. Univariate analyses of clinical variables were

Table II. *Re-administration of chemotherapy (CT-R) or epidermal growth factor receptor-tyrosine kinase inhibitor (TKI-R) in patients with drug-induced interstitial lung disease (ILD).*

	Case	Age, years/ gender	LC histology	Suspected drug			Drug re-administration		Post-therapy	OS months
				Drug	Change of PS	PFS, months	Drug	Response		
Five cases with CT-R	1	64/M	SQ	DTX	3→1	2.8	VNR	PD	BSC	1.5 [†]
	2	66/M	AD	PEM*	2→1	1.4	PTX	SD/ILD	BSC	0.8 [†]
	3	60/M	SQ	DTX	2→1	1.5	PTX	PD	PMB	1.6
	4	70/M	SQ	S-1*	2→1	2.5	PTX	PR	NIV	4.8 [†]
	5	62/M	AD	PEM*	2→0	1.1	PTX	SD	BSC	2.3
Six cases with TKI-R	6	62/M	AD	GEF	2→1	3.3	GEF	SD	BSC	7.6 [†]
	7	64/M	AD	GEF	4→2	10.4	GEF	PR/ILD	AFA	15.5
	8	39/F	AD	ERL	2→1	1.6	GEF	PR	AFA	4.1 [†]
	9	74/F	AD	GEF	3→1	5.5	ERL	PR	BSC	11.9 [†]
	10	71/F	AD	GEF	2→1	2.8	ERL	PR	BSC	5.0 [†]
	11	82/M	AD	GEF	2→0	12.9	GEF	PR	BSC	12.9 [†]

AD, Adenocarcinoma; AFA, afatinib; BSC, best supportive care; DTX, docetaxel; ERL, erlotinib; PFS, progression-free survival from drug-induced ILD; GEF, gefitinib; LC, lung cancer; NIV, nivolumab; OS, overall survival from drug-induced ILD; PD, progressive disease; PEM, pemetrexed; PMB, pembrolizumab; PR, partial response; PS, performance status; PTX, nab-paclitaxel; SD, stable disease; SQ, squamous cell carcinoma; VNR, vinorelbine. *Carboplatin-doublet therapy, [†]died.

performed to identify possible risk factors associated with duration of OS. Variables with $p < 0.10$ in the log-rank tests were included in the Cox proportional-hazards model analysis. The hazard ratio (HR) and corresponding 95% confidence intervals (CIs) are presented. The progression-free survival (PFS) and OS were estimated using the Kaplan–Meier method. A two-tailed p -value of less than 0.05 was considered to indicate a statistically significant difference.

Results

Patient and disease characteristics in patients with drug-induced ILD (Table I). The median age was 70 years in patients with CT-induced ILD and 74 years in patients with TKI-induced ILD. The percentage of men, smokers or cases with squamous cell carcinoma was higher in patients with CT-induced ILD. Among patients with TKI-induced ILD, there were eight cases with L8658R in exon 21, 10 cases with deletion of exon 19 or three cases with other types of *EGFR* mutations. One case with CT-induced ILD had an *EGFR* T790M resistance mutation at diagnosis and received CT.

The median number of previous anticancer therapy was one regimen in patients with CT-induced ILD and no regimen in patients with TKI-induced ILD. The median period from the initiation of the suspected drug until the occurrence of drug-induced ILD was 1.1 and 1.2 months, respectively. The tumor response rate of the suspected drug was lower in patients with CT-induced ILD than in patients with TKI-induced ILD (5% vs. 33%, $p = 0.044$).

There was no difference in the percentage of DAD pattern ILD between patients with CT-induced ILD and patients with

TKI-induced ILD. All of the patients discontinued the suspected drug and received corticosteroid therapy at a starting dose of >10 mg/kg methylprednisolone (62% vs. 90%, $p = 0.067$) or 0.5–1.0 mg/kg prednisolone (38% vs. 10%, $p = 0.067$). Treatment-related death occurred in 19% of patients with CT-induced ILD and in 33% of patients with TKI-induced ILD (all with DAD pattern ILD).

Re-administration with CT or EGFR-TKI (Table II). With concurrent oral administration of 0.5 mg/kg prednisolone, five cases with a PS score of 0–1 after recovery from CT-induced ILD received CT-R with nab-paclitaxel ($n = 4$) or vinorelbine ($n = 1$) and six cases with a PS score of 0–2 after recovery from TKI-induced ILD received TKI-R with gefitinib ($n = 4$) or erlotinib ($n = 2$). The median PFS from the occurrence of drug-induced ILD was shorter in cases treated with CT-R than in those treated with TKI-R (2.3 vs. 3.3 months, $p = 0.012$) (Figure 1A).

One case (20%) treated with CT-R and five cases (83%) treated with TKI-R achieved a partial response ($p = 0.080$). The incidence of grade 3 or more toxicities was higher in cases treated with CT-R than in those treated with TKI-R (100% vs. 16%, $p = 0.047$). Prednisolone dosage was reduced by 5 mg every 2 weeks. One case (case 2) with CT-R exhibited grade 2 ILD on reducing dosage of prednisolone. Three cases treated with TKI-R were re-administered the suspected drug after recovery from gefitinib-induced ILD because they had already experienced a partial response to gefitinib, and one case (case 7) exhibited grade 3 ILD after discontinuation of prednisolone. The median PFS from the initiation of re-administration was

Figure 1. Progression-free survival from the occurrence of drug-induced interstitial lung disease (A) and from initiation of the re-administration (B) for patients treated with chemotherapy re-administration (CT-R) and those treated with epidermal growth factor receptor-tyrosine kinase inhibitor re-administration (TKI-R).

shorter in cases treated with CT-R than in cases treated with TKI-R (1.6 vs. 7.5 months, $p=0.018$) (Figure 1B). With regard to sequential therapy, two cases treated with CT-R received immune checkpoint inhibitor and two cases treated with TKI-R received a third EGFR-TKI.

Prognosis in patients with re-administration of CT or EGFR-TKI. Nineteen patients with CT-induced ILD and 18 patients with TKI-induced ILD died during this retrospective study. No difference in the median OS time from the occurrence of drug-induced ILD was found between patients not treated with CT-R and patients not treated with TKI-R (Figure 2A), but there was significant difference in the median OS from the occurrence of drug-induced ILD between cases treated with CT-R and those treated with TKI-R (7.3 vs. 25.4 months, $p=0.003$) (Figure 2B).

Figure 2. Overall survival from the occurrence of drug-induced interstitial lung disease for patients not treated with chemotherapy re-administration (CT-R) and those not treated with epidermal growth factor receptor-tyrosine kinase inhibitor re-administration (TKI-R) (A), and for those treated with CT-R or with TKI-R (B).

To evaluate whether drug re-administration affected the prognosis, 10 cases of treatment-related death were excluded. Among 17 patients with CT-induced ILD, the median OS from the occurrence of drug-induced ILD was 7.3 months in those treated with CT-R and 1.9 months in cases not treated with CT-R, but there was no statistically significant difference ($p=0.233$) (Figure 3A). Among 14 patients with TKI-induced ILD, there was a significant difference in OS between those treated with TKI-R and those not treated with TKI-R (25.4 vs. 3.5 months, $p=0.015$) (Figure 3B).

Four variables associated with survival following the occurrence of drug-induced ILD in the log-rank tests ($p<0.10$) were included in multivariate analysis, namely: smoking, DAD pattern ILD, the presence of active *EGFR* mutations and drug re-administration. The Cox proportional-hazards model analysis showed that treatment with TKI-R

Figure 3. Overall survival from the occurrence of drug-induced interstitial lung disease for patients treated with and without chemotherapy re-administration (CT-R) (A) and for patients with and without epidermal growth factor receptor-tyrosine kinase inhibitor re-administration (TKI-R) (B). Ten cases of treatment-related deaths were excluded.

reduced the risk of mortality (HR=0.130, 95% CI=0.027-0.613; $p=0.009$). In addition, the presence of active *EGFR* mutation (HR=0.308, 95% CI=0.090-1.059; $p=0.061$) or treatment with CT-R (HR=0.298, 95% CI=0.082-1.089; $p=0.067$) tended to reduce the risk of mortality (Table III).

Discussion

Our results showed that treatment with TKI-R improved the prognosis in patients with advanced NSCLC who had a good PS score after recovery from TKI-induced ILD, as previously reported (11). On the other hand, among patients who had recovered from CT-induced ILD, the median OS in cases treated with CT-R was longer than in cases not treated with CT-R and multivariate analysis showed that CT-R as well as TKI-R tended to reduce the risk of mortality.

It has been reported that paclitaxel or vinorelbine in combination with platinum agents are feasible and effective as CT for patients with NSCLC with ILD (22-25). In the present study, we performed CT-R with nab-paclitaxel or vinorelbine with concurrent prednisolone therapy in five cases after recovery from CT-induced ILD. The median PFS from the occurrence of drug-induced ILD (Figure 1A) and the median PFS from the initiation of re-administration (Figure 1B) was shorter than that in cases treated with TKI-R. The incidence of grade 3 or more toxicities was higher than in TKI-R cases (100% vs. 16%, $p=0.047$), although there was no difference in the incidence of the drug-induced ILD recurrence. Our results showed that CT-R was less effective and more toxic than TKI-R.

It has been reported that the median OS in Japanese patients receiving second-line therapy with nab-paclitaxel, gefitinib or erlotinib is 13.0 months (26), 26.5 months and 31.4 months (27), respectively. As our patients did not discontinue CT or EGFR-TKI because of disease progression, we speculated that patients who were able to receive drug re-administration (if there was no recurrence of drug-induced ILD) achieved the same survival as previously reported. In the present study, the median OS from the occurrence of drug-induced ILD was 7.3 months in CT-R-treated cases or 25.4 months in TKI-R-treated cases. Although the benefit of CT-R was smaller than that of TKI-R, CT-R as well as TKI-R tended to reduce the risk of mortality. If patients and their family desire to receive CT-R, recognize the risk of the recurrence of severe ILD or toxicities, and give their signed informed consent to receive CT-R, CT-R can be administered to patients with NSCLC who had a good PS score after recovery from CT-induced ILD.

Our study has certain limitations. Firstly, the sample size was small because this was a retrospective study at a single institute. Secondly, there was a potential selection bias because patients treated with CT-R were younger and had more improved PS than patients with TKI-R did. As the purpose of this retrospective study was to evaluate whether CT-R is feasible and effective in patients after recovery from drug-induced ILD, not to evaluate which re-administration was more effective in those patients, this bias did not affect our results. Our results show that patients with an improved PS after recovery from ILD have an opportunity to continue CT.

In conclusion, CT-R might be a salvage therapy in patients with advanced NSCLC who have a good PS score after recovery from ILD and desire to continue CT, although the benefit of CT-R was smaller than that of TKI-R.

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Table III. Multivariate analysis (Cox's proportional hazard model) for overall survival from the occurrence of drug-induced interstitial lung disease (ILD).

Factor		Univariate analysis*	Multivariate analysis		
		p-Value	HR	95% CI	p-Value
Age	≥71 vs.<71 Years	0.504			
Gender	Female vs. male	0.207			
Smoking	Yes vs. no	0.008	0.906	0.273-3.011	0.872
Adenocarcinoma	Yes vs. no	0.885			
DAD pattern ILD	Yes vs. no	0.011	1.696	0.754-3.813	0.201
EGFR mutation	Yes vs. no	0.002	0.308	0.090-1.059	0.061
Suspected drug	CT vs. EGFR-TKI	0.183			
Re-administration	Yes vs. no	0.004			
	No		Reference		
	CT		0.298	0.082-1.089	0.067
	EGFR-TKI		0.130	0.027-0.613	0.009

AD, Adenocarcinoma; CI, confidence interval; CT, chemotherapy; DAD, diffuse alveolar damage; EGFR-TKI, epithelial growth factor receptor-tyrosine kinase inhibitor; HR, hazard ratio; SQ, squamous cell carcinoma. *Log-rank test.

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