【 CASE REPORT 】

Eribulin-induced Interstitial Pneumonia: A Case Series and Retrospective Cohort Study

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Abstract:

Eribulin is a chemotherapeutic agent used for advanced breast cancer, but there are some reports of eribulin-induced lung injuries. Three of our patients experienced eribulin-related lung injuries. Radiology revealed organizing pneumonia in two cases and diffuse ground-glass shadows indicative of hypersensitivity pneumonitis in the third. A retrospective survey of patients treated with eribulin at our hospital identified no other cases of eribulin-induced lung injuries. Overall, drug-related lung injuries occurred in 2.8% of our eribulin-treated patients, which is similar to the rates reported for other anticancer drugs. The findings from these three cases provide guidance for the safe use of eribulin.

Key words: eribulin, interstitial pneumonia, breast cancer

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Introduction

Breast cancer is reportedly the most common cancer in women in developed countries, and eribulin is an important drug for metastatic breast cancer (1-5). A phase I clinical trial of eribulin did not report interstitial pneumonia as an adverse event (1). A phase II clinical trial of eribulin in Japan reported one case of eribulin-induced lung injury (2); its frequency was 1.2% (2). In another phase II clinical trial and phase III trial of eribulin, we confirmed that 1 patient had interstitial pneumonia as an adverse event, and its frequency was 0.1% (3, 4). In addition, according to the package insert of eribulin, the frequency of interstitial pneumonia as a side effect is 1.5% (5). This frequency is calculated on the basis of the number of patients confirmed to have interstitial pneumonia in previous clinical trials.

A postmarketing survey by a pharmaceutical company involving 961 patients who received eribulin for breast cancer between July 19, 2011, and May 14, 2012, reported 7 cases of interstitial pneumonia, and the frequency was 0.7% (6). One case resulted in a fatal outcome (6). To date, only two case reports of eribulin-induced lung disease have been pub-

lished, and both described cases of interstitial pneumonia with radiological findings consistent with organizing pneumonia (OP) (7, 8).

In our hospital we have experienced three patients with eribulin-induced lung injuries (Table 1). We herein report these cases and the results of a retrospective medical chart review conducted to determine the frequency of eribulin-induced interstitial pneumonia in our hospital.

Case Reports

Case 1

A 72-year-old Japanese woman with advanced breast cancer presented with exertional dyspnea and a productive cough 5 days after receiving an intravenous eribulin infusion (1.4 mg/m^2). On postinfusion day 7, she was febrile with an 88% arterial oxygen saturation level while breathing ambient air. Her Eastern Cooperative Oncology Group (ECOG) performance status was 0. Immunohistochemical staining revealed that she was positive for estrogen receptor and progesterone receptor and negative for human epidermal growth factor receptor type 2 (HER2). Skin metastasis and axillary/

Table 1.   Summary of Patient Characteristics with Interstitial Pneumonia during Use of Eribulin.

Case	Sex	Age years	Time of onset	Peak Krebs von den Lungen-6	Chest CT Images	Treatments
1	Female	72	Seven days after The First administration of Eribulin(1.4 mg/m^2 administered intravenously during 2-5 minutes)	2,961 IU/mL (After 2 weeks from diagnosis)	Organized pneumonia pattern	- Discontinuation of Eribulin administration Methylprednisolone 60 mg / day - Steroid was decreased gradually and stopped about one month later
2	Female	73	The eighth course administration of Eribulin (1.4 mg/m^2 administered intravenously during 2-5 minutes on days 1 and 8 of a 21-day cycle)	581 IU/mL (After 2 weeks from diagnosis)	Hypersensitivity pneumonia pattern	- Discontinuation of Eribulin administration - Careful attention
3	Female	72	Seven days after the forth course administration of Eribulin (1.4 mg/m^2 administered intravenously during 2-5 minutes on days 1 and 8 of a 21-day cycle)	1,001 IU/mL (After 3 days from diagnosis)	Organized pneumonia pattern	- Discontinuation of Eribulin administration - Methylprednisolone 1,000 mg/day - Steroid was decreased gradually four two months
A case of another report (7)	Female	52	Five days after the second course administration of Eribulin (1.4 mg/m^2 administered intravenously during 2-5 minutes on days 1 and 8 of a 21-day cycle)	3,782 IU/mL	Organized pneumonia pattern	- Discontinuation of Eribulin administration - Methylprednisolone 1 mg/kg/day
A case of another report (8)	Female	48	Six days after the first course administration of Eribulin (1.4 mg/m^2 administered intravenously during 2-5 minutes on days 1 and 8 of a 21-day cycle)	206 IU/mL	Organized pneumonia pattern	- Discontinuation of Eribulin administration - Careful attention
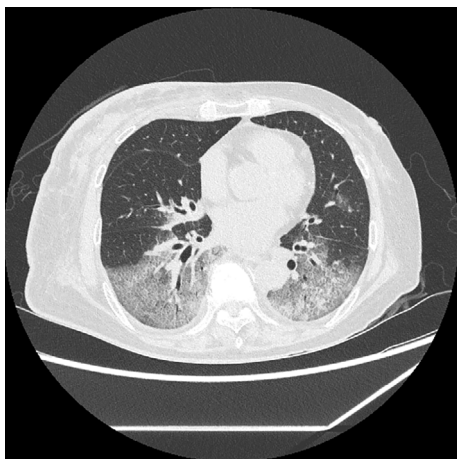
Figure 1.   Axial chest computed tomography scan of Case 1: organizing pneumonia pattern.

mediastinum/hilar lymph node metastasis were observed. No drugs other than eribulin had been recently administered. As treatment for breast cancer, hormone therapy and chemotherapy with anthracycline and taxane, including anaztorozole, tamoxifen, medroxyprogesterone, fulvestrant, capecitabine, doxorubicin, cyclophosphamide, and paclitaxel, had been administered.

One month before eribulin infusion, irradiation of the right breast skin metastasis was performed. Auscultation revealed fine crackles in her bibasilar lung fields. No findings such as edema or jugular vein distention were noted. Laboratory tests showed a white blood cell count of 2,600 μL^{-1}, which is consistent with leukopenia; also noted were a lactate dehydrogenase level of 372 U/L, serum plasma N-

terminal pro-B-type natriuremic peptide level of 390.3 ng/L, and a C-reactive protein level of 20.4 mg/dL. Chest radiography revealed ground-glass shadows in both lung fields. Chest high-resolution computed tomography (CT) revealed consolidation with ground-glass shadows (i.e., an OP pattern) on the dorsal sides of both lungs (Fig. 1).

These findings led us to suspect that she had eribulin-induced lung injuries rather than infectious pneumonia or heart failure, so we discontinued eribulin therapy and administered oxygen therapy and methylprednisolone at 60 mg/day. The lesions in both lungs were ameliorated by the 5 th day of treatment, and oxygen therapy became unnecessary on the 6th day of treatment. On the 11th day of treatment, the methylprednisolone dosage was reduced to 40 mg/day, and the patient was discharged. Her methylprednisolone dosage was gradually tapered off over the following month. In addition, eribulin was not readministered. A drug-induced lymphocyte stimulation test for eribulin-induced effects in peripheral blood returned negative results. We did not plan to perform bronchoscopy because her respiratory condition had not been stable initially.

Case 2

A 73-year-old Japanese woman diagnosed with advanced breast cancer received an initial eribulin dose (1.4 mg/m^2), and 24 weeks later, chest CT revealed diffuse ground-glass shadows [i.e., a hypersensitivity pneumonitis (HP) pattern] on the dorsal sides of both lungs (Fig. 2). Her ECOG performance status was 0. Immunohistochemical staining revealed that she was positive for the estrogen receptor and progesterone receptor and negative for HER2. Metastatic lesions were found in the skin, axillary lymph node, and liver.
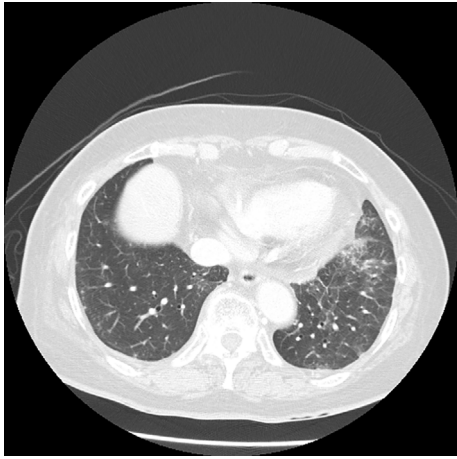
Figure 2. Axial chest computed tomography scan of Case 2: hypersensitivity pneumonitis pattern.
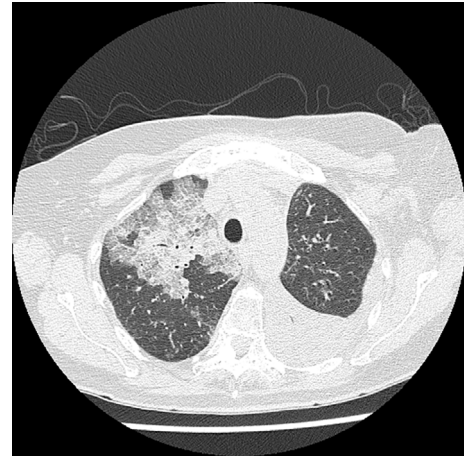
Figure 3. Axial chest computed tomography scan of Case 3: organizing pneumonia pattern.

No medications other than eribulin had been recently administered. She had not previously received radiation therapy. Hormone therapy and chemotherapy with exemestane, anaztorozole, tamoxifen, toremifene, letrozole, medroxyprogesterone, fulvestrant, capecitabine, and paclitaxel had been administered for prior treatment of breast cancer. Her general condition was stable, and no signs of infection, renal failure, or heart failure were observed. Auscultation revealed fine crackles in her bibasilar lung fields. There were no congestive findings such as edema. Laboratory tests did not include evaluation of serum plasma N-terminal pro- B-type natriuremic peptide levels. We therefore suspected that she had eribulin-induced lung injuries.

Eribulin treatment was discontinued, and the diffuse ground-glass shadows disappeared within a month. Bronchoscopy and a drug-induced lymphocyte stimulation test for eribulin-induced effects in peripheral blood were not performed because we considered the lung injury likely to improve with only careful observation.

Case 3

A 72-year-old Japanese woman with advanced breast cancer presented with exertional dyspnea and a productive cough 7 days after receiving eribulin (1.4 mg/m^2). Chest CT revealed consolidation with ground-glass shadows (i.e., an OP pattern) on the right side of the lung (Fig. 3). Her ECOG performance status was 0. Immunohistochemical staining revealed that she was positive for the estrogen receptor and progesterone receptor and negative for HER2. Metastatic lesions were found in the bone, lung, left chest wall, axillary/mediastinum lymph node, and pleural effusion. No new drugs likely to cause drug-induced lung injury except for eribulin had been administered. Prior treatment for breast cancer involved hormone therapy and chemotherapy with letrozole, paclitaxel, tamoxifen, fulvestrant, doxorubicin, cyclophosphamide, and capecitabine. Auscultation revealed fine crackles in her right lung fields. She had not previously received radiation therapy. No findings such as

edema or jugular vein distention were noted. The serum plasma N-terminal pro-B-type natriuremic peptide levels was not evaluated.

Based on the diagnosis of eribulin-induced pneumonia, we discontinued eribulin therapy and initiated oxygen therapy and steroid pulse therapy. Eleven days later, she was discharged with prednisolone at 30 mg/day. Considering her unstable respiratory condition, we did not perform bronchoscopy or a drug-induced lymphocyte stimulation test.

Frequency of eribulin-induced lung injuries

To determine the frequency of eribulin-induced lung injuries at our hospital, we conducted a retrospective chart review. The subjects were 121 patients who received eribulin for breast cancer at St. Luke's International Hospital between October 3, 2016, and May 29, 2018. We found no cases of eribulin-induced lung injuries apart from the three aforementioned cases. Of the 121 cases, 13 were excluded due to missing data. Table 2 shows the characteristics of the 108 remaining patients. The incidence rate of eribulin-induced interstitial pneumonia at our hospital was 2.8%. Because all 3 cases of eribulin-induced interstitial pneumonia developed at ≥70 years of age, we performed further analyses to compare the background characteristics between patients ≥70 years old and those <70 years old. Differences between the two age groups were assessed by Fisher's exact test for categorical variables and a t-test for continuous variables. All tests for significance were 2-tailed, with an α-value of 0.05. The R-3.5.2 software program was used for this statistical analysis. As shown in Table 3, the only statistically significant difference between the two age groups was in the development of eribulin-induced interstitial lung disease.

Discussion

Three of our patients experienced interstitial pneumonia that we suspected was caused by eribulin. These patients

Table 2.   Patient Demographics and Baseline Characteristics (Eligible Population: N=108).

Age, median (range), years	52.0 (27.0-84.0)
Time since original diagnosis, median (range), years	4.0 (0.2-22.6)
ECOG performance status, n (%)	
0	68 (70.0%)
1	32 (29.6%)
2	6 (5.6%)
3	2 (1.9%)
4	0 (0%)
ER and/or PgR positive, n (%)	78 (72.2%)
HER2/neu positive (combined FISH and IHC tests), n (%)	21 (19.4%)
Triple-negative (HER2/neu, ER, PgR), n (%)	25 (23.2%)
No. of organs involved, n (%)	
1	10 (9.3%)
2	35 (32.1%)
3	30 (27.8%)
4	18 (16.7%)
5	11 (10.2%)
6	3 (2.8%)
7	1 (0.9%)
Most common metastatic sites, n (%)	
Lymph nodes	76 (70.4%)
Bone	66 (61.1%)
Liver	65 (60.2%)
Lung	47 (43.5%)
Others	46 (42.6%)
No. of prior anti-cancer drug regimens, n (%)	
1	4 (3.7%)
2	16 (14.8%)
3	14 (13.0%)
4	14 (13.0%)
5	14 (13.0%)
6	19 (17.6%)
≥7	27 (25.0%)
Median (range)	5 (1-14)
Prior anti-cancer drug agent, n (%)	
Anthracycline	89 (82.4%)
Taxane	99 (91.7%)
Capecitabine	41 (38.0%)
Vinorelbine	16 (14.8%)
Tegafur/gimeracil/oteracil potassium	10 (9.3%)
Gemcitabine	13 (12.0%)
Hormonal drugs	74 (68.5%)
Molecular targeted drugs	18 (16.7%)
Others	93 (86.1%)
Prior surgery, n (%)	83 (76.9%)
Prior radiotherapy, n (%)	71 (65.7%)
Eriblin course	
1	14 (13.0%)
2	13 (12.0%)
3	14 (13.0%)
4	13 (12.0%)
5	4 (3.7%)
≥6	50 (46.3%)
Median (range)	5.0 (1.0-65.0)
Smoking History	
Never	93 (86.1%)
Former	14 (13.0%)
Current	1 (0.9%)
Lung Disease	
None	83 (76.9%)
Emphysema	4 (3.7%)
Chronic bronchitis	3 (2.8%)
Interstitial pneumonia	18 (16.7%)

ECOG: Eastern Cooperative Oncology Group, ER: oestrogen receptor, FISH: fluorescence in situ hybridisation, HER2/neu: human epidermal growth factor receptor 2, IHC: immunohistochemistry, PgR: progesterone receptor

had no known lung disorders before the administration of eribulin, and they were not taking any other drugs prone to cause interstitial pneumonia. We did not observe any findings suggestive of infectious pneumonia, and culture tests of sputum and blood revealed no pathogenic bacteria. Two of these patients had CT findings that were very similar to those obtained in previously reported cases of eribulin-induced interstitial pneumonia, and these two patients responded well to steroid treatment, as did the patients in past case reports. The other patient had radiological findings indicative of HP, and her condition improved after eribulin discontinuation. Taken together, these findings indicate that all three of these patients developed interstitial pneumonia due to eribulin.

Only two cases of eribulin-induced pulmonary injuries have been previously reported, and both of those cases featured radiological evidence of interstitial pneumonia with an OP pattern. Two of our patients had similar CT findings after receiving eribulin. We therefore speculate that an OP pattern of pulmonary damage is a characteristic of eribulin-induced interstitial pneumonia.

The HP pattern is common in various forms of drug-induced interstitial pneumonia, such as gemcitabine-induced pulmonary toxicity (9). However, to our knowledge, this is the first report of eribulin-induced interstitial pneumonia with radiological evidence of an HP pattern.

Among the three cases reported this time, in one case, the drug lymphocyte stimulation test (DLST) was performed, but the result was negative. The rate of positive results on the DLST for anticancer drugs has been reported to be 33.3% in the literature (10). Therefore, even though the DLST result was negative, it cannot be said that eribulin does not cause interstitial pneumonia.

In our hospital, the incidence rate of eribulin-induced interstitial pneumonia was 2.8%. This is consistent with the literature concerning other anticancer drugs, for which the incidence rates for drug-induced pulmonary injuries range from 0.5% to 5% (11-13).

However, given that we encountered only three cases of eribulin-induced interstitial pneumonia, it might not be statistically appropriate to compare the characteristics between the patients with eribulin-induced interstitial pneumonia and those without eribulin-induced pulmonary injury. Instead, based on the finding that all patients with eribulin-induced interstitial pneumonia were ≥70 years old, we compared the patients ≥70 years old with those <70 years old in order to explore the risk of drug-associated pulmonary injury. As a result, the only significant difference between the two age groups was in the development of eribulin-induced interstitial pneumonia. Although we were unable to statistically adjust for other possible confounders because of the limited number of event cases, an advanced age may be associated with eribulin-induced interstitial pneumonia.

The characteristics of the present patients were not significantly different from those of patients in a previous study (2). The number of regimens tended to be higher than

Table 3. Patient Group Comparison (Younger than 70 Years vs. 70 Years Old and Older than 70 Years).

	Younger than 70 years (n=92)	70 years old and older than 70 years old (n=16)	p value
ECOG performance status, median (range)	0 (0-3)	0 (0-3)	0.422
Patients with lung metastasis, n (%)	41 (44.6%)	6 (37.5%)	0.786
No. of prior anti-cancer drug regimens, median (range)	5 (1-14)	4 (1-9)	0.755
Prior radiotherapy, n (%)	63 (68.5%)	8 (50.0%)	0.164
Former+current smoker, n (%)	14 (15.2%)	1 (6.3%)	0.462
Background interstitial pneumonia, n (%)	15 (16.3%)	3 (18.8%)	0.728
Eribulin-induced interstitial pneumonia, n (%)	0 (0%)	3 (18.8%)	0.003

ECOG: Eastern Cooperative Oncology Group

that reported in previous studies, probably because the treatment options for advanced breast cancer have increased over the past decade. The incidence rate of eribulin-induced interstitial pneumonia in our hospital tends to be higher than that reported in a prior phase II trial (2). Although no study has reported on the relationship between the incidence of drug-induced interstitial pneumonia and the number of regimens, it is likely that the increase in the number of regimens contributed to the high incidence rate in our hospital.

Breast cancer is the most common cancer in women and is a major cause of cancer deaths (14). Eribulin is an important treatment for advanced breast cancer. Recognition of eribulin-induced lung injuries might improve the safety of women undergoing treatment for breast cancer.

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