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CLINICAL TRIAL REPORT

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A phase II trial of DA-125, a novel anthracycline, in advanced non-small-cell lung cancer

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Abstract *Purpose*: DA-125 is a novel anthracycline derivative developed by Dong-A Pharmaceutical Company, Korea. Preclinical studies have suggested that DA-125 has greater efficacy and less toxicity than doxorubicin. The maximum tolerable dose has been shown to be 100 mg/m^2 in a phase I trial. The purpose of this phase II study was to evaluate the efficacy and toxicity of DA-125 in patients with non-small-cell lung cancer (NSCLC). *Methods*: Chemotherapy-naive patients with histologically confirmed measurable NSCLC which was not curable by surgery or radiation therapy because of metastasis, local invasion, or recurrence were eligible for this trial. Between May 1996 and April 1997, 20 patients entered into this trial and were treated with DA-125 administered as a 5-min intravenous infusion every 3 weeks. The dose of DA-125 was 80 mg/m^2 during the first cycle, and was adjusted to between 60 and 100 mg/m^2 according to the observed toxicities during subsequent cycles. *Results*: Among 19 evaluable patients, there was no objective response to DA-125. Anemia, leukopenia and granulocytopenia of grade 3 or over were observed in 4%, 6% and 12% of chemotherapy cycles, respectively. There were no treatment-related deaths. With regard to nonhematologic toxicities, diarrhea, infection and elevated serum alkaline phosphatase of grade 3 or over were observed in 2% of cycles, but were tolerable and reversible. *Conclusion*: DA-125 at these doses and in this schedule was highly tolerable, but was not active in patients with advanced NSCLC.

Key words Non-small-cell lung cancer · Chemotherapy · DA-125 · Phase II

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Introduction

DA-125 (14-*O*-(3-aminopropionyl)-7-*O*-(2,6-dideoxy-2-fluoro-a-L-talopyranosyl) adriamycinone hydrochloride) is a new anthracycline derivative containing fluorine developed by Dong-A Pharmaceutical Company, Korea, with the aim of providing greater therapeutic activity and less toxicity than doxorubicin [6]. Preclinical studies have demonstrated that DA-125 has more potent antitumor activity against various tumor types and has less cardiotoxicity than doxorubicin [1, 2, 5, 7, 10]. Its superior therapeutic activity in lung cancer has been suggested in in vivo animal models. Compared with doxorubicin, DA-125 shows a higher cure rate in Lewis lung carcinoma in mice and a higher tumor growth inhibition rate in human lung cancer implanted in nude mice [7, 10]. A phase I study has shown that the maximum tolerable dose (MTD) is 100 mg/m^2 with myelosuppression as the dose-limiting toxicity, and 80 mg/m^2 was recommended for phase II trial [11]. The current phase II study was undertaken to determine the activity and toxicity of DA-125 in advanced non-small-cell lung cancer (NSCLC).

Patients and methods

Patient eligibility

Eligible patients had pathologically confirmed, measurable NSCLC not amenable to curative therapy and had no previous history of chemotherapy or immunotherapy. All patients were between 15 and 70 years old, with an Eastern Cooperative Oncology Group performance status of 2, adequate hepatic, renal, marrow and cardiac functions (total serum bilirubin ≤1.5 times normal, serum AST/ALT ≤1.5 times normal, serum BUN ≤1.5 times normal, serum creatinine ≤1.5 times normal, hemoglobin ≥10 g/dl, leukocyte count ≥4000/mm^3, platelet count ≥100,000/mm^3, normal electrocardiogram, left ventricular ejection fraction ≥50% on echocardiography). Patients were excluded if there was a history of serious complications, active infection, heart disease such as congestive heart failure or myocardial infarction, or CNS metastases or epilepsy. Pregnant or lactating women were also excluded. All patients

provided written informed consent. The study protocol was in accord with the Helsinki Declaration and approved by the Korean Ministry of Health and Welfare.

Pretreatment evaluations

Pretreatment evaluations included history taking, physical examination, tumor measurements, and laboratory tests.

Treatment protocol

Each course of therapy consisted of infusions of DA-125 given 3 weeks apart, beginning with a dose of 80 mg/m^2 intravenously (i.v.) for 5 min; the doses for subsequent cycles were adjusted between 60 and 100 mg/m^2 according to toxicity. If there was no grade III/IV hematologic or grade II-IV nonhematologic toxicity in a previous cycle of chemotherapy, the dose was escalated by 20 mg/m^2 in the next cycle. If there was grade IV hematologic or grade III/IV nonhematologic toxicity, the dose was reduced by 20 mg/m^2. However, escalation to more than 100 mg/m^2 or reduction to less than 60 mg/m^2 was not allowed during any cycle. The treatment was repeated unless toxicities of grade IV did not recover 5 weeks after the previous cycle, disease progressed at any time, or did not respond after three cycles of treatment.

Evaluation of tumor response and toxicity

Clinical examinations, vital signs, complete blood counts and biochemical measurements were performed every week during treatment. Evaluation of tumor response was done by physical examination, X-radiography or computed tomography every 3 weeks once treatment had begun. A complete response was defined as disappearance of all tumors for more than 3 weeks, partial response as a decrease of 50% or more in the sum of the sizes of all measurable tumors as measured across the greatest diameter for more than 3 weeks, progressive disease as an increase of at least 25% or appearance of any new lesion, and stable disease as not included in any of the above three criteria [8]. Toxicities were evaluated using the WHO criteria.

Statistical evaluation

The two-stage patient accrual design developed by Fleming was used [3]. This design minimizes the expected number of patients treated with the experimental drug if it proves to be very disappointing or very encouraging. It permits early termination of patient entry after the first 20 response-evaluable patients if there is no response or four or more responses ($P = 0.05$, pA $= 0.20$, $\alpha = 0.05$, $\beta = 0.10$).

Results

Pretreatment patients' characteristics

Between May 1996 and April 1997, a total of 20 patients were registered for the study. Their pretreatment characteristics are shown in Table 1. Of those registered, 15 were men and 5 were women with a median age of 57 years (range 33 to 67 years). All patients had NSCLC (10 squamous cell carcinoma, 8 adenocarcinoma, and 2 unspecified NSCLC).

Table 1 Pretreatment patients' characteristics

No. of patients	
Accrued	20
Evaluable	19
Sex	
Male	15
Female	5
Age (years)	
Median	58
Range	33–67
Performance status (ECOG)[a]	
1	18 (90%)
2	2 (10%)
Histology	
Squamous cell carcinoma	10 (50%)
Adenocarcinoma	8 (40%)
Unspecified	2 (10%)
T stage	
T1	2 (10%)
T2	7 (35%)
T3	1 (5%)
T4	9 (45%)
N stage	
N0	2 (10%)
N1	1 (5%)
N2	4 (20%)
N3	12 (60%)
M stage	
M0	10 (50%)
M1	9 (45%)
Stage	
IIIB	9 (45%)
IV	10 (50%)
Recurrent	1 (5%)

[a] Eastern Cooperative Oncology Group

Tumor response

One patient was inevaluable for response based on failure to obtain a second tumor assessment, leaving 19 patients evaluable for tumor response. There was no objective tumor response to DA-125. A best response of stable disease was shown by 13 patients (68%), and 6 (32%) showed progression.

Salvage treatment was required by 16 patients (cisplatin-based combination chemotherapy 15; radiotherapy 1) after withdrawal from the study. Among the 12 evaluable patients who received salvage chemotherapy, there were 4 partial responses (33%).

The median survival of the 20 patients was 8.8 months and the 1-year survival rate was 21%.

Toxicity

The patients received one to three (median three) cycles of chemotherapy. Among 18 patients who received a second cycle of chemotherapy, the dose of DA-125 was able to be escalated to 100 mg/m^2 in 16 patients (89%), while there was no patient whose dose was reduced to 60 mg/m^2. The 20 patients received a total of 51 cycles of chemotherapy, 49 cycles of which were evaluable for toxicities of DA-125 chemotherapy (Table 2). Hemato-

Table 2 Toxicities of DA-125 chemotherapy by WHO grade (*AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *BUN* blood urea nitrogen, *Cr* creatinine)

Toxicities	WHO grade									
	0		I		II		III		IV	
	No.	%	No.	%	No.	%	No.	%	No.	%
Hematologic toxicities (total 49 cycles)										
Anemia	27	55	11	23	9	18	1	2	1	2
Leukopenia	26	53	14	29	6	12	2	4	1	2
Granulocytopenia	26	53	14	29	3	6	4	8	2	4
Thrombocytopenia	49	100	0		0		0		0	
Nonhematologic toxicities (total 49 cycles)										
Bilirubin	48	98	0		1	2	0		0	
AST/ALT	44	90	4	8	1	2	0		0	
Alkaline phosphatase	46	94	1	2	1	2	0		1	2
BUN/Cr	47	96	2	4	0		0		0	
Stomatitis	45	92	3	6	1	2	0		0	
Nausea/vomiting	19	39	23	47	7	14	0		0	
Diarrhea	41	84	6	12	1	2	1	2	0	
Proteinuria	48	98	1	2	0		0		0	
Hematuria	44	90	4	8	1	2	0		0	
Infection	0		0		0		1	2	0	
Cardiotoxicity	47	96	0		2	4	0		0	
Alopecia[a]	8	42	11	58	0		0		0	

[a] Total 19 patients

logic toxicities were evaluated based on complete blood counts performed every week during treatment. There were two cycles (4%) of anemia grade 3, three cycles (6%) of leukopenia grade 3 and six cycles (12%) of granulocytopenia grade 3, and there was no thrombocytopenia. Two cycles required treatment delay for 1 week because the recovery of WBC count was delayed. There was one episode of pneumonia after chemotherapy, which was successfully treated with antibiotics, and there was no bleeding episode. No patient required a dose reduction for grade 4 hematologic toxicity. Ten patients (56%) developed alopecia. The most common side effect was nausea/vomiting, reported in 30 cycles (61%); it was generally mild.

Alkaline phosphatase was elevated in three cycles (6%), one of which (2%) was grade 4. One cycle required treatment delay for 2 weeks because the recovery of hepatic function was delayed. With regard to cardiotoxicity, ventricular premature beats (grade 2) developed in two cycles (4%). All chemotherapy toxicities were reversible, and there were no chemotherapy-related deaths. When the toxicities were evaluated according to the dose of DA-125 administered, no significant differences were found between the cycles at the doses of 80 mg/m^2 (22 cycles) and 100 mg/m^2 (27 cycles) (data not shown).

Discussion

Lung cancer is one of the leading causes of death in the world and its incidence is increasing. Approximately 75% of lung cancer is NSCLC and surgical resection is thought to be the only method of cure for NSCLCs. However, more than 75% of NSCLCs are not suitable for surgical resection at diagnosis and nearly 90% of patients will eventually require systemic therapy [4]. Thus, improved systemic therapies are critical to improving the prognosis of NSCLCs. However, NSCLC is one of the tumors most refractory to chemotherapy. Although a recent metaanalysis has shown that cisplatin-based combination chemotherapy can prolong the survival of these patients, the benenfit is only minor: the 1-year survival rate increased from 5% in patients who received supportive care only to 15% in patients who received chemotherapy [9]. Therefore, the identification of new active agents should remain a major area of clinical research in NSCLC. The object of our study was to evaluate the efficacy and toxicity of the novel agent DA-125 administered as first-line chemotherapy for patients with advanced NSCLC. The results of this phase II trial indicate that i.v. DA-125 beginning at a dose of 80 mg/m^2 and increasing up to 100 mg/m^2 at each infusion is highly tolerable, but lacks activity in advanced NSCLC.

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