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Preexisting Interstitial Lung Disease and Lung Injury Associated with Irinotecan in Patients with Neoplasms

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Abstract. *Background/Aim: The aim of this study was to reveal risk factors for lung injury following irinotecan administration for the treatment of neoplasms. Patients and Methods: This study included 204 patients who received irinotecan from October 2005 to November 2014 and had evaluable chest CT images before initiation of irinotecan. Results: Six (2.9%) patients developed lung injury and, of these, 2 had preexisting interstitial lung disease (pre-ILD). The frequency of lung injury in patients with pre-ILD was 11% (2 of 19) while that in patients without pre-ILD was 2.2%. Risk factor analysis for the lung injury showed pre-ILD was the most predictable factor [odds ratio (OR) 5.00, p=0.07]. Combination with other agents, origin of neoplasms (lung or not), initial dose or minimum interval were not observed to be related to risk. Conclusion: The risk of lung injury with irinotecan was high when pre-ILD was present and the risk was comparable with previously reported other agents.*

Lung injury related to anti-cancer agents is one of the most noticeable adverse events in systemic anti-cancer treatment. Kudoh *et al*. previously explored the risk factors for lung injury related to anti-cancer agents and found that preexisting interstitial lung disease (pre-ILD) before administration of anti-cancer agents increased the risk of lung injury related to both epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKI) and cytotoxic agents (1). Of note, although cytotoxic agents mostly work through the inhibition of DNA synthesis, previous studies showed pulmonary toxicity was distinctive depending on specific agents (2).

Irinotecan is a cytotoxic anti-cancer agent that potently inhibits DNA topoisomerase I. Although it is one of the most popular anti-cancer agents due to the extensive range of target neoplasms including gastric, colorectal, breast, and lung cancer, irinotecan is recognized to have high pulmonary toxicity because two phase II trials previously showed high frequency of lung injury, 8-13%, after irinotecan administration in patients with non-small cell and small cell lung cancer (3, 4). In several countries of Asia including Japan, patients with “interstitial pneumonia" have been specified to avoid irinotecan because of the anticipated high risk of lung injury. However, no study has explored the specific factors related to lung injury after irinotecan administration including radiological pretreatment.

Thus, this study aimed to reveal the factors associated with lung injury after irinotecan administration taking into consideration the radiological evaluation of chest computed tomography (CT) images before irinotecan administration.

Patients and Methods

Patient population and preexisting interstitial lung abnormality evaluation. The clinical records and radiological findings of patients who were administered irinotecan as a monotherapy or in combination with other agents for the treatment of neoplasms from October 2005 to November 2014 were retrospectively reviewed. The records of 204 patients with evaluable chest CT images taken within 12 months prior to drug administration were analyzed. Dose of irinotecan was defined as the planned dose for the chosen regimen; the dosing interval of irinotecan was defined as the shortest period between irinotecan administrations at the scheduled regimens (*i.e.*, when the regimen defined weekly administration of irinotecan for days 1, 8, 15 at a 4-week cycle, the interval was set as 1 week). Pre-

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ILD was defined as the presence of independent ground-glass opacities, reticular abnormalities, traction bronchiectasis, non-emphysematous cysts, and honeycombing (5-7). Cases were evaluated and classified as definite, possible, or not present for the presence of pre-ILD independently by 2 pulmonologists and 1 radiologist; a patient was determined to have pre-ILD when more than 1 evaluator classified the patient as definite or when more than 2 evaluators classified the patient as possible. For the cases with pre-ILD, chest CT images were scored by 2 pulmonologists and 1 radiologist for the area of the lung field occupied and usual interstitial pneumonia (UIP) compatibility of pre-ILD as reported previously (2, 5). Briefly, the area occupied was classified into 4 grades as follows: 0-10%, 10-25%, 25-40%, and >40%. The compatibility of the UIP pattern was evaluated according to the American Thoracic Society/European Respiratory Society consensus statement of 2011 (8) and ranked as definite UIP, possible UIP, and inconsistent with UIP. Radiation pneumonitis was excluded from pre-ILD. All ratings were completed independently without any preliminary knowledge regarding the patients or other doctors' decisions. Final decisions were made by a majority, and when the ratings were equally divided, the most severe rating was chosen as the final rating. The Seirei Mikatahara General Hospital ethics committee approved the current study (#15-14).

Lung injury associated with irinotecan. We defined lung injury associated with irinotecan using the following features as defined in a previous study: 1) non-segmental pulmonary ground-glass or infiltrative shadow; 2) newly emerged lesion within 30 days after the final administration of irinotecan; and 3) no indication of pulmonary infection, including purulent sputum, improvement by antibiotic treatment, and positive results for sputum and/or blood cultures (2). Patients with an abnormal shadow accompanied by relevant bronchial obstruction, apparent heart failure, or pulmonary invasion of lung cancer were excluded. Patients with lung injury who received irradiation to an area including the lungs, within 30 days before irinotecan administration were also excluded. The severity of lung injury was evaluated based on "pneumonitis" using the National Cancer Institute Common Terminology Criteria version 4.03. Specifically, the criteria were as follows: 1) grade 1, asymptomatic, clinical, or diagnostic observations only, medical intervention not indicated; 2) grade 2, symptomatic and medical intervention indicated, instrumental activities of daily living limited; 3) grade 3, severe symptoms, self-care activities of daily living limited, oxygen indicated, life-threatening respiratory compromise; 4) grade 4, urgent intervention indicated; and 5) grade 5, death.

Statistical analysis. Clinical characteristics and treatment-related factors including age, sex, pack-years, Eastern Cooperative Oncology Group Performance Status (0-1 *vs.* ≥2), primary organ of neoplasms, combination with other anti-cancer agents, planned initial dose and interval of irinotecan were reviewed and analyzed using logistic regression models. For all analyses, $p<0.05$ was defined as statistically significant. All statistical analyses were performed using JMP version 5.01a (SAS Inc., Cary, NC, USA).

Results

Patient characteristics. Patient characteristics were described in Table I. Among 204 enrolled patients, 82 had lung cancer, of which 52 were non-small cell and 30 were small cell. Colorectal cancer, gastric cancer, ovarian cancer, and cervical cancer cases were 75, 29, 8, and 3, respectively. Three cases with cancer of unknown origin and 1 each of diffuse large B cell lymphoma, peritoneal cancer, appendix cancer, and primitive neuroectodermal tumor were also treated with irinotecan. Performance status at the time of irinotecan administration was 0-1 at 95% of all enrollments; 28% of them were administered irinotecan as monotherapy and others had treatment combined with platinum agents, 5-FU, and bevacizumab. Initial doses administered for 2, 83, 41, and 71 patients were <59, 60-99, 100-149, and 150 mg/m^2, respectively. The scheduled minimum interval of irinotecan was 1, 2, and 4 weeks in 105, 98, and 1 patient, respectively. With pre-treatment chest CT evaluations, nineteen patients (9%) had pre-ILD.

Table I. *Patient characteristics*.

No. of cases	204
Age, years [median (range)]	65 (30-84)
Gender, male	133 (65)
Pack-years of smoking [median (range)] (N=198)	23 (0-140)
PS	
0	102 (50)
1	91 (45)
2	9 (4)
3	2 (1)
Primary organ of neoplasms	
Lung	82 (40)
Colorectum	75 (37)
Stomach	29 (14)
Ovary	8 (4)
Cervix	3 (1)
Others	7 (3)
Combined anti-cancer agents	
Any	146 (72)
5-FU and leucovorin	52 (25)
Cisplatin/carboplatin	49 (24)
Bevacizumab	31 (15)
Paclitaxel	29 (14)
S-1	13 (6)
Others	3 (1)
Dose of irinotecan (mg/m^2)	
<59	2 (1)
60-99	83 (41)
100-149	49 (24)
150	71 (35)
Interval of irinotecan administration	
1 week	105 (51)
2 weeks	98 (48)
4 weeks	1 (0)

Values are number (percentage) unless specified. PS: Eastern Cooperative Oncology Group performance status.

Clinical features of lung injury. Lung injury associated with irinotecan was recognized in 6 cases (2.9%). Of these, 3 had lung cancer (2 non-small cell and 1 small cell lung cancer), 2 had colorectal cancer, and 1 had gastric cancer. The

Table II. *Risk factors associated with lung injury.*

Factor	No. of patients	Lung injury cases, N (%)	Odds ratio	95%CI	*p*-Value
Age, year					
<65	99	2 (2)	Reference		
≥65	105	4 (4)	0.52	0.07 to 2.73	0.46
Gender					
Male	133	5 (4)	Reference		
Female	71	1 (1)	0.37	0.02 to 2.33	0.36
PS					
0 to 1	193	6 (3)	Reference		
2 to 3	11	0 (0)	NR	NR	0.92
Initial dose of irinotecan					
<99 mg/m^2	84	3 (4)	Reference		
≥100 mg/m^2	120	3 (3)	0.69	0.13 to 3.82	0.66
Interval of irinotecan					
1 week	105	3 (3)	Reference		
≥2 weeks	99	3 (3)	1.1	0.19 to 5.86	0.94
Combined with another agent					
No	58	1 (2)	Reference		
Yes	149	5 (3)	2.08	0.33 to 40.3	0.51
Primary organ of neoplasms					
Not lung	122	3 (2)	Reference		
Lung	82	3 (4)	1.51	0.27 to 8.31	0.62
Presence of Pre-ILD					
No	185	4 (2)	Reference		
Yes	19	2 (11)	5.00	0.66 to 27.5	0.07

CI: Confident interval; PS: Eastern Cooperative Oncology Group performance status; pre-ILD: preexisting interstitial lung disease; NR: not reached.

frequency of lung injury was 2.4%, 2.7%, and 3.4% in lung, colorectal, and gastric cancer patients, respectively. The median days from irinotecan initial treatment to the appearance of lung injury was 139 (range=41-312 days) and 5 of 6 patients developed lung injury more than 8 weeks after the first irinotecan administration. Two patients had pre-ILD; the frequency of lung injury in patients with pre-ILD was 11% while it was 2.2% in patients without pre-ILD. Treatment with corticosteroids for the lung injury was required in only one patient.

Radiological features of pre-ILD. Of 19 patients who had pre-ILD, the lung area occupied by pre-ILD was 0-10% in 10 (53%) and ≥25% in 2. For UIP probability, definite UIP, possible UIP, and inconsistent with UIP patterns were found in 2, 13, and 4 cases, respectively.

In 2 patients who had pre-ILD and developed lung injury after irinotecan administration, the area occupied by pre-ILD was 0-10% and 25-40% and the UIP probability was inconsistent with UIP and definite UIP.

Risk factor analysis. Factors associated with lung injury development after irinotecan administration were analyzed using logistic regression model (Table II). Pre-ILD was found to be the most predictable factor for lung injury although not statistically significant (odds ratio 5.00, p=0.07). Combination with other agents, primary organ of neoplasms (lung cancer or not), and dose or interval of irinotecan were not related to the risk of lung injury.

Discussion

We retrospectively investigated risk factors for lung injury associated with irinotecan among patients with neoplasms and found that pre-ILD tended to increase the risk of lung injury. Primary organ of neoplasms, combination with other agents, initial dose or minimum interval of irinotecan were not related to the risk of lung injury.

Presence of pre-ILD has been repeatedly shown to increase the risk of lung injury associated with cytotoxic agents, EGFR-TKI, or radiotherapy(1, 2, 5, 9-13). Kudoh, *et al*. reported that the risk of systemic treatment varied from 4.8 to 25.3 depending on severity of pre-ILD and extent of normal lung (1). Although the extent of normal lung was not evaluated, the risk of lung injury associated with irinotecan (5.00) seemed to be equivalent to a previous report, which was 4.80 to 6.08 in patients with mild pre-ILD (1). Furthermore, the frequency of lung injury in patients with pre-ILD in the current study was 11%, which was also similar to previous reports about docetaxel, topotecan, and

pemetrexed, which showed a frequency of 14-18%, 22%, and 12%, respectively (2, 9, 10, 13).

The severity of lung injury associated with irinotecan in this study was mild; all cases were grade 2 or less and only 1 patient required treatment with corticosteroids. A retrospective analysis of patients with colorectal cancer also showed that none of 3 lung-injury cases that developed during FOLFIRI (5-FU, leucovorin, and irinotecan), were fatal while 4 of 8 lung injury cases that developed during FOLFOX (oxaliplatin instead of irinotecan) died due to respiratory failure (14). However, according to a post-marketing surveillance on patients treated with irinotecan in Japan, 46 of 123 (37.4%) lung injury cases were severe (15) and 20 of these patients died (16). One patient in each of the two phase II trials of irinotecan monotherapy against small cell or non-small cell lung cancer also died because of severe lung injury (3, 4). Considering these, lung injury associated with irinotecan should still be a serious concern.

The median days from the first administration of irinotecan to lung injury was 139, and 17% and 33% of lung injury cases had an onset within 8 and 16 weeks, respectively. Because Kudoh, *et al*. reported that lung injury after EGFR-TKI or chemotherapy developed at 71%, 49% within the first 4 weeks and 85%, 84% within the first 8 weeks, lung injury associated with irinotecan was indicated to develop at a comparatively later term in the current study. Although median days after first administration of irinotecan to lung injury in post-marketing surveillance and self-reported cases of only severe lung injury was 54 days (17), our data indicate that increased attention should be given for the possibility of lung injury development for a period of more than 16 weeks while treating patients with irinotecan.

Although two phase II trials with lung cancer published in 1990s showed high frequency of lung injury after irinotecan administration (3, 4), patients in trials with other neoplasms at the same age did not report pulmonary toxicities (18, 19). Because irinotecan has been widely used as part of many kinds of regimens in various types of neoplasms, we explored the possibility that the primary organ of neoplasms, initial dose, or interval of irinotecan might be related to the risk of lung injury. Although weekly regimen of docetaxel administration was reported to increase the risk of lung injury compared to once in three weeks regimen (20), a clear association between these factors and lung injury development was not found.

Among the limitations of this study is the fact that more than 70% of cases were administered with irinotecan in combination with other agents, which could have affected the development of lung injury. However, combined agents were mostly low pulmonary-toxicity agents like platinums, 5-FU, and taxanes, and their influence should be limited. In a single-institutional retrospective analysis, there is considerable bias on the timing of CT examination or choice of irinotecan. The current study extracted cases with chest CT images taken within 12 months before first irinotecan administration; the chest CT images may not always show the condition of the lung at the time of the first irinotecan administration. Also, pre-ILDs in the current study occupied a comparatively smaller area of the lung field (≥10%; 47%) and were less compatible with a UIP pattern (definite UIP; 11%) than the previous report about patients treated with S-1 or docetaxel; 61% and 21%, respectively (2). Because the presence of UIP pattern and the occupying area by pre-ILD were reported to be associated with a risk of lung injury associated with cytotoxic agents (2, 21), there is a possibility that the risk might be underestimated.

In conclusion, our analysis indicated that presence of pre-ILD could increase the risk of lung injury associated with irinotecan independent of the primary organ of neoplasms, initial dose, or interval of irinotecan and the risk was similar to other previously reported cytotoxic agents. We suggest that patients should be carefully monitored for lung injury after irinotecan administration especially when pre-ILD was present in pre-treatment CT images as with other cytotoxic agents.

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