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Prognosis of Patients With Interstitial Lung Disease Induced by Different Pharmacological Types of Anticancer Drugs

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Abstract. *Background/Aim: The aim of this study was to evaluate the effect of drug-induced interstitial lung disease (DILD) on treatment outcomes by comparing the mortality of patients with DILD induced by different pharmacological types of anticancer drugs. Patients and Methods: Japanese patients with lung cancer who had received chemotherapy at Fujita Health University Hospital were enrolled. The primary outcome was the short-term mortality rate from the administration of chemotherapy that might have caused DILD. Results: Eleven, 16, and 20 patients with DILD were assigned to the kinase inhibitor (KI), immune-checkpoint inhibitor (ICI), and cytotoxic anticancer drug groups, respectively. The 90-day mortality rate after the DILD event in the group treated with cytotoxic anticancer drugs was significantly higher than in the KI and ICI groups. Conclusion: Patients with DILD induced by cytotoxic anticancer drugs have poorer prognoses than those with DILD induced by KIs or ICIs.*

Drug-induced interstitial lung disease (DILD) has been recognized as a common cause of discontinuation of chemotherapy, and patients with DILD have a mortality rate of approximately 30% (1, 2). In patients treated with kinase inhibitors (KIs) or immune-checkpoint inhibitors (ICIs), the rate of DILD is approximately 3% (3-7). Although the overall frequency of DILD is lower than that of other adverse reactions, the risk is higher in patients treated with KIs or ICIs than in those treated with cytotoxic anticancer drugs (8, 9). To prevent the development of DILD, discontinuation of chemotherapy (10) and initiation of corticosteroid therapy should be considered (11). However, these therapeutic interventions increase the cost of treatment and might reduce the efficacy of chemotherapy in patients with lung cancer.

Severe DILD has been reported in patients treated with KIs or ICIs (12-14). Since severe DILD is often resistant to corticosteroid therapy, accurate prediction of such DILD events is important. Male sex and a history of smoking have been reported as risk factors for DILD (15). However, limited studies have documented DILD induced by KIs or ICIs. In particular, the effect of DILD induced by these drugs on the treatment outcome in patients with lung cancer remains unclear.

The pharmacological action of KIs and ICIs differ from that of cytotoxic anticancer drugs. These differences might affect the severity of DILD. However, the frequency of DILD induced by cytotoxic anticancer drugs is lower than that induced by KIs or ICIs (8, 9). Furthermore, as far as we are aware, no study has compared the severity of DILD induced by different types of anticancer drugs. In the present study, we compared the mortality of patients with DILD induced by different types of anticancer drugs to evaluate the effect of DILD on the treatment outcome in patients with lung cancer.

Patients and Methods

Data source and study design. Japanese patients with lung cancer who had received chemotherapy at Fujita Health University Hospital from January 2017 to December 2018 were enrolled in the retrospective cohort study which has been described in a previous report (16). The follow-up period was until September 2019. All data were collected from the medical records of Fujita Health University Hospital. The exclusion criteria were patients a) Aged <20 years, b) who had received chemotherapy for cancer other than lung cancer, c) undergoing renal replacement therapy, and d) with a history of ILD. DILD was diagnosed using the following criteria (17): a)

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Key Words: Kinase inhibitor, immune-checkpoint inhibitor, cytotoxic anticancer drug, interstitial lung disease.

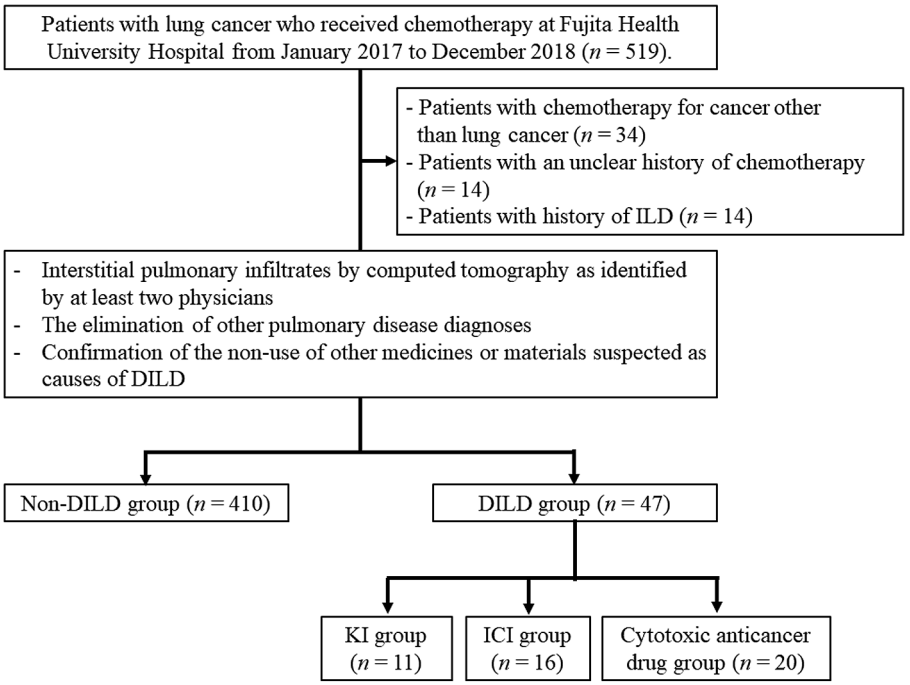

Figure 1. *Study design. DILD: Drug-induced interstitial lung disease; ICI: immune checkpoint inhibitor; KI: kinase inhibitor.*

Interstitial pulmonary infiltrates identified on computed tomography by at least two physicians, b) elimination of other disease diagnoses (*e.g.* tumor progression, pulmonary infection, and cardiovascular disease), and c) no exposure to other medicines or materials that might cause DILD. The severity of DILD was determined using the Common Terminology Criteria for Adverse Events Ver. 5.0 (18). Patients with DILD were divided into three groups according to the type of anticancer drug that might have caused DILD: DILD caused by KIs, ICIs, and cytotoxic anticancer drugs.

Outcome measures. The primary outcome was the mortality rate at 30, 60, and 90 days after the DILD event. The severity of DILD was the secondary outcome, which was evaluated by determining the time from the DILD event to the need for oxygen inhalation. Furthermore, based on previous reports that suggested the presentation of severe DILD within 3 weeks (12, 13), we measured the time from the administration of suspected drugs to the DILD event.

Statistical analyses. All data were analyzed using their mean value and range. The analysis of variance and Kruskal–Wallis tests were used for parametric and nonparametric analyses, respectively, to compare the three groups. The chi-square test was used to analyze the nominal scales. Time-to-event curves were plotted using the Kaplan–Meier method, and the groups were compared using the log-rank test. A two-sided *p*-value of less than 0.05 was considered significant in all statistical analyses, which were performed using SPSS version 22.0 (IBM, Armonk, NY, USA).

Ethics approval. This retrospective study involving human participants was in accordance with the ethical standards of the Fujita Health University Hospital ethics board (Ethics Committee approval number: HM20-364) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. An opt-out approach of informed consent was used, as approved by the Ethics Board, as it was a retrospective cohort study.

Results

Patient characteristics. The total number of patients enrolled in this study was 519. Thirty-four patients who received chemotherapy for cancer other than lung cancer and 14 patients with an unclear history of chemotherapy were excluded. To distinguish between DILD and pre-existing ILD, 14 patients with a history of ILD were also excluded. No patient was under 20 years of age or undergoing renal replacement therapy. Finally, 457 patients were included in this study. Of these, 11, 16, and 20 patients with DILD were divided into the KI, ICI, and cytotoxic anticancer drug groups, respectively (Figure 1). Drugs suspected of having caused DILD were osimertinib in five, gefitinib in two, afatinib in two, alectinib in one, and erlotinib in one in the KI group; nivolumab in nine and pembrolizumab in seven in the ICI group; and docetaxel in four, pemetrexed in three, docetaxel plus ramucirumab in three, amrubicin in two, tegafur/gimeracil/oteracil in two, irinotecan/abraxane/cisplatin plus etoposide in one, carboplatin plus gemcitabine, docetaxel plus nedaplatin, and carboplatin plus abraxane in one each in

Table I. *Baseline characteristics of study patients.*

Characteristic		Drug suspected of inducing DILD			*p*-Value
		KI (n=11)	ICI (n=16)	Cytotoxic (n=20)	
Age, years	Mean (range)	68 (48-81)	70 (42-83)	70 (58-85)	0.769
Gender, n (%)	Male	8 (72.7%)	13 (81.3%)	18 (90.0%)	0.461
	Female	3 (27.3%)	3 (18.7%)	2 (10.0%)	
History of smoking, n (%)	Previous/current	8 (72.7%)	13 (81.3%)	18 (90.0%)	0.461
	Never	3 (27.3%)	3 (18.7%)	2 (10.0%)	
	Unknown	0 (0.00%)	0 (0.00%)	0 (0.00%)	
History of radiation, n (%)	Previous	3 (27.3%)	6 (37.5%)	10 (50.0%)	0.447
	Never	8 (72.7%)	10 (62.5%)	10 (50.0%)	
Pathology, n (%)	Large-cell carcinoma	0 (0.00%)	0 (0.00%)	0 (0.00%)	0.018
	Adenocarcinoma	11 (100%)	11 (68.8%)	7 (35.0%)	
	Squamous cell carcinoma	0 (0.00%)	3 (18.8%)	6 (30.0%)	
	Small-cell lung carcinoma	0 (0.00%)	0 (0.00%)	4 (20.0%)	
	Other	0 (0.00%)	2 (12.5%)	3 (15.0%)	
Stage, n (%)	III	0 (0.00%)	0 (0.00%)	1 (5.0%)	0.240
	IV	11 (100%)	16 (100%)	19 (95.0%)	
Number of chemotherapy cycles before DILD event	Mean (range)	2.3 (1-4)	2.4 (1-5)	2.8 (1-7)	0.732

DILD: Drug-induced interstitial lung disease; ICI: immune checkpoint inhibitor; KI: kinase inhibitor.

the cytotoxic anticancer drug group. Baseline characteristics of these groups are shown in Table I. Although the pathological types of lung cancer were significantly different among the three groups (p=0.018), there were no other differences between them.

Mortality rate after the DILD event and time from the DILD event to the need for oxygen inhalation. To compare the effect of DILD induced by different pharmacological types of anticancer drugs on the prognosis of patients with lung cancer, we measured the mortality rate at 30, 60, and 90 days after the DILD event. The mortality rate within 90 days after the DILD event in the cytotoxic anticancer drugs group was 5-fold or more, higher than in the KI and ICI groups (p=0.010) (Table II).

The mean times (95% confidence interval) to the need for oxygen in the KI, ICI, and cytotoxic anticancer drug groups were 678 (83-973), 450 (280-620), and 152 (58-247) days, respectively. The KI and ICI groups showed a trend towards having a longer time from the DILD event to the need for oxygen inhalation than did the cytotoxic anticancer drug group (KI group; p=0.088, ICI group; p=0.075) (Figure 2). In addition, the number of patients with over grade 3 adverse events in the cytotoxic anticancer drug group was non-significantly higher than in the KI and ICI groups (Table III). The time from the administration of the drug to the DILD event was significantly longer in the KI group than in the cytotoxic anticancer drug group (p<0.01) (Figure 3). Furthermore, the ICI group showed a trend towards a longer time from the administration of drug to the DILD event than did the cytotoxic anticancer drug group (p=0.066) (Figure 3).

Table II. *Mortality after drug-induced interstitial lung disease event.*

Mortality, n (%)	Drug suspected of inducing DILD			*p*-Value
	KI (n=11)	ICI (n=16)	Cytotoxic (n=20)	
30-Day	1 (9.1%)	1 (6.3%)	2 (10.0%)	0.920
60-Day	1 (9.1%)	1 (6.3%)	5 (25.0%)	0.329
90-Day	2 (18.2%)	1 (6.3%)	10 (50.0%)	0.010

ICI: Immune checkpoint inhibitor; KI: kinase inhibitor.

Treatment for the DILD and chemotherapy resumption after the DILD event. To evaluate the effect of DILD on chemotherapy, we investigated the types of DILD treatments and the number of chemotherapy sessions after the DILD event. In all patients with DILD, the administration of the drug suspected as the cause of DILD was stopped, and most patients were treated with corticosteroid therapy. The number of patients treated with corticosteroid pulse therapy was non-significantly lower in the ICI group than in other groups (Table III). In the cytotoxic anticancer drug group, the number of patients with chemotherapy resumption and the number of chemotherapy sessions after the DILD event were also non-significantly lower than in the other groups (Table III).

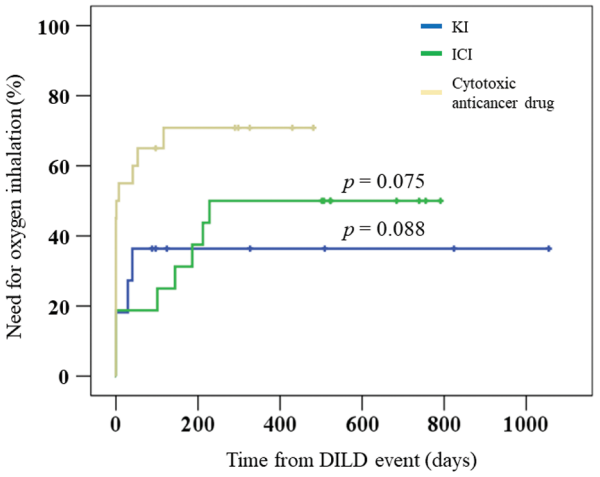

Figure 2. *Time from drug-induced interstitial lung disease (DILD) event to the need for oxygen inhalation. The mean times (95% confidence intervaI) to the need for oxygen in the kinase inhibitor (KI), immune checkpoint inhibitor (ICI), and cytotoxic anticancer drug groups were 678 (83-973), 450 (280-620), and 152 (58-247) days, respectively.*

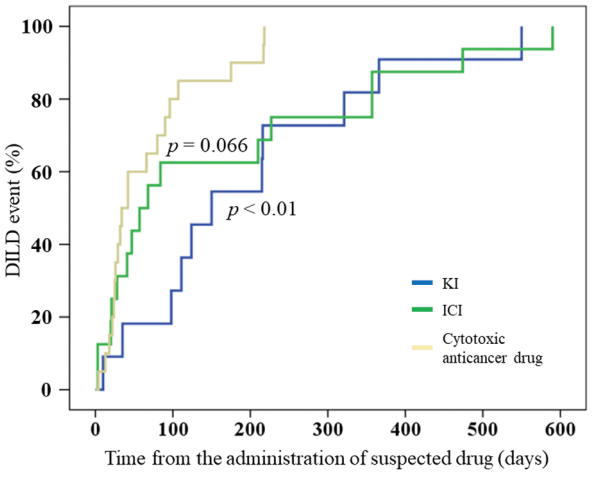

Figure 3. *Time from the administration of suspected drugs to drug-induced interstitial lung disease (DILD) event. The mean times (95% confidence intervaI) to DILD event for the kinase inhibitor (KI), immune checkpoint inhibitor (ICI) and cytotoxic anticancer drugs groups were 200 (105-294), 162 (70-253), and 68 (39-97) days, respectively.*

Table III. *Severity of and treatment for drug-induced interstitial lung disease (DILD).*

	Drug suspected of inducing DILD			
Characteristic	KI (n=11)	ICI (n=16)	Cytotoxic (n=20)	*p*-Value
CTCAE grade ≥3, n (%)	4 (36.3%)	8 (50.0%)	14 (70.0%)	0.172
Treatment for DILD, n (%)				
Discontinued chemotherapy	11 (100%)	16 (100%)	20 (100%)	>0.99
Corticosteroid	9 (81.8%)	13 (81.3%)	17 (85.0%)	0.950
Corticosteroid pulse therapy	5 (45.5%)	4 (25.0%)	8 (40.0%)	0.496
Chemotherapy resumption, n (%)	6 (54.5%)	7 (43.8%)	5 (25.0%)	0.231
Mean number of chemotherapy cycles after DILD event (range)	1.0 (0-3)	0.7 (0-3)	0.6 (0-3)	0.415

CTCAE: Common Terminology Criteria for Adverse Events (18); DILD: drug-induced interstitial lung disease; ICI: immune checkpoint inhibitor; KI: kinase inhibitor.

Discussion

Patients with ICI-induced severe DILD have poor prognoses (2), and the reason for this remains unclear. In addition, most literature on KI- or ICI-induced DILD refers to case reports. To our knowledge, no study has investigated whether DILD induced by KIs or ICIs is more severe than that induced by cytotoxic anticancer drugs. Here, we focused on the differences in the pharmacological action of cytotoxic anticancer drugs. We investigated the effect of DILD induced by different types of anticancer drugs on treatment outcomes in patients with lung cancer by comparing the short-term mortality rate.

In this study, patients with DILD induced by cytotoxic anticancer drugs showed a poorer prognosis than those with DILD induced by KIs and ICIs. Since ICIs were used as second- or third-line chemotherapy for lung cancer, it is possible that the prognosis after ICI treatment was worse than that after treatment with cytotoxic anticancer drugs. However, the short-term mortality rate after the DILD event in the ICIs group was better than that in the cytotoxic anticancer drugs group. In addition, the progression of DILD in the cytotoxic anticancer drug group was more rapid than in the ICI group. Furthermore, the number of patients treated with corticosteroid pulse therapy was lower in the ICI group than in the cytotoxic anticancer drugs group. These results

suggest that DILD induced by ICIs is milder than that induced by cytotoxic anticancer drugs.

The time from the initiation of chemotherapy to the DILD event was shorter in the cytotoxic anticancer drug group than in the KI and ICI groups. Although it is recommended that patients treated with gefitinib or erlotinib be monitored for ILD symptoms for 4 weeks after chemotherapy (19), the mean time from the initiation of chemotherapy to the DILD event induced by KIs or ICIs was 5 to 6 months in the present study, while that for cytotoxic anticancer drugs was only 2 months. We found that the time to DILD after the initiation of chemotherapy varied with the type of drug used. This has implications for policy making regarding the duration of monitoring patients undergoing chemotherapy. Based on the present results, patients treated with cytotoxic anticancer drugs should be monitored for 2 months after the initiation of chemotherapy.

A limitation of this study was that the pathological characteristics of DILD were not evaluated. The difficulty in diagnosing ILD has been reported as a limitation in previous studies (20, 21). Although two physicians diagnosed DILD using computed tomography in our study, the pathological types were not determined. As our study was a retrospective cohort study, a prospective study should be conducted to overcome this limitation.

In conclusion, patients with DILD induced by cytotoxic anticancer drugs have poorer prognoses than those with DILD induced by KIs or ICIs and should be monitored for at least 2 months after the initiation of chemotherapy.

Conflicts of Interest

The Authors declare that they have no conflicts of interest.

Authors' Contributions

Kohei Iwashita, Tomohiro Mizuno, and Satomi Kumazawa designed this study. Kohei Iwashita and Satomi Kumazawa carried out the survey of electronic records. Kohei Iwashita and Tomohiro Mizuno performed the statistical analyses. Kohei Iwashita, Tomohiro Mizuno, Kazuyoshi Imaizumi, and Shigeki Yamada drafted the article. All Authors approved the final article.

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