Efficacy of Amrubicin for Non-small Cell Lung Cancer after Failure of Two or More Prior Chemotherapy Regimens

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Abstract. *Background: No investigation of amrubicin monotherapy in pre-treated advanced non-small cell lung cancer (NSCLC) patients has yet been reported. Patients and Methods: The records were reviewed of NSCLC patients who had received amrubicin monotherapy between 2003 and 2007 with the following eligibility criteria: previously treated with at least two regimens including platinum and docetaxel for non-adenocarcinoma patients and platinum, docetaxel and epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKI) for adenocarcinoma patients. Amrubicin was administered to both groups at 35 mg/m^2 or 40 mg/m^2 for 3 consecutive days, every 3 weeks. Results: Thirty-nine patients were registered. The median number of prior chemotherapy regimens was three (range: 2 to 7). The median number of courses per patient was three (range one to 9). The toxicity profile was acceptable with no grade 3 or higher non-hematological toxicity. The overall response rate was 10.2%. The median survival time was 4.8 months. Conclusion: Amrubicin exhibits activity and acceptable toxicity as third or subsequent line of chemotherapy for advanced NSCLC.*

Combinations of platinum and the new agents developed in the 1990s are more useful against advanced non-small cell lung cancer (NSCLC) than old-generation combination chemotherapy and doublets of platinum and new-generation anticancer agents are now considered as standard chemotherapy regimens for advanced NSCLC (1, 2). However, among the patients receiving these as first-line chemotherapy, most present either NSCLC refractory to the chemotherapy or relapse after having been sensitive to the chemotherapy. Docetaxel has been considered a more reasonable standard therapy for NSCLC patients who experienced first-line failure compared with best supportive care (BSC) (3, 4). Equally importantly, two recent studies concerning the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKI) reported that erlotinib exhibited significant overall survival benefit in a second- or third-line setting compared to placebo for unselected patients (5) and that gefitinib was not inferior to docetaxel in clinical efficacy for pre-treated patients with advanced NSCLC (6). Additionally, previous studies reported that adenocarcinoma histology was one of the predictive factors for response and survival in NSCLC patients treated with gefitinib (7, 8).

On the other hand, we have inevitably encountered difficulties in the treatment of patients with advanced NSCLC relapsed to second-line regimens such as docetaxel and EGFR-TKI. Whereas it is recognized that this patient population has been increasing, the insufficiency of a consistent approach to treatment for patients who have failed second-line therapy is apparent.

Amrubicin hydrochloride is a totally synthetic 9-aminoanthracycline and is metabolically activated to amrubicinol by a liver enzyme. Two phase II studies of amrubicin in patients with previously untreated advanced NSCLC successively demonstrated an overall response rate of 27.9% and 18.3% and median survival time of 9.8 months and 8.2 months (9, 10). Thus amrubicin was equivalent to newer agents such as taxanes, gemcitabine, vinorelbine and irinotecan in single-agent activity for NSCLC. These findings suggested that amrubicin might be a promising anti-tumor agent for the treatment of NSCLC. To our knowledge, no evaluation of such single-agent treatment in pre-treated advanced NSCLC patients has yet been reported. In the present study, the clinical efficacy of amrubicin for pre-treated patients with advanced NSCLC was investigated.

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Key Words: Amrubicin, NSCLC, chemotherapy failure, third-line treatment.

Patients and Methods

Patient selection. This retrospective cohort study enrolled 39 patients previously treated for NSCLC between March 2003 and October 2007 at Shizuoka Cancer Center. Study participants were consecutively registered according to the following criteria: measurable disease target lesions on physical examination by chest X-ray, computed tomography (CT) of the chest and abdomen, or other procedures as indicated, including MRI of the head, positron-emission tomography (PET), or combined PET/CT; histologically confirmed advanced NSCLC and relapsed or progressive disease after first-line platinum-based chemotherapy; histologically confirmed adenocarcinoma and receiving each of EGFR-TKI and docetaxel following the first-line therapy; other histological subtypes of NSCLC and previously receiving docetaxel following the first-line therapy; age less than 80 years; Eastern Cooperative Oncology Group Performance Scale status (ECOG PS) of 2 or less; adequate bone marrow, hepatic, and renal function; no other serious disease and written informed consent.

Treatment methods. In a previous study amrubicin at a dose of 40 mg/m^2 showed efficacy and tolerability in previously treated small cell lung cancer (SCLC) patients (11). Furthermore, amrubicin at a dose of 35 mg/m^2 also exhibited significant activity as third-line chemotherapy against SCLC (12). Thus, a reduced dose of 35 to 40 mg/m^2 per day × 3 days was chosen for the present study in view of the history of previous chemotherapy in the patients. The treatment schedule comprised intravenous infusion of amrubicin in 50 ml normal saline over 5 minutes on days 1 to 3 every three weeks.

Before the start of treatment, the patients were required to have an absolute neutrophil count (ANC) of 1,500/mm^3 or more, a platelet count of 100,000/mm^3 or more, asparatate aminotransferase (AST) and alanine aminotransferase (ALT) values less than 3 times the maximum values of the normal range, and total bilirubin and creatinine values less than 1.5 times the maximum values of the normal range. The administration of granulocyte colony-stimulating factor (G-CSF) was permitted as a therapeutic intervention but was not mandatory as a prophylactic agent against the hematological toxicity of neutropenia. Subsequent doses were modified on the basis of the hematological and non-hematological toxicities at the discretion of the physician in charge. Peripheral blood and biochemistry examinations were repeated at least once a week after the initial evaluation.

Evaluation of response and toxicity. Tumor response was classified in accordance with the Response Evaluation Criteria for Solid Tumors. The patients were evaluated to determine the stage of their disease before the start of treatment and at the time of determination of disease progression or relapse, by complete medical history and physical examination, chest X-ray, CT of the chest and abdomen, and other staging procedures, such as MRI of the head and PET. The adverse events were recorded and graded using the National Cancer Institute Common Toxicity Criteria, Version 3.0 grading system (13).

Statistical analysis. Overall survival was measured from the first day of amrubicin treatment to the day of death or last follow-up. Progression-free survival was defined as the time between the initiation of treatment and failure (*i.e.* death or disease progression) or last follow-up. The time-to-event outcomes were compared using the log-rank test.

Table I. *Patient characteristics*.

No. of patients	39
Gender: female/male	15/24
Age (years): median (range)	60 (41-77)
Smoking history: +/–	24/15
ECOG PS: 0/1/2	14/17/8
Stage: IIIB/IV	6/33
Brain metastasis: +/–	10/29
Histology: Ad/SQ/Other	22/14/3
Number of prior regimens 2/3/>=4	3/20/16

Ad: Adenocarcinoma, SQ: squamous cell carcinoma.

Table II. *Hematological toxicity by dose*.

	Pts	ANC		Hb		PLT		FN
Dose		G3	G4	G3	G4	G3	G4	G3
35 mg/m^2	28	8	6	3	0	2	2	2
40 mg/m^2	11	4	4	2	0	1	0	0
Total	39	12	10	5	0	3	2	2

ANC: Absolute neutrophil count, Hb: hemoglobin, PLT: platelets, FN: fibrile neutropenia.

Results

Patient characteristics. The characteristics of the patients with recurrent or refractory NSCLC enrolled in this study are listed in Table I. The majority (31 patients, 79%) had an ECOG PS of 1 or 0. The histological subtypes of NSCLC in the patients were: adenocarcinoma in 22 patients (56%), squamous cell carcinoma in 14 (36%), and other histological subtypes in 3 (8%). Amrubicin was administered at 35 mg/m^2 to 28 patients and at 40 mg/m^2 to 11 patients. For the whole study population, the best responses to prior therapy were: no complete response (CR); two (5%) partial response (PR); 15 (39%) stable disease (SD) and 22 (56%) progressive disease (PD).

Toxicity. In total 102 courses were given (median courses per patient, 3: range 1 to 9). All of these courses were included in the toxicity analysis. The principal toxicity of amrubicin monotherapy was neutropenia. The hematological toxicities in the 39 patients are summarized in Table II, which shows the highest level of toxicities in each patient. Grade 3 or higher neutropenia, grade 3 decrease in hemoglobin, and grade 3 or higher thrombocytopenia were observed in 22 patients (56%), 5 patients (13%) and 5 patients (13%), respectively. The incidence of grade 4 neutropenia was less frequent in patients receiving 35 mg/m^2 (21%) than in those receiving 40 mg/m^2 (36%). Febrile neutropenia was

Table III. *Non-hematological toxicity by dose.*

	Grade 2	
	35 mg/m^2 (n=28)	40 mg/m^2 (n=11)
Anorexia	3	1
Fatigue	2	1
Nausea	3	1
Vomiting	2	-
Rash	1	2
Constipation	-	-
Stomatitis	-	1
AST/ALT	-	1
Creatinine	1	-

Table IV. *Response by dose.*

	Dose (mg/m^2)		Total
	35	40	
PR	4	0	4
SD	6	3	9
PD	18	8	26
RR (%)	14.2%	0%	10.2%
DCR (%)	35.7%	27.2%	33.3%

PR: Partial response, SD: stable disease, PD: progressive disease; RR: response rate, DCR: disease control rate.

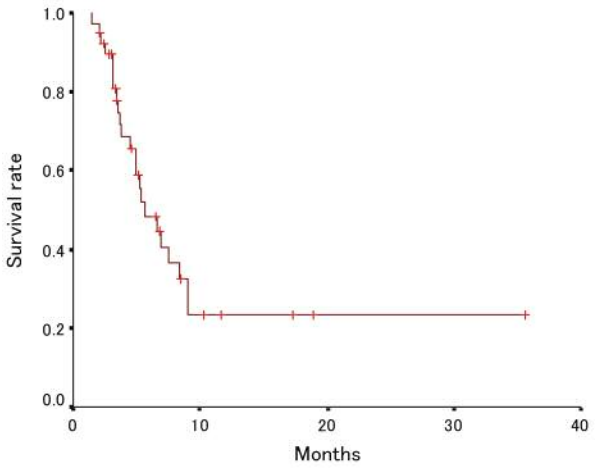

Figure 1. *Survival curve. Median survival time was 5.7 months (95% confidence interval, 3.4 to 7.9 months).*

observed in 2 patients (5%). The non-hematological toxicities are listed in Table III, and amrubicin caused no grade 3 or higher toxicities.

Response to therapy and survival. The objective tumor responses are shown in Table IV. Among the 39 patients, 4 achieved a confirmed partial response and 9 had stable disease, for an overall response rate of 10.2% (95% CI, 2.9 to 24.2%) and disease control rate of 33.3% (95% CI, 19.1 to 50.2%). The patients receiving the 35 mg/m^2 dose had a response rate of 14.2% and a disease control rate of 35.7%, while those receiving the 40 mg/m^2 dose had no response and a disease control rate of 27.2% and overall survival data are shown in Figure 1. The overall median survival time (MST) and one-year survival rate were 5.7 months (95% CI, 3.4 to 7.9 months) and 28%, respectively. The overall progression-free survival was 1.5 months (95% CI, 1.2 to 1.7 months).

Discussion

It has not been demonstrated whether third-line or more chemotherapy would actually increase survival in patients with second-line failure. It was reported that among 43 patients (extracted from over 700 patient records with recurrent NSCLC) who had received two prior chemotherapy regimens including platinum and docetaxel for recurrent NSCLC, the response rates decreased with each line of treatment (third-line, 2.3%; fourth-line, 0%), the disease control rate also decreased (third-line, 30.2%; and fourth-line, 21.4%) and the median overall survival time from the start of the last treatment was 4 months (14). The results of the presented study indicated that amrubicin monotherapy had variable clinical outcomes (overall response rate, MST, and progression-free survival were 10.2%, 5.7 months and 1.5 months, respectively) and acceptable toxicity profiles among the NSCLC patients with failure of second-line or subsequent therapy, including docetaxel and EGFR-TKI.

This study could serve as a foundation in regard to the investigation of the antitumor activity of amrubicin in the aforementioned setting. Additionally, the safety profile of the drug, such as tolerable hematological toxicity and slight non-hematological toxicity beyond the second-line setting, is certainly valuable. Neutropenia has been recognized as the principal toxicity of amrubicin monotherapy (9, 10). In this study, the incidence of severe neutropenia was less frequent in the patients receiving 35 mg/m^2 in comparison with those receiving 40 mg/m^2, and the clinical response of the patients receiving 35 mg/m^2 was not inferior to that of the patients receiving 40 mg/m^2. The information presented in the study serves to strengthen the rationale for use of the drug at 35 mg/m^2 in the third-line setting and beyond.

In conclusion, amrubicin is an active agent against NSCLC that may play a prominent role in third-line treatment and beyond. The information presented in this study might provide a new direction for clinical research on the treatment of recurrent NSCLC in the third-line setting. However, because of the retrospective nature of this study,

the conclusions cannot be completely definitive and a prospective study aiming at elucidating the efficacy of this agent for recurrent NSCLC is proposed.

References

1 Schiller JH, Harrington D, Belani CP *et al*: Comparison of four chemotherapy regimens for advanced non-small cell lung cancer. N Engl J Med *346*: 92-98, 2002.

2 Ohe Y, Ohashi Y, Kubota K *et al*: Randomized phase III study of cisplatin plus irinotecan *versus* carboplatin plus paclitaxel, cisplatin plus gemcitabine, and cisplatin plus vinorelbine for advanced non-small cell lung cancer: Four-Arm Cooperative Study in Japan. Ann Oncol *18*: 317-323, 2007.

3 Shepherd FA, Dancey J, Ramlau R *et al*: Prospective randomized trial of docetaxel *versus* best supportive care in patients with non-small cell lung cancer previously treated with platinum-based chemotherapy. J Clin Oncol *18*: 2095-3013, 2000.

4 Roszkowski K, Pluzanska A, Krzakowski M *et al*: A multicenter, randomized phase III study of docetaxel plus best supportive care *versus* best supportive care in chemotherapy-naïve patients with metastatic or nonresectable localized non-small cell lung cancer (NSCLC). Lung Cancer *27*: 145-157, 2000.

5 Shepherd FA, Rodrigues Pereira J *et al*: Erlotinib in previously treated non-small cell lung cancer. N Engl J Med *353*: 123-132, 2005.

6 Douillard J-Y, Kim ES, Hirsh V *et al*: Phase III, randomized, open-label, parallel-group study of oral gefitinib (IRESSA™) *versus* intravenous docetaxel in patients with locally advanced or metastatic non-small cell lung cancer who have previously received platinum-based chemotherapy (INTEREST). Eur J Cancer *5*: 2007 (suppl.).

7 Thatcher N, Chang A, Parikh P *et al*: Gefitinib plus best supportive care in previously treated patients with refractory advanced non-small cell lung cancer: results from a randomised, placebo-controlled, multicentre study (Iressa™ Survival Evaluation in Lung Cancer). Lancet *366*: 1527-1537, 2005.

8 Ando M, Okamoto I, Yamamoto N *et al*: Predictive factors for interstitial lung disease, antitumor response, and survival in non-small cell lung cancer patients treated with gefitinib. J Clin Oncol *24*: 2549-56, 2006.

9 Sawa T, Yana T, Takada M *et al*: Multicenter phase II study of amrubicin, 9-amino-anthracycline, in patients with advanced non-small cell lung cancer (Study 1): West Japan Thoracic Oncology Group (WJTOG) trial. Invest New Drugs *24*: 151-158, 2006.

10 Takeda K, Takifuji N, Negoro S *et al*: Phase II study of amrubicin, 9-amino-anthracycline, in patients with advanced non-small cell lung cancer: a West Japan Thoracic Oncology Group (WJTOG) study. Invest New Drugs *25*: 377-383, 2007.

11 Onoda S, Masuda N, Seto T *et al*: Phase II trial of amrubicin for treatment of refractory or relapsed small cell lung cancer: Thoracic Oncology Research Group Study 0301. J Clin Oncol *24*: 5448-53, 2006.

12 Igawa S, Yamamoto N, Ueda S *et al*: Evaluation of the recommended dose and efficacy of amrubicin as second- and third-line chemotherapy for small cell lung cancer. J Thorac Oncol *2*: 741-4, 2007.

13 Cancer Therapy Evaluation Program. Common Terminology Criteria for Adverse Events (CTCAE). Version 3.0, DCTD, NCI, NIH, DHHS. August 9, 2006.

14 Massarelli E, Andre F, Liu DD *et al*: A retrospective analysis of the outcome of patients who have received two prior chemotherapy regimens including platinum and docetaxel for recurrent non-small cell lung cancer. Lung Cancer *39*: 55-61, 2003.

Received July 22, 2008
Revised October 7, 2008
Accepted October 15, 2008