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Evaluation of the clinical characteristics of everolimus-induced lung injury and determination of associated risk factors

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ABSTRACT

Background: Everolimus (ERL), a mammalian target of rapamycin (mTOR) inhibitor, has been used for the management of several advanced cancers. ERL frequently causes lung injury, although the clinical and radiographic features have not been clarified. The aim of this study was to assess the clinical features of ERL-induced lung injury and determine the associated risk factors.

Methods: This single-center, retrospective study included 45 patients (29 men, 16 women; age, 12–78 years) who had received ERL at our hospital between August 2010 and March 2016. Drug-induced lung injury (DILI) was diagnosed using the Japanese Respiratory Society criteria. We obtained information regarding the clinical course, symptoms, clinical findings, blood test findings, and chest computed tomography findings from the patients' medical records. Risk factors for DILI onset were investigated using the Wilcoxon rank sum test.

Results: Fifteen patients (33%) were diagnosed with DILI. The median time from ERL administration to DILI onset was 64 days. High Serum Krebs von den Lungen-6 (KL-6) levels and a low estimated glomerular filtration rate (eGFR) before ERL administration were found to be significant risk factors for DILI. KL-6 and lactate dehydrogenase (LDH) were significantly elevated at the onset of DILI. All 15 patients recovered; 11 were without steroids.

Conclusions: Our results suggest that patients with high KL-6 levels and a low eGFR at baseline are at increased risk of ERL-induced lung injury. In addition, KL-6 and LDH may be useful biomarkers of ERL-induced lung injury.

1. Introduction

Drug-induced lung injury (DILI) is defined as lung injury that results from the specific use of a drug, including not only prescription drugs but also over-the-counter drugs, herbal medicines, supplements, and illegal narcotics [1]. DILI includes various phenotypes, the most common pattern being interstitial pneumonia [1]. DILI induced by anticancer drugs, including molecular-targeted drugs, has been frequently reported [2–5].

Everolimus (ERL) is an inhibitor of mammalian target of rapamycin (mTOR), which is a key modulator of ageing and age-related diseases [6] and has been used for the management of several malignancies, including advanced renal cell carcinoma (RCC), advanced breast cancer (BC), advanced pancreatic neuroendocrine tumors (PNETs), renal angiomyolipoma, and subependymal giant cell astrocytoma associated with tuberous sclerosis complex. However, it causes DILI more frequently than other anticancer drugs. In the RECORD-1 (REnal Cell cancer treatment with Oral RAD001 given Daily) trial [7], a phase III study of RCC, the incidence of ERL-induced noninfectious pneumonitis was 8.0% (22 of 272 patients), while in the BOLERO-2 (Breast cancer trials of Oral EveROlimus-2) trial [8], a phase III study of BC, the incidence was 3.2% (16 of 485 patients). Nozawa et al. reported that the incidence of ERL-induced noninfectious pneumonitis was 38% in patients with RCC, with men being at a significant risk according to their multivariate analysis [2]. Furthermore, White et al. reported that the incidence of ERL-induced noninfectious pneumonitis in patients with RCC was 13.1% (36 of 374 patients), with radiographic changes identified in 53.9% patients [3].

The clinical features of ERL-induced lung injury have not been clarified. Knowledge of these features will enable the early detection of DILI and continued administration of ERL. Moreover, determination of the risk factors for ERL-induced lung injury will aid in the appropriate selection of patients eligible to receive ERL. Therefore, we conducted the present study to evaluate the clinical features of ERL-induced lung

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List of abbreviations

ALB	albumin
BC	breast cancer
BNP	brain natriuretic peptide
Cre	creatinine
CRP	C-reactive protein
CTCAE	Common Terminology Criteria for Adverse Events
CYP3A4	cytochrome P450 3A4
DILI	drug-induced lung injury
eGFR	estimated glomerular filtration rate
ERL	everolimus
FVC	forced vital capacity
CT	computed tomography
HRCT	high-resolution computed tomography
GGO	ground-glass opacity
JRS	Japanese Respiratory Society
KL-6	Krebs von den Lungen-6
LDH	lactate dehydrogenase
mTOR	mammalian target of rapamycin
PNET	pancreatic neuroendocrine tumor
RCC	renal cell carcinoma
SD	standard deviation
TKI	tyrosine kinase inhibitor
WBC	white blood cell

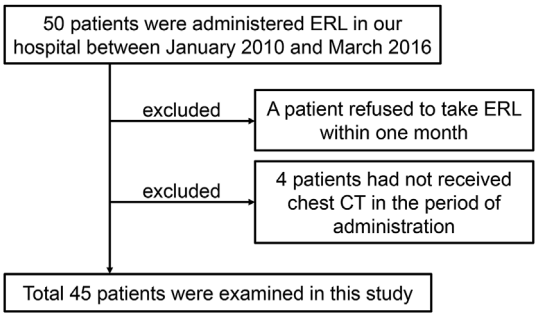

Fig. 1. Study flow chart.
Between January 2010 and March 2016, 50 patients received ERL at Chiba University Hospital. From these 50 patients, one who refused ERL after a month and four who did not undergo CT during the period of administration were excluded.

injury and determined the associated risk factors.

2. Methods

This single-center, retrospective study was performed in accordance with the amended Declaration of Helsinki. The research protocol was approved by the Human Ethics Committee of Chiba University Hospital.

2.1. Patients

Between January 2010 and March 2016, 50 patients received ERL at Chiba University Hospital. Of these patients, one who refused to continue ERL after a month and four who did not undergo chest computed tomography (CT) during the period of administration were excluded. Eventually, the clinical course, laboratory data, and radiographic findings of 45 patients (29 men, 16 women; age, 12–78 years old) were retrospectively reviewed (Fig. 1).

Table 1
Baseline characteristics of total 45 patients.

	Total (n = 45)	DILI group (n = 15)	Non-DILI group (n = 30)	p value
Mean age (years)	61	67	63	0.64*
Male/Female	29/16	9/6	19/11	1.0#
Smoker (current/former) (%)	24 (53%)	8	16	1.0#
Primary Disease				
Renal cell carcinoma (%)	26 (58%)	12	14	0.38#
Breast cancer (%)	10 (22%)	2	8	
PNET (%)	5 (11%)	1	4	
Others (%)	4 (9%)	1	3	
Lung metastasis (%)	21 (47%)	9	12	0.22#
Interstitial change (%)	4 (9%)	2	2	0.59#
Emphysema (%)	13 (28%)	5	8	0.73#
Prior therapy				
None (%)	8 (18%)	1	7	0.23#
Cytotoxic agent (%)	7 (16%)	2	5	1.0
TKI (%)	26 (58%)	11	15	0.20#
Endocrine therapy (%)	10 (22%)	2	8	0.45#
Interferon (IFN) (%)	4 (9%)	1	3	1.0#
< Laboratory findings >				
ALB (g/dL)	3.8 ± 0.6	3.7 ± 0.7	3.9 ± 0.6	0.54*
Cre (mg/dL)	0.97 ± 0.44	1.13 ± 0.48	0.90 ± 0.41	0.10*
eGFR (mL/min)	65 ± 28	52 ± 18	73 ± 30	0.007*
KL-6 (U/mL)	358 ± 173	438 ± 156	289 ± 161	0.011*
BNP (pg/mL)	57 ± 119	41 ± 32	68 ± 152	0.70*
WBC (/mm^3)	6170 ± 2330	5940 ± 2370	6280 ± 2330	0.63*
Eosinophils/WBC (%)	2.1 ± 2.0	2.7 ± 1.9	1.8 ± 2.1	0.12*
< Spirometry >				
FVC(L)	3.36 ± 0.73	3.11 ± 0.79	3.52 ± 0.67	0.14*
%FVC	94 ± 15	89 ± 15	97 ± 16	0.23*

Data are expressed as mean ± standard diviation, DILI: drug-induced lung injury, PNET: Pancreas neuroendocrine tumor, TKI: Tyrosine kinase inhibitor, ALB: albumin, Cre: creatinine, eGFR: estimated glomerular filtration rate, KL-6: Krebs von den Lungen-6, BNP: brain natriuretic peptide, WBC: white blood cell, FVC: Force Vital Capacity, *:Mann-Whitney *U* test, #: Fisher's exact test.