Severe Interstitial Lung Disease Associated with Amrubicin Treatment

Kiyotaka Yoh, MD, Hirotsugu Kenmotsu, MD, Yoko Yamaguchi, MD, Kaoru Kubota, MD, Hironobu Ohmatsu, MD, Koichi Goto, MD, Seiji Niho, MD, Yuichiro Ohe, MD, Nagahiro Saijo, MD, and Yutaka Nishiwaki, MD

Background: Amrubicin is a novel anthracycline agent that is well known to exert significant activity against small cell lung cancer (SCLC), but the adverse pulmonary effects of amrubicin are less well known. We investigated the incidence of acute interstitial lung disease (ILD) in SCLC patients who had been treated with amrubicin.

Methods: Medical records were used to retrospectively investigate a total of 100 cases of SCLC patients treated with single-agent amrubicin therapy at the National Cancer Center Hospital East between June 2003 and March 2008. The patients' radiographic records and clinical data were reviewed to identify patients who had developed acute ILD after being treated with amrubicin.

Results: After receiving amrubicin, seven of the 100 SCLC patients subsequently developed pulmonary infiltrates, and they were identified as cases of acute ILD associated with amrubicin. Of the seven patients who developed ILD, six were treated with corticosteroids, and the ILD improved in three of them, but the other three patients died of respiratory failure. The incidence of ILD was 33% (4/12) among the patients with pre-existing pulmonary fibrosis (PF) and 3% (3/88) among the patients without PF, and the difference between the two groups was statistically significant ($P = 0.0036$).

Conclusions: The results of this study indicated that amrubicin may cause severe ILD and that pre-existing PF was associated with a higher rate of ILD among SCLC patients treated with amrubicin. We recommend not administering amrubicin in the treatment of SCLC patients with pre-existing PF.

Key Words: Amrubicin, Interstitial lung disease, Toxicity, Small cell lung cancer, Chemotherapy.

(*J Thorac Oncol.* 2010;5: 1435–1438)

Amrubicin is a novel, totally synthetic 9-aminoanthracycline that is converted to an active metabolite, amrubicinol, as a result of reduction of its C-13 ketone group to a hydroxy group. Despite the similarity between the chemical structure of amrubicin and doxorubicin, amrubicin has a different mode of action. Amrubicin and amrubicinol are DNA topoisomerase II inhibitors, which exert their cytotoxic effects by stabilizing a topoisomerase II-mediated cleavable complex, and they are approximately 1/10 weaker than doxorubicin as a DNA intercalator. The in vitro cytotoxic activity of amrubicinol is 18 to 220 times more potent than that of its parent compound, amrubicin.[1,2] An in vivo comparison with doxorubicin showed that amrubicin has a more potent antitumor effect and lower toxic effects on the heart, which is a site of delayed toxicity with doxorubicin, and on the liver and kidneys.[3–5]

Amrubicin is a promising agent for the treatment of small cell lung cancer (SCLC).[6] Most patients with SCLC treated with standard chemotherapy, such as cisplatin plus etposide or cisplatin plus irinotecan, tend to experience a relapse within a year of the completion of treatment, and patients with relapsed SCLC historically have a poor outcome.[4,7] Some multicenter phase II trials in Japan or North America have shown that amrubicin has significant activity in patients with refractory or relapsed SCLC.[8,9] Randomized controlled trials with amrubicin for the treatment of SCLC patients are ongoing in the United States. The major toxicity of amrubicin is hematologic, and more than half of the patients treated with amrubicin develop grade 3 or 4 neutropenia. Nonhematologic toxicities, such as gastrointestinal toxicity or alopecia, are relatively mild. Surprisingly, several patients in Japanese phase II trials developed interstitial lung disease (ILD).[10,11] However, because the adverse pulmonary effects of amrubicin are less well known, in this study, we investigated the incidence of acute ILD in SCLC patients who had been treated with amrubicin.

PATIENTS AND METHODS

Medical records were used to retrospectively investigate a total of 100 consecutive cases of SCLC treated with single-agent amrubicin therapy at the National Cancer Center Hospital East between June 2003 and March 2008. The patients' radiologic reports and clinical data were reviewed to identify patients who had developed acute ILD after being treated with amrubicin. The study was approved by the institutional review board of our institution.

Three independent pulmonologists (K.Y., H.K., and Y.Y.) who had no knowledge of the patients' outcome diagnosed pre-existing lung conditions, i.e., pulmonary fibrosis (PF) and emphysematous change, based on the chest radiographic and

From the Division of Thoracic Oncology, National Cancer Center Hospital East, Kashiwanoha, Kashiwa, Chiba, Japan.

Disclosure: The authors declare no potential conflict of interest.

Address for correspondence: Kiyotaka Yoh, MD, Division of Thoracic Oncology, National Cancer Center Hospital East, 6-5-1 Kashiwanoha, Kashiwa, Chiba 277-8577. E-mail: kyoh@east.ncc.go.jp

ISSN: 1556-0864/10/0509-1435

computed tomographic (CT) findings before the start of amrubicin therapy. The diagnostic criteria for PF were a linear, ground-glass attenuation, or reticular shadows on chest radiographs and CT scans that were predominant in the lower zone of the lung. ILD was diagnosed on the basis of chest radiograph and CT findings (diffuse ground-glass opacity, reticular shadow, or consolidation without segmental distribution and honey-comb pattern), a serum lactate dehydrogenase (LDH) and/or KL-6, which is a mucin-like high-molecular-weight glycoprotein and shown to correlate well with the activities of several different kinds of interstitial pneumonia, elevation, and no evidence of underlying heart disease, infection, or lymphangitic carcinomatosis. Objective tumor response was assessed as complete response, partial response, stable disease ≥8 weeks, or progressive disease according to the Response Evaluation Criteria in Solid Tumors. Toxicity was graded by using the Common Terminology Criteria for Adverse Events version 3.0.

Univariate and multivariate analyses were performed to identify risk factors for ILD associated with amrubicin therapy. All comparisons between proportions were performed by the χ^2 test or Fisher's exact test, as appropriate. Multivariate analyses were performed using the logistic regression procedure to assess the relationship between several factors and the onset of ILD. *P* values less than 0.05 were considered statistically significant. Two-sided statistical tests were used in all analyses.

TABLE 1. Patient Characteristics

	Patients (n = 100)	
	N	%
Age (yr)		
Median	66	
Range	48–81	
Sex		
Female	17	17
Male	83	83
Performance status		
0/1	3/76	77
2/3	20/1	21
Smoking history		
Current/former smoker	98	98
Never smoker	2	2
No. of prior chemotherapy regimens		
1	43	43
2/3	51/6	57
Prior thoracic radiotherapy		
Yes	42	42
No	58	58
Pre-existing pulmonary fibrosis		
Yes	12	12
No	88	88
Pulmonary emphysematous change		
Yes	41	41
No	59	59
Amrubicin dose per square meter body surface area		
45 mg/m^2	37	37
40/35/30 mg/m^2	48/12/3	63

RESULTS

Patient Characteristics

The patients' characteristics are listed in Table 1. Their median age was 66 (range, 48–81) years, 17% of them were women, and 77% had an Eastern Cooperative Oncology Group performance status 0 and 1. Current smokers or exsmokers accounted for 98% of the patients, and emphysematous change was detected in 41% of the patients. Pre-existing PF was detected in 12% of the patients, but none of them had dyspnea. Amrubicin was used as a second-line treatment in 43% of the patients, and 57% had received two or more prior chemotherapy regimens. Amrubicin was diluted in 50 ml of normal saline and administered as a 5-minute daily intravenous injection at a dose of 30 to 45 mg/m^2 on 3 consecutive days, every 3 to 4 weeks.

Incidence and Outcome of ILD

After receiving amrubicin, 7 (7%) of the 100 SCLC patients developed pulmonary infiltrates in the absence of un-

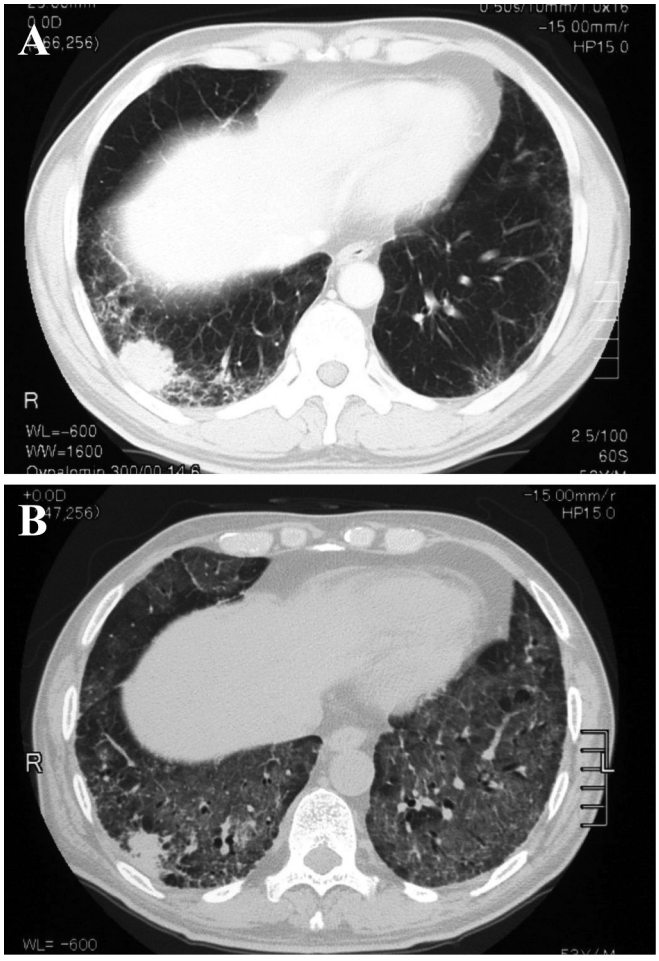

FIGURE 1. Computed tomography (CT) scans of the chest before and after treatment with amrubicin (patient 2 in Table 2). *A*, This CT scan of the chest before treatment with amrubicin shows a bilateral reticular shadow just beneath the pleura and a primary tumor in the right lower lobe. *B*, CT scan of the chest on day 17 of the first course of amrubicin therapy showing bilateral diffuse ground-glass opacities.