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.

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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

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

[a]The 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

