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The Safety and Efficacy of Second-line Single Docetaxel (75 mg/m^2) Therapy in Advanced Non-Small Cell Lung Cancer Patients who were Previously Treated with Platinum-based Chemotherapy

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Purpose: **When used in the second-line setting, single-agent chemotherapy has produced response rates of more than 10% or median survival times greater than 4 months. We studied the safety and efficacy of using second-line single docetaxel (75 mg/m^2) for advanced NSCLC patients who were previously treated with platinum-based chemotherapy in Korea.**

Materials and Methods: **Thirty-three patients with advanced NSCLC received chemotherapy from May 2002 to January 2005. We retrospectively reviewed the charts of these patients. The patients received 75 mg/m^2 of doxetaxel on day 1 and this was repeated at 3-week intervals.**

Results: **The median age was 63 years (range: 42～77 years); 16 patients had adenocarcinoma and 8 patients had squamous cell carcinoma. The median number of cycles was 4 (range: 1～7 cycles). Of the 33 patients, 6 patients had partial responses, 13 patients had stable disease and 14 patients had progressive disease. The response rate was 18.2%. The median overall survival was 11 months (range: 7～15 months), and the median progression free survival was 5 months (range: 3～7 months). The median response duration was 5 months (range: 4～9 months). A total of 137 cycles were evaluated for toxicity. We observed grade 3 or 4 neutropenia in 79 cycles (57.6%), grade 3 or 4 leukopenia in 46 cycles (33.6%), and grade 3 febrile neutropenia in 2 cycles (1.5%). The median nadir day was day 9 (range: day 5～19), and the median number of G-CSF injections was 2 (range: 0～6). The most common non-hematologic toxicities were myalgia/arthralgia and neurotoxicity, but any grade 3 or 4 non-hematologic toxicity was not observed. The major toxicity of this therapy was neutropenia. The absolute neutrophil count decreased relatively rapidly, but neutropenic fever or related infection was rare. There were no treatment-related deaths.**

Conclusion*:** **These results revealed a satisfactory response rate (18.2%) with using docetaxel as the second-line chemotherapy for NSCLC. The second-line docetaxel was an active and well-tolerated regimen in patients with advanced NSCLC pretreated with platinum-based chemotherapy.** ***(Cancer Res Treat. 2005;37:339-343)

Key Words: **Non-small cell lung neoplasm, Docetaxel, Chemotherapy**

INTRODUCTION

Platinum-based combination chemotherapy improves the prognosis of patients with unresectable advanced non-small cell lung cancer (NSCLC), and such regimens are now commonly in use (1,2). Although this combination chemotherapy increases the anti-tumor effect, the response duration is short and recurrence of tumor is inevitable. For the patients who progress after being treated with a platinum-based combination chemotherapy, even if they have a good performance status, the usefulness of second-line chemotherapy had not been documented (2～4). Recently, the TAX 320 trial was conducted with randomized 373 patients showing disease progression following their platinum chemotherapy, and they received either docetaxel versus the control arm that was treated with vinorebine or ifosfamide. The response rate to docetaxel in that study was low, but the 1-year survival of the docetaxel-treated patients was significantly higher than that of the control arm patients (32% *vs* 10%, respectively, $p < .01$) (5). In another phase III trial, single docetaxel therapy for the NSCLC patients who

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were previously treated with platinum-based chemotherapy showed a low response rate (7%), but it significantly improved the median survival (7 *vs* 5 months, respectively) in comparison to the best supportive care (6).

Based on the result of these studies, the American Society of Clinical Oncology (ASCO) in 2003 recommended single docetaxel therapy as the second-line therapy for patients with an adequate performance status who progressed after first-line, platinum-based therapy (7). We studied the safety and efficacy of using second-line single docetaxel therapy (75 mg/m^2) for the advanced NSCLS patients who were previously treated with platinum-based chemotherapy in Korea.

MATERIALS AND METHODS

1) Patient evaluation

The patients of this study were required to have histologically proven NSCLC, bidimensionally measurable lesions, the ECOG performance status less than or equal to 2, and adequate bone marrow, renal and hepatic function. The clinical, biological and radiologic assessments were performed before the start of treatment and also after the treatment had commenced. We retrospectively reviewed the charts of these patients.

2) Chemotherapeutic regimen and dose modification

Docetaxel 75 mg/m^2 was dissolved in 250 ml of 5% glucose solution and it was administered intravenously for 1 hour. The treatments were repeated every three weeks.

If the patient had the ECOG performance status of 2 or a history of severe neutropenia during the previous chemotherapy, the starting dose of docetaxel was reduced by 20%. Treatment was delayed for up to 2 weeks if the absolute number of neutrophils was lower than 1,500/μl and the platelet count was lower than 100,000/μl. The docetaxel dose was reduced by 20% for the subsequent courses if National Cancer Institute Common Toxicity Criteria (NCI-CTC) grade 4 neutropenia, grade 3 thrombocytopenia, grade 3 febrile neutropenia or grade 3 non-hematologic toxicity occurred, except for alopecia or nausea/vomiting. If NCI-CTC grade 4 neutropenia reoccurred after the first dose reduction, prophylactic granulocyte colony-stimulating factor (G-CSF) was used in the subsequent cycle. Treatments continued until disease progression or unacceptable toxic effects were noted, or the patient refused further treatment.

3) Pretreatment and follow-up evaluation

Before the first treatment course and before each of the subsequent treatment courses, physical examinations including neurologic examination, routine hematology and biochemistry analyses and chest x-ray were performed. Chest CT scans were performed to define the extent of the disease during the pretreatment evaluation. The tumor size was measured by chest CT scan, x-ray or with using other available techniques at every 2 cycles or sooner if there was evidence of any clinical deterioration. The patients were assessed using the NCI-CTC version 2 guidelines before starting each 3 week cycle.

4) Assessment of response

The anti-tumor activity was evaluated according to the WHO criteria (8), and the dose intensity was calculated as the total cumulative dose divided by the duration of the dosing. The relative dose intensity was calculated as the dose-intensity divided by the planned dose-intensity, and then it was multiplied by 100.

5) Statistical analysis

Survival durations were calculated from the start of the study treatment until the time of death. Progression free survival was calculated from the first day of the chemotherapy to the date of progressive disease. The progression free survival and overall survival curves were obtained by using the Kaplan-Meier method. The response duration was calculated from the date of response confirmation to the date of disease progression.

Table 1. Patient characteristics

Enrolled patients	33
Age, years	
Median	62
Range	42～77
Gender, Male/Female	21/12
Smoking history	
Yes	22 (66.7%)
No	11 (33.3%)
Performance	
0	2 (6.1%)
1	28 (84.8%)
2	3 (9.1%)
Stage	
IIIB	16 (48.5%)
IV	17 (51.5%)
Pathology	
Adenocarcinoma	16 (48.5%)
Squamous carcinoma	8 (24.9%)
Poorly differentiated carcinoma	9 (27.3%)
Previous treatment	
Combination chemotherapy	
G*+C†	18 (54.5%)
T‡ +C†	8 (24.2%)
G*+N§	2 (6.1%)
T‡ +Carboplatin	1 (3.0%)
Paclitaxel concurrent chemoradiotherapy	4 (12.1%)
Response of 1st line chemotherapy	
＞PR‖	19 (57.5%)
SD¶	10 (30.3%)
PD**	4 (12.1%)

*gemcitabine, †cisplatin, ‡paclitaxel, §navelbine, ‖partial response, ¶stable disease, **progressive disease.

RESULTS

1) Patient characteristics

From May 2002 to January 2005, 33 advanced NSCLC patients received chemotherapy at St. Vincent's Hospital. The patients' characteristics are listed in Table 1.

2) Toxicity

A total of 137 cycles were evaluated for toxicity, and the incidence of toxicity is summarized in Table 2. This regimen was well tolerated, but we observed grade 3 or 4 neutropenia in 79 cycles (57.6%) and leukopenia in 46 cycles (33.6%). The neutropenia was immediately normalized with instituting G-CSF treatment. Two incidences of grade 3 febrile neutropenia were observed. The median nadir day was day 9 (range: day 5～19) and the median number of G-CSF injections was 2 (range: 0～6 injections).

Grade 3 anemia was observed in 6 cycles (4.4%), whereas none of the patients had grade 3 or 4 thrombocytopenia. The most common non-hematologic toxicities were myalgia/arthralgia and neurotoxicity, but no grade 3 or 4 non-hematologic toxicity was observed.

One patient died due to obstructive pneumonia and infection with grade 1 neutropenia on day 21 after a single cycle, but the obstructive pneumonia was related to the progression of disease. There was no treatment-related death. The relative dose intensity of the docetaxel was 88.8% of the planned doses. The first cycle of 8 patients was treated with a 20% dose reduction, and prophylactic G-CSF was used in 11 patients.

3) Efficacy

The median number of cycles was 4 (range: 1～7). Of the 33 evaluated patients, 6 patients achieved a partial response, 13 patients had stable disease and 14 patients had progressive disease. The response rate was 18.2%. The median follow up duration was 10 months (range: 1～37 months). The median overall survival was 11 months (range: 7～15 months), and the median progression free survival was 5 months (range: 3～7 months). The median response duration was 5 months (range: 4～9 months) (Fig. 1). The 1-year survival rate was 39.4%. The low dose group (the initial 20% reduction patients and a 20% reduction after the first cycle) included 11 patients. In the low dose group patients, 1 patient had a partial response, 7 patients had stable disease and 3 patients had progressive disease; the disease control rate was 72.7%, and the response rate was 9%. In the 22 remaining patients, 5 patients had a partial response, 6 patients had stable disease and 11 patients had progressive disease; the disease control rate was 50% and the response rate was 22.7%. However, a significant statistical difference for the overall survival and the time to progression was not shown between the two groups. Seventy percent of the patients were treated with third-line chemotherapy, using gefitinib, gemcitabine plus vinorelbine, paclitaxel and irinotecan etc.

DISCUSSION

Up until 2 years ago, the second-line chemotherapy for advanced NSCLC had not been established. Several active new agents (gemcitabine, vinorelbine and paclitaxel) have been studied in the first-line setting as second-line treatments, but the single drug phase II data for these drugs as second-line agents for treating advanced NSCLC has not merited conducting phase III study (9～11). Similarly, combinations of two drugs have been used with promising results in the phase II studies of second-line NSCLC (12～14). A recent phase II study of docetaxel and ifosfamide for patients with a platinum resistant or

Table 2. Toxicity

	Toxicity grade			
	Grade I (%)	Grade II (%)	Grade III (%)	Grade IV (%)
Hematologic toxicity per cycle (n=137)				
Anemia	63 (46.0%)	20 (14.6%)	6 (4.4%)	-
Leukopenia	16 (11.7%)	33 (24.1%)	44 (32.1%)	2 (1.5%)
Neutropenia	13 (9.5%)	10 (7.3%)	35 (25.5%)	44 (32.1%)
Thrombocytopenia	2 (1.5%)	1 (0.7%)	-	-
Febrile neutropenia	-	-	2 (1.5%)	-
Non-hematologic per cycle (n=137)				
Myalgia/arthralgia	22 (16.1%)	2 (1.5%)	-	-
Neuropathy	21 (15.3%)	3 (2.2%)	-	-
Nausea/ Vomiting	4 (2.9%)	1 (0.7%)	-	-
Mucositis	3 (2.2%)	2 (1.5%)	-	-
Diarrhea	1 (0.7%)	2 (1.5%)	-	-
Rash	1 (0.7%)	1 (0.7%)	-	-
Infection with normal ANC* or G1 or 2	-	-	-	1 (0.7%)

*absolute neutrophil count.

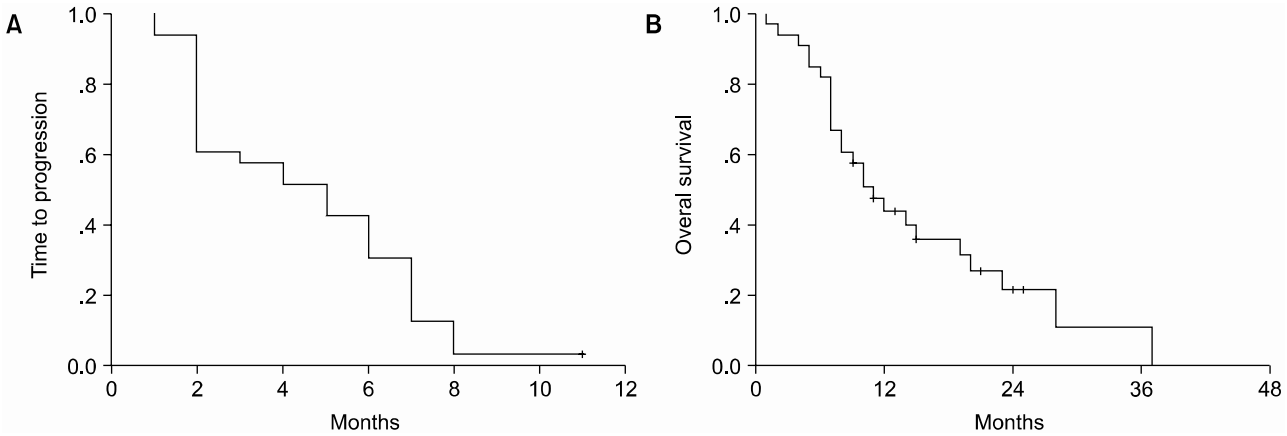

Fig. 1. (A) Time to progression and (B) the overall survival curve.

refractory NSCLC in a salvage setting showed a response rate of 12.5%, a median time to progression of 2.65 months and a median survival of 5.24 months (15). However, these combination regimens have yet to be compared with either single docetaxel or with each other in phase III randomized trials. Whereas several phase II trials of single docetaxel have shown relatively high response rates for the second-line treatment of NSCLC, and these response rates have ranged from 16% to 25% (16～18). These encouraging results of the phase II trials have prompted two phase III trials. Shepherd et al. Have compared docetaxel (100 or 75 mg/m^2) to the best supportive care for 204 NSCLC patients who were previously treated with platinum-based chemotherapy (6). Although the objective response rate was only 7%, the final results showed a significant improvement in the median survival (7 *vs* 5 months) and quality of life. A second randomized trial (TAX 320 study) compared two doses of docetaxel (arm 1 = 100 mg/m^2, arm 2 = 75 mg/ m^2) with a control arm that was treated with vinorelbine or ifosfamide (arm 3) (5). Significant differences were observed that favored the docetaxel arm for the response rate, the time to progression and the 1-year survival. Based on the result of these two studies, the ASCO in 2003 recommended single docetaxel therapy as a second-line therapy for NSCLC. Our study showed an 18.2% response rate and an 11 month median survival time. The results from our study showed a similar response rate and a little bit superior median survival time as compared to the previous study of phase II and phase III single docetaxel for the second-line therapy of non-small cell lung cancer. These favorable results may be due to the enrolled patients' good performance status and that a large proportion of the patients were treated with third-line and forth-line therapy at the time of disease progression.

Gefitinib was also recommended by the ASCO in 2003 for locally advanced or metastatic non-small cell lung cancer after failure of both platinum-based chemotherapy and docetaxel chemotherapy. Gefitinib, which an orally active inhibitor of epidermal growth factor receptor tyrosine kinase, was studied by two phase II trials for previously treated non-small cell lung cancer (19,20). The overall response rates of the two studies were about 10%. However, a recent phase III study compared gefitinib plus the best supportive care with placebo for the patients with NSCLC who had received one or two prior chemotherapy regimens (21). In that study, gefitinib was not observed to have any statistically significant survival benefit except in the non-smokers, the oriental patients and the adenocarcinoma. The U.S. Food and Drug Administration has limited the usage of gefitinib in 2005. However several Asian studies have shown effective antitumor activity with an improved survival outcome in the never-smokers, the female patients and the adenocarcinoma (20,22).

Premetrexed, a mutitarget antifolate, is another promising drug to use as a second-line therapy for non-small cell lung cancer. A phase II study with a single agent, premetrexed, for non-small cell lung cancer included patients who had progressive disease while on first-line chemotherapy or their disease had progressed within 3 months after the last administration, and they were grouped according to treatment failure after a platinum-containing or a non-platinum-containing regimen (23). The response rates of that study were 4.5% in the first group and 14.1% in the latter group. Hanna et al. Compared pemetrexed (500 mg/m^2) to docetaxel (75 mg/m^2) in a phase III trial of 571 non-small cell lung cancer patients who were previously treated with chemotherapy (24). The overall response rates of both arms were not significantly different (9.1% for pemetrexed v 8.8% for docetaxel); however, the premetrexed arm demonstrated a significantly improved safety profile. Based on these results, premetrexed was considered as a treatment option for second-line non-small cell lung cancer.

In our study, grade 3/4 neutropenia (57.6%) was the most common serious toxicity and the median nadir day was day 9 (range: day 5～19). The incidence of grade 3/4 neutropenia in the other phase II and III studies of second-line single docetaxel (75～100 mg/m^2) was 54～77% (5,6,16,18). The characteristics of neutropenia that developed after docetaxel treatment were that the absolute neutrophil count decreased relatively rapidly, but neutropenic fever or the related infections were relatively rare.

The relative dose intensity of docetaxel was 88.8% in this study. In our opinion, safety is of considerable importance since the principal goal for the second-line treatment of patients with non-small cell lung cancer is palliation. A phase II study of low-dose docetaxel (60 mg/m^2) as the second-line treatment for

non-small cell lung cancer showed a similar response rate (18.5%) and median survival time (9.4 months) (25). Docetaxel 60 mg/m^2 is the standard dose used in Japan, and this has shown the possibility of low dose docetaxel therapy as being effective. Our study also showed a relatively high disease control rate for the patients treated with low dose docetaxel.

CONCLUSIONS

Docetaxel therapy (75 mg/m^2) achieved a relatively high response rate in the advanced non-small cell lung cancer patients who were previously treated with platinum-based chemotherapy. The major toxicity was neutropenia; the absolute neutrophil count decreased relatively rapidly, but neutropenic fever or any related infections were rare.

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