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Interstitial Lung Disease Associated With Cetuximab in Patients With Head and Neck Carcinoma: A Single-Institution Experience in Japan

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Objective: This study retrospectively analyzed the risk of interstitial lung disease with cetuximab using risk factors known to be associated with interstitial lung disease during administration of epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI).

Summary of background data: Cetuximab is an inhibitor of EGFR commonly used for advanced squamous cell carcinoma of the head and neck. Interstitial lung disease is a rare but serious adverse event of cetuximab. EGFR-TKIs are molecularly targeted drugs resembling cetuximab and show increased risk of interstitial lung disease associated with positive smoking history, age >55 years, preexisting lung disorder, and poor performance status.

Methods: Among 44 patients treated with cetuximab for advanced squamous cell carcinoma of the head and neck between March 2013 and April 2015 at Tokyo Medical University, 6 patients developed interstitial lung disease. Smoking history, age, preexisting lung disorder, and performance status were examined for these 6 patients.

Results: Two of these 6 patients died due to interstitial lung disease. All patients with interstitial lung disease were >55 years old and had a history of smoking. Three patients with interstitial lung disease had a preexisting lung disorder. Performance status was 0 in 4 patients and 1 in 2 patients.

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Conclusions: Age >55 years, smoking history, and preexisting lung disease may represent risk factors for interstitial lung disease during cetuximab treatment for head and neck carcinoma, whereas performance status may not.

Key words: Cetuximab – Head and neck carcinoma – Interstitial lung disease – Radiotherapy – Recurrent head and neck carcinoma

Cetuximab is an epidermal growth factor receptor (EGFR) inhibitor and is one of the standard pharmacotherapies for advanced squamous cell carcinoma of the head and neck (SCCHN).[1,2] In Japan, cetuximab was only approved drug for coverage by the National Health Insurance system in the treatment of advanced SCCHN in December 2012. As a result, Japan does not have sufficient experience with the use of cetuximab for patients with head and neck carcinoma. Interstitial lung disease (ILD) is a rare adverse event of cetuximab. Among patients with metastatic colorectal carcinoma treated using cetuximab in Japan, ILD occurred in 1.2%.[3] ILD is one of the worst adverse events associated with cetuximab, due to the high risk of mortality. However, the reasons for the high risk of mortality, the development and risk factors of ILD are unclear throughout the world, particularly in Japan. EGFR-tyrosine kinase inhibitors (TKIs) are classified as molecularly targeted drugs, similar to cetuximab. The risk of ILD during EGFR-TKI administration is relatively high among Japanese, reportedly in association with the risk factors of a positive smoking history, age >55 years, preexisting lung disorder, and poor performance status (PS; Table 1).[4–7] The purpose of this study was to retrospectively analyze the risk of ILD with cetuximab using risk factors associated with ILD during EGFR-TKI administration.

Materials and Methods

A total of 44 patients (43 men, 1 woman) were treated with cetuximab at Tokyo Medical University between March 2013 and April 2015. All patients provided written informed consent to undergo treatment with cetuximab. Background characteristics for the overall patient cohort are shown in Table 2. Mean age was 68 years (range, 40–85 years). PS was 0 in 35 patients, 1 in 8 patients, and 3 in 1 patient. The primary site was the hypopharynx in 19 patients, oropharynx in 13 patients, larynx in 7 patients, oral cavity in 1 patient, maxillary sinus in 1 patient, and unknown in 3 patients. Cetuximab was used concomitant with radiotherapy in 28 patients and was used for recurrent or metastatic SCCHN in 16 patients. ILD was diagnosed according to chest X-rays and computed tomography (CT). ILD developed in 6 of the 44 patients. We retrospectively analyzed these 6 patients for smoking history, age, preexisting lung disorder, and poor PS, as these are reported risk factors for ILD under EGFR-TKI treatment. Smoking history was elicited from the patient. Patients >55 years old were defined as elderly.[5] Preexisting lung disorder was diagnosed from CT results, and pulmonary emphysema was considered a positive result if moderate or severe disease according to the Goddard classification was apparent.[8] PS was assessed using Eastern Cooperative Oncology Group criteria. Severities of adverse events were assessed mainly according to the Common Terminology Criteria for Adverse Events, version 4.0.

The ethics committee at Tokyo Medical University approved this study.

Results

Background characteristics of patients

Background characteristics of the patients who developed ILD are shown in Table 3. All patients

Table 1 Risk factors for ILD

Ando *et al* (4)	Kudoh *et al* (5)	Nakagawa *et al* (6)	Akamatsu *et al* (7)
Smoking	Smoking	Smoking	Smoking
Preexisting lung disorder	Preexisting lung disorder	Preexisting lung disorder	
Male	Poor PS	Poor PS	
	Elderly	Lung infection	
	Cardiac disease		

ILD, interstitial lung disease; PS, performance status.

Table 2 Clinical characteristics of all patients treated with C-mab (n = 44)

Age (years)	Average (range)	68 (40–85)
Sex	Male	43
	Female	1
ECOG PS	0	35
	1	8
	3	1
Stage	II	2
	III	6
	IV	36
Treatment	C-mab + radiotherapy	28
	C-mab/5-FU/CBDCA	6
	C-mab/paclitaxel	10

PS, performance status.

with ILD were male, with a mean age of 68 years (range, 59–81 years). Primary sites were the hypopharynx in 2 patients, oropharynx in 2 patients, larynx in 1 patient, and unknown in 1 patient. Stage was III in 1 patient, IVA in 4 patients, and rIVC in 1 patient. The regimen including cetuximab was concomitant radiotherapy in 5 patients and paclitaxel in 1 patient. Chief complaints with ILD were fever in 5 patients, malaise in 2 patients, and dyspnea in 2 patients. The mean number of courses of cetuximab was 3.4 (range, 2–11). Two patients died due to ILD. Figure 1 shows pulmonary CT from Patient 1.

Age

All patients with ILD were elderly (*i.e.*, >55 years old; Table 4).

Smoking history

All patients with ILD had a positive history of smoking (Table 4).

Preexisting lung disorder

Three patients with ILD had previously been diagnosed with pulmonary emphysema (Table 4).

PS

PS was 0 in 4 patients and 1 in 2 patients (Table 4).

Discussion

Cetuximab is an effective agent in patients with SCCHN, but this pharmacotherapy is complicated by a number of toxicities, with cutaneous events as the most common. Other adverse events include gastrointestinal complaints, headache, and infusion reactions. ILD is rare and one of the worst adverse events during cetuximab treatment. In patients with metastatic colorectal carcinoma, drug-induced ILD was identified in 24 of 2006 cetuximab-treated patients (1.2%), and 10 of these 24 patients with ILD died.[9] In fact, 2 of the 6 patients who developed ILD in the present study died. The Bonner trial found no cases of ILD among 208 patients,[1] and the EXTREME trial encountered only 1 case among 219 patients (0.5%).[2] No incidents of ILD were seen in two phase II trials in Japan, comprising 22 and 33 patients.[10,11] Cetuximab-induced ILD is thus considered a very rare adverse event. In contrast, ILD was identified in 6 of the 44 patients (14%) in our study, representing a rate that is not particularly lower. Another case of fatal ILD after treatment with cetuximab and radiotherapy was recently reported in Japan.[12] We therefore consider that risk factors for ILD in association with cetuximab among Japanese SCCHN patients warrant attention.

All antimalignant agents carry a risk of ILD. In particular, EGFR-TKIs such as gefitinib and erlotinib are known to greatly increase the risk of ILD. Cetuximab is likewise an EGFR inhibitor, despite acting through different mechanisms to EGFR-TKIs.

Table 3 Clinical characteristics of the 6 patients who developed ILD

No.	Age	Sex	Primary site	Stage	Treatment	C-mab (course)	Initial symptom	ILD[a]	Outcome
1	67	M	HPC	IVA	BRT	4	Fever, fatigue	5	Death
2	81	M	HPC	IVA	BRT	2	Fever	3	Death
3	73	M	MPC	IVA	BRT	2	Fever, dyspnea	3	Improvement
4	71	M	LC	III	BRT	2	Fever	2	Improvement
5	59	M	MPC	IVA	BRT	7	Fever	2	Improvement
6	76	M	Unknown	RIVC	C-mab/PTX	11	Dyspnea, fatigue	2	Improvement

ILD, interstitial lung disease.

[a]ILD, CTCAG grade.

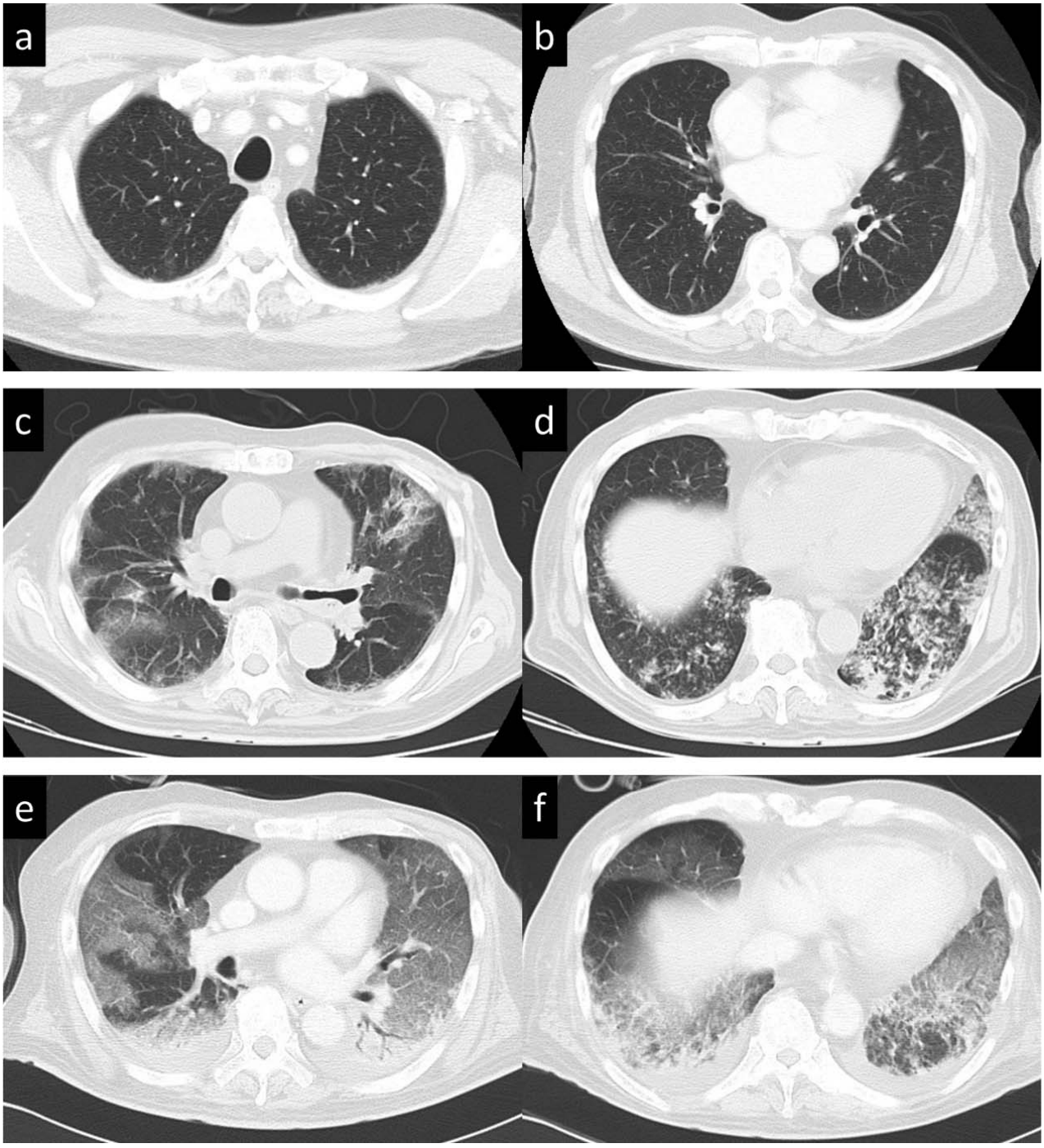

Fig. 1 Pulmonary CT representing ILD before cetuximab exposure (a, b), ground glass opacities in both upper and middle lung fields (c), consolidation in the lower left lung field (d) at the onset of ILD, extensive ground glass opacities in both lung fields, and traction bronchiectasis at 7 days after onset of ILD (e, f).

Given this similarity, we decided to examine ILD through the lens of risk factors identified for EGFR-TKI–related ILD. In our study, all 6 patients with ILD were elderly and had a history of smoking. On the other hand, only 3 of the 6 patients had a preexisting lung disorder. PS was also relatively good, including 4 patients with PS 0. These results suggest that patients older than 55 years old and

Table 4 Clinical characteristics of 6 patients who developed ILD

No.	Age > 55 years	PS[a]	BI[b]	Preexisting lung disorder	ILD[c]	Outcome
1	Yes	1	1200	No	5	Death
2	Yes	0	500	Yes	3	Death
3	Yes	1	540	Yes	3	Improvement
4	Yes	0	500	No	2	Improvement
5	Yes	0	800	No	2	Improvement
6	Yes	0	1000	Yes	2	Improvement

BI, Brinkman index; ILD, interstitial lung disease; PS, performance status.

[a]PS: ECOG performance status.

[b]BI: Brinkman index (smoking index: cigarettes/day × years).

[c]ILD: CTCAG grade.

with a history of smoking may carry an increased risk of ILD during cetuximab treatment for head and neck carcinoma. The limitation of this study was the small number of ILD patients. Given the difficulty collecting a suitable number of ILD patients from a single institute, we hope to conduct a multicenter study in the future.

Smoking and alcohol exposures represent risk factors for head and neck carcinoma, and a high proportion of patients with these pathologies are smokers and older than 55 years old. If older than 55 years and smoking history are risk factors for ILD associated with cetuximab treatment, cetuximab may not be appropriate for many patients with head and neck carcinoma. On the other hand, human papillomavirus (HPV) status is a significant risk factor for oropharyngeal carcinoma,[13,14] and HPV-positive oropharyngeal carcinoma is more frequent among relatively young people. HPV-positive oropharyngeal carcinoma patients may thus be well indicated for cetuximab, because these patients tend to be relatively young.

Five of the 6 ILD patients received cetuximab in combination with radiotherapy. Usually, the apices of lung are within the field of radiotherapy. However, ILD lesions were not in the apices in all these patients. We therefore consider that no direct causal relationship exists between ILD and radiotherapy. Evidence is therefore lacking that inclusion of the lung apices in the irradiation field causes radiation-related lung disease.

We conclude that attention should be paid to the risk of ILD with cetuximab treatment, and oropharyngeal carcinoma with HPV-positive status in relatively young nonsmokers may be a good indication for radiotherapy with concomitant cetuximab.

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