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ORIGINAL ARTICLE

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Japanese experience with second-line chemotherapy with low-dose (60 mg/m^2) docetaxel in patients with advanced non-small-cell lung cancer

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Abstract *Purpose*: To assess the efficacy and toxicity of relatively low-dose docetaxel (60 mg/m^2) for previously treated advanced non-small-cell lung cancer (NSCLC). *Patients and methods*: Patients with advanced (clinical stage IIIA–IV) NSCLC who had previously undergone at least one series of chemotherapy were enrolled. Previous paclitaxel use was allowed, but docetaxel was not. Docetaxel was administered at an initial dose of 60 mg/m^2 intravenously on day 1 over 90 min every 3 weeks. *Results*: From June 1997 to November 1999, 22 patients were entered into this study. The total number of cycles delivered to 22 patients was 53, with a median per patient of 2. Four patients achieved a partial response (PR), and the overall response rate was 18.2% (95% confidence interval 5.1–40.3%). The median time to progression was 13.7 weeks. The median survival time was 7.8 months, and the 1-year survival rate was 25%. About 73% of patients experienced grade 3 or 4 neutropenia. Neutropenic fever was observed in four patients (18%). Non-hematologic toxicities were generally mild. No treatment-related deaths occurred. *Conclusions*: Although the validity of the results of this study is limited due to the small and monoracial study population examined, low-dose (60 mg/m^2) docetaxel for previously treated advanced NSCLC appears to yield antitumor activity and survival benefit comparable to those obtained with the conventional dose (100 mg/m^2).

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Introduction

Although a meta-analysis and a randomized study have shown that platinum-based chemotherapy yields a survival benefit in first-line treatment of advanced non-small-cell lung cancer (NSCLC), this benefit is only modest [15, 16]. Treatment of refractory or relapsed cases after first-line therapy is considered far more difficult [5]. No classic single agent (vindesine, etoposide, epirubicin, or cisplatin) has yielded a response rate greater than 10% in the second-line setting [9, 10, 11]. Thus, in the era of the use of classical agents, even the value of second-line chemotherapy itself was debatable [5].

In the 1990s, however, several new generation drugs (docetaxel, paclitaxel, gemcitabine, vinorelbine, and irinotecan) were introduced, and these demonstrated substantial antitumor activity in the first-line setting [17]. Several phase II studies reconsidering the usefulness of second-line therapy were subsequently performed with each new agent. Among such agents, docetaxel (100 mg/m^2) yielded the most promising results, with response rates of 16–22% [3]. Encouraged by the favorable reports in the series of phase II studies, two large randomized phase III trials have been completed in the USA and by a multinational group [7, 19]. In both of the trials, however, a lower dose (75 mg/m^2) of docetaxel as the experimental arm yielded better survival than the other arms.

In Japan, on the other hand, docetaxel has been used at a relatively lower dose (60 mg/m^2) in both clinical trials and clinical treatment than in European and American countries, in accordance with the recommended dose determined by a Japanese phase I trial [20]. One Japanese cooperative phase II study in the first-line setting yielded a response rate slightly lower (18.7%) than, but not significantly different from, other phase II

trials at higher doses. The median survival time (42 weeks) and the severity of neutropenia, a dose-limiting toxicity of docetaxel, were comparable to those in earlier European and American phase II trials [13].

These results suggested that it was reasonable to assess the efficacy and toxicity of low-dose docetaxel (60 mg/m^2) for previously treated advanced NSCLC.

Patients and methods

Patient selection

Patients with histologically or cytologically documented advanced NSCLC (clinical stage IIIA–IV at the time of enrollment), who had previously undergone at least one series of chemotherapy but not docetaxel-containing regimens, were eligible for entry into this study. Previous paclitaxel use was allowed. An interval of at least 1 month from previous chemotherapy was required. Each patient was required to meet the following criteria: bidimensionally measurable lesion; Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0–2; age 75 years or less; adequate bone marrow reserve (WBC count in the range 4,000–12,000/μl, neutrophil count ≥2,000/μl, platelet count ≥100,000/μl, and hemoglobin ≥9.5 mg/dl); and adequate hepatic and renal function (serum creatinine ≤ 1.1 mg/dl, total bilirubin ≤ 1.5 mg/dl, and serum AST and ALT levels less than twice the upper limit of normal).

Patients with active infection or severe cardiovascular disorders were excluded. Patients with peripheral neuropathy, pleural or pericardial effusion that required drainage, symptomatic brain metastasis, or concomitant malignancy were also excluded. Informed consent was obtained from each patient.

Patient evaluation

Complete blood cell counts, white cell differential, and routine chemistry measurements were performed before treatment, and repeated at least once a week after the first administration of docetaxel. At least one measurable lesion had to be detected by chest roentgenography, computed tomographic (CT) scan, brain CT or magnetic resonance imaging (MRI). All reference lesions were assessed every 4 weeks in principle.

Treatment schedule

Docetaxel diluted in 500 ml 0.9% saline was administered at an initial dose of 60 mg/m^2 intravenously on day 1 over 90 min. This was repeated every 21 days for at least two cycles, unless unacceptable toxicity or disease progression (PD) occurred. Responders could continue the treatment after completion of the second cycle. For patients who had episodes such as grade 4 neutropenia or neutropenic fever, the dose in subsequent courses was reduced by 10 mg/m^2. The treatment was discontinued when non-hematologic toxicities of grade 3 or more excluding nausea/vomiting and alopecia occurred. Premedication and prophylactic antiemetic therapy were administered at the investigator's discretion.

Evaluation of response, survival and toxicity

Tumor response was evaluated using the World Health Organization (WHO) criteria [22]. Evaluation as complete response (CR) required disappearance of all measurable and assessable lesions. A partial response was defined as greater than 50% decrease in the sum of the perpendicular diameters of all measurable lesions and sites evaluated. Both CR and PR had to be maintained for more than 4 weeks.

Toxicity was evaluated and graded according to the Japan Clinical Oncology Group (JCOG) toxicity criteria [21]. Time to progression was calculated as time from first docetaxel infusion to the first objective evidence of progression. Survival was estimated by the product limit method of Kaplan and Meier and calculated from the date of first administration of docetaxel to time of death or last follow-up [12].

Results

Patient characteristics

From June 1997 to November 1999, 22 patients were enrolled in this study. The patients characteristics are presented in Table 1. Two patients had received radiation therapy and five patients had undergone surgery. Almost all patients had undergone a platinum-based regimen as prior therapy, and all but three had undergone only one series of chemotherapy. Nine patients achieved PR, 12 showed no response, and one PD as a result of previous treatment regimens.

Treatment received

The total number of cycles delivered to 22 patients was 53, the median number was 2 per patient, and 47 courses (88.7%) were performed at the planned dose without reduction. For 16 patients (73%), chemotherapy was

Table 1 Patient characteristics

Patients (no., %)	22	
Assessable for response	22	100
Assessable for toxicity	22	100
Gender (no., %)		
Male	17	77
Female	5	23
Age (years)		
Median	67	
Range	43–74	
Performance status (ECOG) (no., %)		
0	2	9
1	17	77
2	3	14
Clinical stage (no., %)		
IIIA	2	9
IIIB	1	5
IV	19	86
Histology (no., %)		
Adenocarcinoma	13	59
Squamous cell carcinoma	7	32
Other	2	9
Prior treatment (no., %)		
Surgery	5	23
Radiotherapy	2	9
Prior regimens (no., %)		
One	19	86
Two	3	14
Platinum-based	20 (19 patients)	
Paclitaxel-containing	0	
Other	5	
Response to last chemotherapy (no., %)		
Partial	9	41
No change	12	55
Progressive disease	1	5

stopped at the end of the second cycle or earlier. Half of the 16 patients were withdrawn because of lack of response, another five due to PD, and the remaining three experienced prolonged leukopenia, AST/ALT elevation, and worsening general status. About 70% of cycles were able to be performed without delay with an interval of 3 weeks. The major reason for delay to subsequent cycles was hematologic toxicity, especially prolonged neutropenia.

Response

All patients were evaluable for response to treatment. Four patients achieved PR, and the overall response rate was 18.2% (95% confidence interval 5.1–40.3%). With the patients divided into two groups based on whether they had responded to prior chemotherapy, the difference between groups in response rate was not significant (Table 2). The median time to progression from day of first administration was 13.7 weeks. Durations of response for four patients were 125, 127, 229, and 338 days, with a median of 178 days.

Survival

The minimum follow-up time was 164 days. The Kaplan-Meier survival curve is shown in Fig. 1. Eight patients were still alive at the time of this analysis, and the median survival time was 7.8 months. The 1-year survival rate was 25%.

Toxicities

Toxicity was evaluated for all patients. No treatment-related deaths occurred. About 73% of patients experienced grade 3 or 4 neutropenia. Neutropenic fever was observed in four patients (18%), but all recovered within a few days with immediate use of antibiotics with or without G-CSF. Non-hematologic toxicities were generally mild and reversible. Patients with grade 3 dermatitis and anaphylaxis recovered with antihistamine and corticosteroid administrations, respectively. Only one patient experienced fluid retention, in the form of leg edema and bilateral pleural effusion, which was able to be controlled with diuretics (Table 3).

Table 2 Response analysis (*CI* confidence interval, *CR* complete response, *CT* chemotherapy, *NC* no change, *PD* progressive disease, *PR* partial response, *PS* performance status, *RR* response rate)

	n	CR	PR	NC	PD	RR (%)	95% CI
Overall	22	0	4	13	5	18.2	5.1–40.3
Response to prior CT							
PR	10	0	2	4	3	20.0	3.0–72.1
NC-PD	12	0	2	9	2	16.7	1.9–48.4
PS							
0–1	19	0	4	12	3	21.1	6.0–45.6
2	3	0	0	1	2	0.0	

Discussion

In phase II studies of docetaxel in first-line settings, in which the dose of docetaxel varied from 60 to 100 mg/m^2, lower doses of docetaxel appeared to have less anticancer activity than higher doses [2, 4, 6, 13, 14]. Several subsequent phase II studies of docetaxel for previously treated NSCLC were conducted in European and American countries with the drug used at 100 mg/m^2 [2, 4, 6, 8, 19]. In both randomized phase III trials

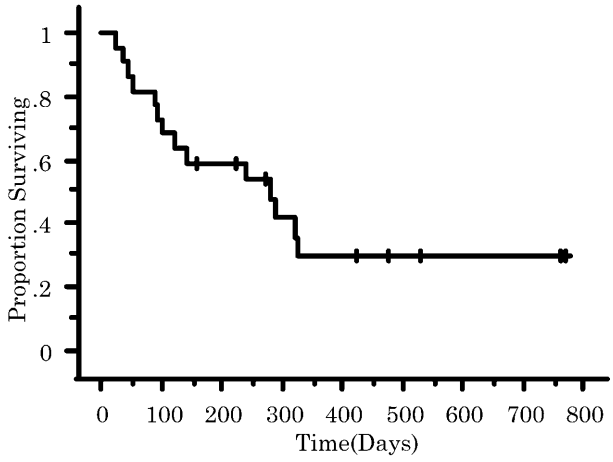

Fig. 1 Survival of patients treated with docetaxel (Kaplan-Meier analysis)

Table 3 Toxicities by patient (any cycle, $n = 22$)

Toxicity	Grade (JCOG)				
	1	2	3	4	3–4 (%)
Leukopenia	1	5	11	3	63.6
Neutropenia	0	5	3	13	72.7[a]
Anemia	7	7	1	–	4.5
Thrombocytopenia	1	0	0	0	0
Alopecia	7	5	0	–	0
Nausea/vomiting	5	1	1	–	4.5
Dermatitis	3	1	1	0	4.5
Fever	0	4	0	0	0
Loss of appetite	3	0	0	0	0
AST/ALT elevation	1	0	1	0	4.5
Facial suffusion	2	0	0	0	0
Anaphylaxis	0	0	1	0	4.5
Constipation	0	1	0	0	0
Diarrhea	1	0	0	0	0
Stomatitis	1	0	0	0	0
Photophobia	1	0	0	0	0
Peripheral edema	1	0	0	0	0
Dizziness	1	0	0	0	0

[a]Neutropenic fever was observed in four patients (18%)

completed in the USA and by a multinational group, however, a 75 mg/m^2 docetaxel arm was employed. The American study, which included two docetaxel arms (75 and 100 mg/m^2 over 1 h), compared with vinorelbine or ifosfamide as a control arm, revealed 75 mg/m^2 docetaxel to have the best 1-year survival rate among the three arms (statistically significant when compared to the control arm).

The multinational phase III study, which also found efficacy for and tolerability of 75 mg/m^2 docetaxel compared to best supportive care (BSC) as control arm in a second-line setting, decreased the docetaxel dose from 100 mg/m^2 to 75 mg/m^2 following interim safety data monitoring because of a higher death rate due to toxicity at 100 mg/m^2. Furthermore, this study failed to reveal an advantage in survival with 100 mg/m^2 docetaxel over BSC [19]. In a recently published American study, the authors noted that earlier treatment discontinuation in the 100 mg/m^2 group and a median of six cycles in the 100 mg/m^2 and ten cycles in the 75 mg/m^2 groups might have accounted for the better survival in the 75 mg/m^2 group. They suggested that lower tolerance of treatment in the 100 mg/m^2 group might at least in part have explained earlier removal from the study of patients in this group than those in the 75 mg/m^2 group.

The present study yielded response and survival profiles similar to those in higher-dose (100 mg/m^2) phase II studies. Adding to the results of the two phase III studies noted above, our findings indicate that a low dose (60 mg/m^2) may be sufficient for adequate efficacy of docetaxel. However, our results cannot be applied globally for two reasons. One is that the present study was performed with a relatively small number of patients, which weakens the validity of the results. The other is that racial differences may affect response to docetaxel, as suggested by the discrepancy in the recommended dose of docetaxel between Japan and American or European countries. The fact that the present regimen overlooked hematologic toxicities similar to those in earlier European and American trials at higher dosages may also indicate the existence of adequate dosage in relation to racial differences. Taguchi et al. have reported that pharmacokinetic data for docetaxel in Japanese patients do not differ from those in American and European individuals, indicating that the issue of racial difference is difficult to resolve [20]. Therefore the results of the present study need to be confirmed in a larger group of Japanese patients and in other countries.

In subset analysis, no PS 2 patients achieved a partial response, and in the present study two of three PS 2 patients died relatively early, within 4 months from the first administration of docetaxel. The results of such subset analyses in previous studies are not consistent. No significant difference in response between PS ≤ 1 and PS 2 patients was found in two other phase II studies [2, 6]. On the other hand, Fossella et al. and Shepherd et al. found in their phase III study that PS ≤ 1 could be a predictor of response [7, 19]. Furthermore, even for first-line chemotherapy, there are considerable differences in prognosis between PS ≤ 1 patients and patients with PS 2 or over [1]. The usefulness of second-line chemotherapy for PS 2 thus remains to be determined.

In the present study, response to prior therapy did not appear to be related to response to docetaxel, as found in all phase II studies of docetaxel in the second-line setting, with the exception of that of Alexopoulos et al. [2, 4, 6, 8, 18]. This is not consistent, however, with the findings of the phase III studies of Fossella et al. and Shepherd et al., in which patients who had responded to prior therapies also tended to respond to second-line treatment with docetaxel [7, 19].

In two Japanese studies of docetaxel, including the present one, the median number of delivered cycles was only two, while in European and American studies a median of three to five cycles were delivered [2, 4, 13]. In the present study, eight patients were withdrawn from treatment at the end of the second cycle due to lack of response at that point because we considered that patients showing no response at the end of the second cycle could not obtain further benefit from additional cycles. However, the American phase III study suggested, as described above, that treatment continued for longer may lead to better survival [7]. This information intensifies the need for reconsideration of the propriety of early discontinuation of treatment in Japan. In the present study, both hematologic and non-hematologic toxicities were generally manageable. No patient discontinued treatment due to cumulative forms of toxicity such as fluid retention or neurotoxicity, perhaps due to a lower dose and shorter-term use of docetaxel. These findings suggest that it may be possible for this regimen to be delivered for a larger number of cycles to selected patients and thus produce better outcomes.

In conclusion, the use of relatively low-dose docetaxel for previously treated advanced NSCLC may yield antitumor activity and survival benefit comparable to those previously reported for higher-dose regimens. However, these results must be interpreted cautiously because this study was carried out in only a small number of exclusively Japanese patients.

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References

1. Albain KS, Ctowley JJ, Leblanc M, Livingston RB (1991) Survival determinants in extensive-stage non-small-cell lung cancer: the Southwest Oncology Group experience. J Clin Oncol 9:1618
2. Alexopoulos K, Kouroussis C, Androulakis N, Papadakis N, Vaslamatzis M, Kakolyris S, Samelis G, Patila E, Vossos A, Samantas E, Georgoulias V (1999) Docetaxel and granulocyte colony-stimulating factor in patients with advanced non-small-lung cancer previously treated with platinum-based chemotherapy: a multicenter phase II trial. Cancer Chemother Pharmacol 43:257

3. Belani CP (1998) Single agents in the second-line treatment of non-small cell lung cancer. Semin Oncol 25[Suppl 8]:10
4. Burris H, Eckardt J, Fields S (1993) Phase II trials of taxotere in patients with non-small cell lung cancer (abstract). Proc Am Soc Clin Oncol 12:335
5. Fossella FV (1997) Single-agent docetaxel in patients with refractory non-small-cell lung cancer. Oncology [Suppl] 7:11
6. Fossella FV, Lee JS, Shin DM, Calayag M, Huber M, Perez-Soler R, Murphy WK, Lippman S, Benner S, Glisson B, Chasen M, Hong WK, Raber M (1995) Phase II study of docetaxel for advanced or metastatic platinum-refractory non-small-cell lung cancer. J Clin Oncol 13:645
7. Fossella FV, Devore R, Kerr R, Crawford J, Natale R, Dunphy F, Kalman L, Miller V, Lee JS, Moore M, Gandara D, Karp D, Vokes E, Kris M, Kim Y, Gamza F, Hammershaimb L, and the TAX 320 Non-Small-Cell Lung Cancer Study Group (2000) Randomized phase III trial of docetaxel mg/m^2 versus vinorelbine or ifosfamide in patients with advanced non-small cell lung cancer (NSCLC) previously treated with platinum-based chemotherapy regimen. J Clin Oncol 18:2354
8. Gandara DR, Vokes E, Green M, Bonomi P, Devore R, Comis R, Carbone D, Karp D, Belani C (2000) Activity of docetaxel in platinum-treated non-small-cell lung cancer: result of a phase II multicenter trial. J Clin Oncol 18:131
9. Ginsberg RJ, Kris MG, Armstrong JG (1993) Cancer of the lung. In: Devita VT, Hellman S, Rosenberg SA (eds) Cancer: principle and practice of oncology, 4th edn. J.B. Lippincott, Philadelphia, p 673
10. Ihde DC (1992) Chemotherapy of lung cancer. N Engl J Med 327:1432
11. Johnson DH (1990) Chemotherapy for unresectable non-small cell lung cancer. Semin Oncol [Suppl] 17:20
12. Kaplan EL, Meier P (1958) Nonparametric estimation from incomplete observations. J Am Stat Assoc 14:457
13. Kunitoh H, Watanabe K, Onoshi T, Furuse K, Niitani H, Taguchi T (1996) Phase II trial of docetaxel in previously untreated advanced non-small cell lung cancer: a Japanese cooperative study. J Clin Oncol 14:1649
14. Miller VA, Rigas JR, Francis PA, Grant SC, Pisters KM, Venkatraman ES, Woolley K, Heelan RT, Kris MG (1995) Phase II trial of a 75 mg/m^2 dose of docetaxel with prednisone premedication for patients with advanced non-small cell lung cancer. Cancer 75:968
15. Non-Small Cell Lung Cancer Collaborative Group (1995) Chemotherapy in non-small cell lung cancer: a meta-analysis using updates on individual patients from 52 randomised clinical trials. BMJ 311:899
16. Rapp E, Pater JL, Willan A, Cormier Y, Murray N, Evans WK, Hodson DI, Clark DA, Feld R, Arnold AM, Ayoub JI, Wilson KS, Latreille J, Wierzbicki RF, Hill DP (1988) Chemotherapy can prolong survival in patients with non-small cell lung cancer: report of Canadian multicenter randomized trial. J Clin Oncol 6:633
17. Rigas JR (1998) Do newer chemotherapeutic agents improve survival in non-small cell lung cancer? Semin Oncol 25:5
18. Robinet G, Kleisbauer JP, Thomas P, Perol M, Carles P, Paillotin D, Lena H, Poirier R, Clouet P, Lenseigne S, Soares JA (1997) Phase II study of docetaxel (taxotere) in first- and second-line NSCLC (abstract). Proc Am Soc Clin Oncol 16:480a
19. Shepherd F, Dancey J, Ramrau R, Mattson K, Gralla R, O'Rourke M, Levitan N, Gressot L, Vincent M, Burkes R, Coughlin S, Kim Y, Berille J, Bergman B (2000) 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
20. Taguchi T, Furue H, Niitani H, Ishitani K, Kanamaru R, Hasegawa K, Ariyoshi Y, Noda K, Furuse K, Fukuoka M, Yakushiji M, Kashimura M (1994) Phase I clinical trial of RP 56976 (docetaxel), a new anticancer drug (in Japanese). Jpn J Cancer Chemother 21:1997
21. Tobinai K, Kohno A, Shimada Y, Watanabe T, Tamura T, Takeyama K, Narabayashi M, Fukutomi T, Kondo H, Shimoyama M (1993) Toxicity grading criteria of the Japan Clinical Oncology Group. The Clinical Trial Review Committee of the Japan Clinical Oncology Group. Jpn J Clin Oncol 23(4):250
22. World Health Organization (1979) Handbook for reporting results of cancer treatment. WHO Offset Publications, Geneva