

Radiation Pneumonitis in Patients with Non–Small-Cell Lung Cancer Treated with Erlotinib Concurrent with Thoracic Radiotherapy

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Introduction: The aim of this study was to investigate the incidence of radiation pneumonitis in patients with non–small-cell lung cancer treated with concurrent thoracic radiotherapy and erlotinib.

Methods: Patients with inoperable stages IIIA to IV non–small-cell lung cancer who were treated with concurrent thoracic radiotherapy and erlotinib were analyzed. The incidence of radiation pneumonitis was evaluated using the Common Toxicity Criteria (CTC) 3.0 Grading System. The development of grade 2 or higher radiation pneumonitis was the study end point.

Results: Among the 24 patients analyzed, there were nine developed radiation pneumonitis of grade 2 or higher (37.5%), including four cases of grade 2 radiation pneumonitis (16.7%), two of grade 3 radiation pneumonitis (8.3%), and three of grade 5 radiation pneumonitis (12.5%). Three patients developed fatal pneumonia and died of bilateral lung radiation pneumonitis.

Conclusions: Radiation pneumonitis should be considered in patients treated with concurrent thoracic radiotherapy and erlotinib.

Key Words: Erlotinib, Thoracic radiotherapy, Radiation pneumonitis, NSCLC.

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Erlotinib has achieved promising therapeutic efficacy in the treatment of non–small-cell lung cancer.^{1–3} Thoracic radiotherapy is another important therapeutic approach for this cancer. Nevertheless, concurrent thoracic radiotherapy and erlotinib have been investigated in a limited number of studies.^{4–6} In this study, we summarized the clinical data from

patients with stages III to IV non–small-cell lung cancer treated with concurrent thoracic radiotherapy and erlotinib and analyzed the incidence of radiation pneumonitis to provide guidelines for the treatment of these patients.

MATERIALS AND METHODS

Clinical Data

We collected the medical records of patients with stages III to IV non–small-cell lung cancer who received concurrent thoracic radiotherapy and erlotinib between September 2009 and June 2012 (ClinicalTrials.gov Identifier: NCT00973310). The inclusion criteria were as follows: (1) patients with stages III to IV non–small-cell lung cancer and (2) patients receiving concurrent thoracic radiotherapy and erlotinib. The exclusion criteria were as follows: (1) patients with non–small-cell lung cancer after receiving surgical intervention; (2) patients receiving re-irradiation therapy; and (3) patients with a history of interstitial lung disease. The detailed clinical data of the patients are shown in Table 1. This study was conducted in accordance with the amended Declaration of Helsinki and was conducted under the review, approval, and supervision of Tianjin Cancer Hospital. All the enrolled patients met the ethical requirements.

Therapeutic Approach

All patients underwent a computed topography scan for positioning, and a precise or pinnacle planning system was applied to complete the intensity-modulated radiotherapy. The gross tumor volume was contoured during quiet/normal breathing at end-inhale and end-exhale phases. The clinical target volume (CTV) was defined as subclinical (microscopic) disease. Internal target volume was determined from 4-dimensional computed tomography (4DCT) images. The planning tumor volume (PTV) was expanded 0.5 cm from the internal target volume. The lung organs at risk (OAR) was defined as the whole lung volume with the exception of the gross tumor volume. The fractionated dose was 1.8 to 2.1 Gy/f (median dose, 2 Gy). The dose for thoracic radiotherapy was 46 to 66 Gy (the dose was prescribed according to the PTV) depending on the treatment regimen for each patient (some patients with stages IIIB–IV non–small-cell lung cancer received palliative therapy). The treatment plan was evaluated using dose–volume histograms. The dosimetric parameters, including

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TABLE 1. Patient Characteristics and Treatment Modalities

Factors	Value
Sex	
Male	9 (38%)
Female	15 (62%)
Age	
Median	64
Range	33–85
Location	
Upper lobe	14 (58%)
Middle and lower lobe	10 (42%)
Clinical stage	
IIIA	11 (46%)
IIIB	7 (29%)
IV	6 (25%)
ECOG PS	
0	6 (25%)
1	18 (75%)
FVC	
Median	2.46
Range	1.4–4.2
FVC1	
Median	1.90
Range	0.9–3.2
DLco	
Median	2.05
Range	1.2–4.7
Pathology	
Squamous	5 (21%)
Adenocarcinoma	17 (71%)
Adenosquamous carcinoma	1 (4%)
Sarcomatoid carcinoma	1 (4%)
Radiotherapy dose (Gy)	
Median	57
Range	46–66
Dose per fraction (Gy)	
Median	2
Range	1.8–2.1
GTV size (ml)	
Median	35.50
Range	8.6–454.4
PTV size (ml)	
Median	279.70
Range	32.9–794.1
Neoadjuvant chemotherapy	
Yes ^a	13 (54%)
No	11 (46%)
Adjuvant chemotherapy	
Yes ^a	12 (50%)
No	12 (50%)
Taking time of erlotinib concurrent with RT (days)	
Median	41.5
Range	30–45

(Continued)

TABLE 1. Continued

Factors	Value
Total taking time of erlotinib (mo)	
Median	3.2
Range	1.2–27

^aThe most frequently used regimen for chemotherapy was cisplatin-based doublet. DLco, carbon monoxide diffusing capacity; ECOG PS, Eastern Cooperative Oncology Group performance status; FVC, forced vital capacity; GTV, gross tumor volume; RT, radiotherapy.

V5, V10, V15, V20, V30, and mean lung dose (MLD), were recorded. Patients were treated by fixed-gantry intensity-modulated radiotherapy. Erlotinib was administered orally at 150 mg/d from the first day to at least the end of radiotherapy (Table 1).

Evaluation of Radiation Pneumonitis

Patients presenting with symptoms of radiation pneumonitis were evaluated promptly. The follow-up assessment of pulmonary function was conducted on the third week of the radiotherapy course and 1 and 3 months after the completion of radiotherapy. The follow-up interval was determined by the presence of radiation pneumonitis and subsequently by the disease condition. Nevertheless, follow-up evaluations were performed every 3 months (or more often if recommended by the treating physician) for the first year after the radiotherapy course and at the discretion of the treating physician thereafter. A chest radiograph or computed topography scan was performed to evaluate the patients' lung conditions. CTC 3.0 was used as a reference to evaluate radiation pneumonitis.⁷ Radiation pneumonitis of grade 2 or above was the primary end point of the study. Treatment for radiation pneumonitis was aimed at decreasing the inflammation. Steroids, such as methylprednisolone, were often administered at 40 to 80 mg once or twice daily until the inflammation subsided and then slowly decreased over time.

RESULTS

The Incidence of Radiation Pneumonitis

A total of 24 patients were included in the study with a median follow-up duration of 31.5 months (range, 7–48 mo). Among these patients, nine (37.5%) had grade 2 or higher radiation pneumonitis, including four (16.7%) with grade 2 radiation pneumonitis, two (8.3%) with grade 3 radiation pneumonitis, and three (12.5%) with grade 5 radiation pneumonitis.

Clinical Factors and Lung Dosimetric Parameters in the Three Cases with Grade 5 Toxicity

Among the patients analyzed, three died from grade 5 radiation pneumonitis. The basic information on these patients including lung dosimetric parameters, erlotinib treatment, and occurrence and development of radiation pneumonitis was summarized to provide a reference (Table 2). We emphasized that the three pneumonitis fatalities had planning characteristics that were acceptable, indicating that the risk of pneumonitis should

TABLE 2. Characteristics of the Three Died Cases

Factors	Case 1	Case 2	Case 3
Sex	Male	Male	Male
Age (yr)	74	70	65
Pre-RT FVC	2.04	3.78	1.74
Pre-RT FEV1	1.71	3.1	1.41
Pre-RT DLco	3.7	3.27	1.96
Whole lung volume (ml)	3771.4	3369.1	4120
RT dose/fraction	58.8 Gy/28 f	60 Gy/30 f	56 Gy/23 f (unfinished)
GTV size (ml)	26.5	102	111.6
PTV size (ml)	438.9	397.2	794.1
Taking time of erlotinib concurrent with radiotherapy (days)	38	42	32
Total taking time of erlotinib (days)	60	46	32
With vs. without neoadjuvant chemotherapy	No	No	Yes
With vs. without adjuvant chemotherapy	No	No	No
MLD (cGy)	1209	1446	1453
V5 (%)	55	47	67
V10 (%)	40	42	44
V15 (%)	33	23	32
V20 (%)	26	20	26
V30 (%)	14	18	17
Occurrence time of radiation pneumonitis	3 weeks after radiotherapy (21 days)	2 days after the radiotherapy	During the radiotherapy
Bilateral or unilateral lung of radiation pneumonitis	Bilateral	Bilateral	Bilateral
Time of onset of symptoms to death	3 weeks (23 days)	1 week (7 days)	6 weeks

RT, radiotherapy; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 second; GTV, gross tumor volume.

have been low. In addition, it was suggested that erlotinib may have contributed to the patients' risk of radiation pneumonitis.

Imaging Characteristics of the Three Fatalities

As shown in Figure 1, severe radiation pneumonitis and interstitial lung changes were observed in three patients. The images of case 1 showed that both lungs had diffuse infiltration, which was more obvious in the right lung. The images of case 2 showed a poor response of the lesion to treatment, despite a decrease in bilateral lung transparency and extensive infiltration. Considering the treatment history, this patient showed typical radiation pneumonitis. In the third patient, the lesion showed obvious improvement, and widespread patchy infiltration of the lung was observed bilaterally. Furthermore, the infiltration correlated with the radiation fields. In addition, interstitial lung changes were obvious after the treatment (Fig. 1). Although all three cases were treated with methylprednisolone, the pneumonitis could not be reversed.

DISCUSSION

The preliminary results of the present study indicate that the potential development of radiation pneumonitis should be considered in patients treated with concurrent thoracic radiotherapy and erlotinib.

The combined effect of radiation and erlotinib on the pulmonary interstitium was considered to be the cause of radiation pneumonitis. Radiation pneumonitis was caused by radiation damage to type II pneumocytes and the alveolar septum.

The radiation also caused swelling of the capillary endothelium, interstitial congestion, and alveolar edema, thereby resulting in the infiltration of inflammatory cells, desquamation of the alveolar epithelial lining, and protein substance exudation caused by interstitial inflammation of the lung.⁸⁻¹⁰ Several studies have reported that erlotinib has adverse effects on the pulmonary interstitium.^{11,12} Although the underlying mechanism has not yet been fully elucidated and further studies are required, both erlotinib and radiation can damage the pulmonary interstitium. Concurrent therapy might result in a synergistic effect of radiation and erlotinib, which further increases the risk of radiation pneumonitis.

Some previous study showed that the incidence of radiation pneumonitis is low in patients receiving combination treatment with erlotinib and thoracic radiotherapy.¹³ Nevertheless, this may be related to the smaller lung irradiation volume and lower lung radiation dose. Several other studies^{14,15} reported high radiation pneumonitis rates in patients treated with the combination of erlotinib and radiation, but all the studies had small sample sizes, and further reports with a larger number of patients are needed. In this study, we not only analyzed the incidence rate of radiation pneumonitis but also focused on the fatalities. The results provide useful information for physicians and physicists.

In summary, we conducted a valuable investigation of radiation pneumonitis in the treatment of concurrent erlotinib and thoracic radiotherapy. Our preliminary results indicate that patients treated with concurrent thoracic radiotherapy and erlotinib should be carefully monitored.

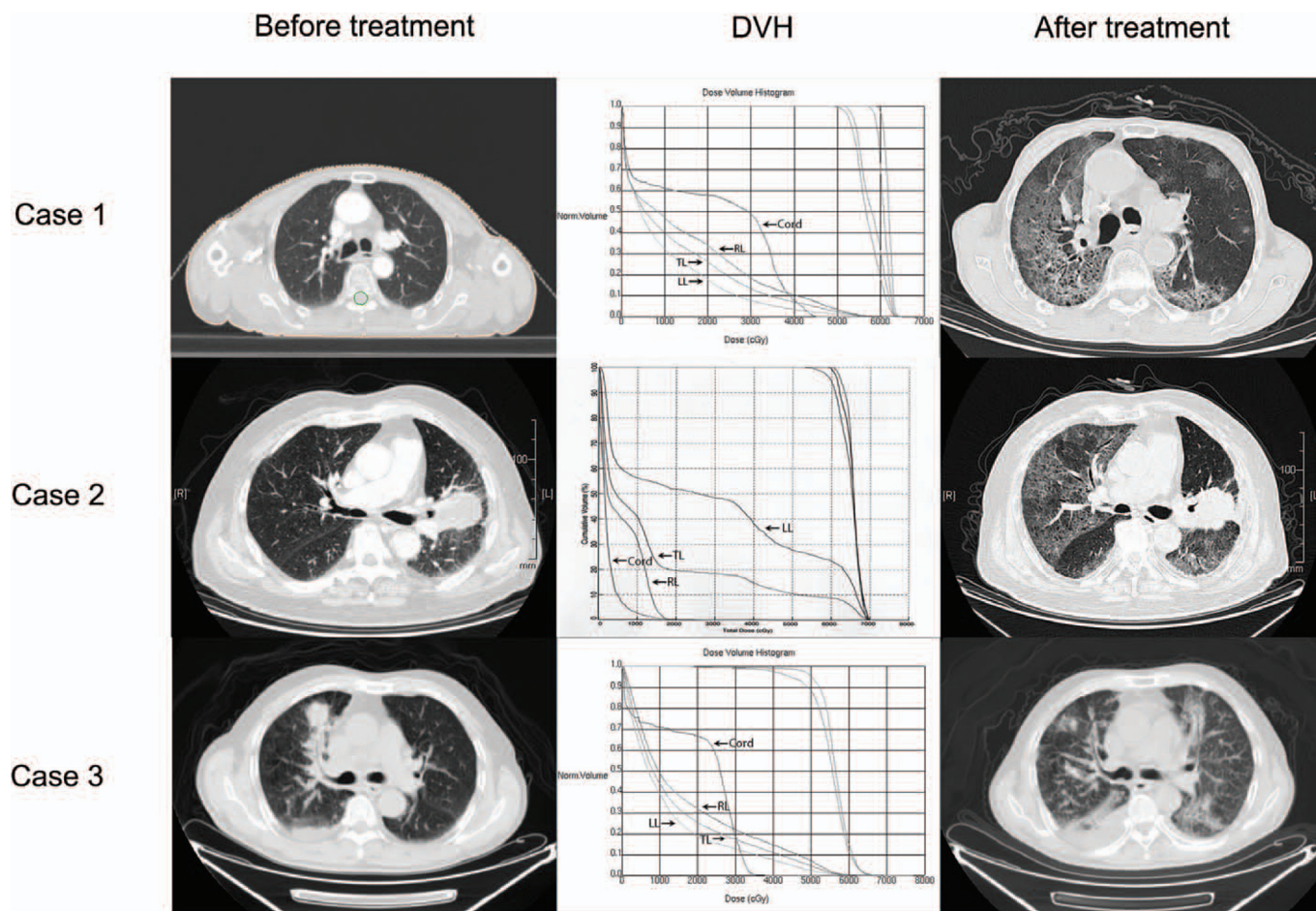


FIGURE 1. The images and DVHs of the three cases of grade 5 radiation pneumonitis. LL, left lung; RL, right lung; TL, total lung; DVHs, dose-volume histograms.

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