Cancer Chemother Pharmacol (2003) 52: 19–24
DOI 10.1007/s00280-003-0618-8

ORIGINAL ARTICLE

Seiji Niho · Kaoru Kubota · Koichi Goto
Hironobu Ohmatsu · Taketoshi Matsumoto
Ryutaro Kakinuma · Yutaka Nishiwaki

Combination second-line chemotherapy with gemcitabine and docetaxel for recurrent non-small-cell lung cancer after platinum-containing chemotherapy: a phase I/II trial

Received: 12 November 2002 / Accepted: 6 March 2003 / Published online: 24 April 2003

Abstract *Purpose*: In a randomized trial, docetaxel monotherapy yielded longer survival than the best supportive care in patients with non-small-cell lung cancer (NSCLC) previously treated with platinum-based chemotherapy, and combination chemotherapy regimens containing docetaxel have been assessed to enhance the efficacy of second-line chemotherapy. We conducted a phase I/II trial of gemcitabine and docetaxel in patients with recurrent NSCLC after platinum-based chemotherapy and with an ECOG performance status (PS) of 0 or 1. *Patients and methods*: Docetaxel administration was fixed at a dosage of 60 mg/m^2 on day 8, and gemcitabine was administered on days 1 and 8. The starting dose level of gemcitabine was 800 mg/m^2 (level 0), and the subsequent dose level of gemcitabine was 1000 mg/m^2 (level +1). Treatment was repeated every 3 weeks. *Results*: In the phase I study, 13 patients were enrolled, and in the phase II study, 29 patients were enrolled. Neutropenic fever and omission of treatment on day 8 due to leukopenia (leukocyte count less than 3000/mm^3) were dose-limiting toxicities (DLTs). Three of six patients experienced DLTs at level +1, which was the maximum tolerated dose. Gemcitabine 800 mg/m^2 on days 1 and 8 plus docetaxel 60 mg/m^2 on day 8 (level 0) was recommended for the phase II study. An objective response was observed in 8 (28%) of the 29 patients. The median time to disease progression was 4.2 months (95% CI 0.9–7.7 months). The median survival time was 11.1 months (95% CI 9.9–12.4 months), and the 1-year survival rate was 41%. The most common toxicity, though mild, was hematologic, and consisted of grade 4 neutropenia (18%), grade 3 febrile neutropenia (11%), and grade 3 thrombocytopenia (11%). There were no toxic deaths. Grade 3 non-hematologic toxicities included nausea (4%) and rash (4%). *Conclusions*: The combination chemotherapy of gemcitabine and docetaxel is active and well tolerated in patients with recurrent NSCLC after platinum-based chemotherapy and with a good PS.

Keywords Gemcitabine · Docetaxel · Second-line · Non-small-cell lung cancer

S. Niho (✉) · K. Kubota · K. Goto · H. Ohmatsu
T. Matsumoto · R. Kakinuma · Y. Nishiwaki
Division of Thoracic Oncology,
National Cancer Center Hospital East,
Kashiwanoha 6-5-1, Kashiwa, 277-8577 Chiba, Japan
E-mail: siniho@east.ncc.go.jp
Tel.: +81-471-331111
Fax: +81-471-314724

Introduction

Previous meta-analyses have demonstrated that cisplatin-based chemotherapy produces a modest but significant survival benefit in advanced non-small-cell lung cancer (NSCLC) [6, 14, 17, 24]. Several randomized trials have recently been conducted to compare platinum-based combination regimens containing vinorelbine, gemcitabine, paclitaxel, and docetaxel [11, 20], and since no significant differences were found in survival between them, platinum plus any one of those new agents has become the standard regimen for advanced NSCLC. Initial chemotherapy, however, rarely results in long-term tumor control.

For a long time, second-line chemotherapy for advanced NSCLC has not been considered because of the poor outcome with old cytotoxic agents. Docetaxel, however, has been found to be active against advanced NSCLC in second-line settings. In two randomized trials, docetaxel provided a survival benefit over best supportive care or single-agent chemotherapy with vinorelbine or ifosfamide [2, 22]. A docetaxel dose of 100 mg/m^2 was not well tolerated, and seemed to provide poorer survival than a dose of 75 mg/m^2, and docetaxel 75 mg/m^2 every 3 weeks is now recommended for second-line chemotherapy. Docetaxel monotherapy for recurrent NSCLC after platinum-based chemotherapy has several limitations, however, including low response rates (7–11%), brief duration of disease

control, and minimal survival advantage (especially compared with vinorelbine or ifosfamide).

Gemcitabine is also active against recurrent NSCLC after platinum-based chemotherapy [1, 5, 21, 28]. Gemcitabine 1000 mg/m^2 once a week for 3 weeks every 28 days produced a 19% response rate in a phase II trial [1], and it shows significant activity mainly in patients previously responsive to chemotherapy. Single-agent gemcitabine has a low toxicity profile and is well tolerated.

Docetaxel and gemcitabine have distinct mechanisms of action and non-overlapping toxicities except for neutropenia. Combination chemotherapy generally enhances antitumor activity over single-agent chemotherapy, and several phase I or II studies of the combination of docetaxel and gemcitabine have been conducted in first- and second-line settings [3, 4, 7, 8, 9, 12, 18, 19, 25, 26]. The following doses and schedule have been adopted in most studies: docetaxel 80–100 mg/m^2 on day 1 or 8 and gemcitabine 800–1000 mg/m^2 on days 1 and 8 or on days 1, 8, and 15. However, the recommended dose of docetaxel in Japan is 60 mg/m^2 [27]. We conducted a phase I trial to determine the maximum tolerated dose (MTD) and recommended dose of gemcitabine combined with 60 mg/m^2 of docetaxel. The objective of the subsequent phase II trial was to determine the safety and efficacy of the combination of these agents in recurrent NSCLC after platinum-based chemotherapy.

Patients and methods

Phase I

Patients were required to have histologically or cytologically confirmed NSCLC and failure of a prior platinum-based chemotherapy regimen. Previous exposure to gemcitabine or docetaxel was allowed if the response was not progressive disease. The interval between completion of prior chemotherapy or chemoradiotherapy and the start of the combination chemotherapy had to be at least 4 weeks. All patients had evaluable or measurable disease. Other requirements were: (1) age 20 years or more and less than 76 years; (2) ECOG performance status (PS) of 0 or 1; (3) evaluable or measurable disease; (4) adequate organ function (i.e., total bilirubin $\leq$ 1.1 mg/dl, AST and ALT $<$ 60 IU/l, serum creatinine $\leq$ 1.1 mg/dl, leukocyte count 3,500–12,000/mm^3, neutrophil count $\geq$1500/mm^3, hemoglobin $\geq$9.0 g/dl, and platelets $\geq$100,000/mm^3); (5) no uncontrolled pleural or pericardial effusion; (6) no prior irradiation to areas encompassing more than a third of the pelvis plus spine; (7) neither severe heart disease nor uncontrolled angina; (8) no cardiac infarction within the previous 6 months; (9) no uncontrolled diabetes mellitus; (10) no active infection; (11) no active concomitant malignancy; and (12) no pregnancy or breast-feeding. All patients were required to provide written informed consent. The institutional review board at the National Cancer Center approved the protocol.

Treatment schedule

Docetaxel administration was fixed at a dose of 60 mg/m^2 on day 8. Gemcitabine was administered on days 1 and 8. The starting dose level (level 0) of gemcitabine was 800 mg/m^2, and the subsequent dose levels were defined in advance as outlined in Table 1. Treatment was started within a week of enrollment in the study. Patients received docetaxel 60 mg/m^2 diluted in 250 ml 5% glucose as a 1-h intravenous infusion with infusion of 8 mg dexamethasone and 3 mg granisetron just before the docetaxel infusion. Immediately after completion of the docetaxel infusion, patients were infused intravenously over 30 min with gemcitabine diluted in 100 ml normal saline. Treatment was repeated every 3 weeks. Docetaxel and gemcitabine were not administered on day 8 if the leukocyte count was $<$3000/mm^3 and/or the platelet count was $<$75,000/mm^3. In the event of grade 4 leukopenia or thrombocytopenia, grade 3 neutropenic fever, and/or omission of treatment on day 8 due to leukopenia or thrombocytopenia, gemcitabine was reduced to the next lower level in the following course of chemotherapy. The next course of chemotherapy was started if the leukocyte count was 2,000–12,000/mm^3, the neutrophil count was $\geq$1000/mm^3, platelets $\geq$75,000/mm^3, total bilirubin $\leq$ 2.0 mg/dl, AST and ALT $<$60 IU/l, serum creatinine $\leq$ 1.5 mg/dl, and ECOG PS 0–1, and the patient was afebrile. Therapy was continued for at least two courses unless the patient experienced unacceptable toxicity or had progressive disease. The maximum number of courses of chemotherapy was six.

Table 1 Dose escalation and toxicity (phase I)

	Level −1	Level 0	Level +1
Gemcitabine (mg/m^2)	600	800	1000
Docetaxel (mg/m^2)	60	60	60
Number of evaluable patients	0	6	6[a]
Grade 0/1/2/3			
Leukopenia		2/0/2/2	1/0/2/3
Neutropenia		2/0/2/2	2/1/1/2
Thrombocytopenia		3/3/0/0	3/2/0/1
Neutropenic fever		6/–/–/0	5/–/–/1
Omission of treatment on day 8 due to leukopenia		1	2

[a]One patient developed a bleeding gastric ulcer on day 6 of the first course. He had been treated for a bleeding gastric ulcer 5 months previously. We concluded that the bleeding gastric ulcer was unassociated with the chemotherapy. The case could not be evaluated.

At least three patients were entered at each dose level. If dose-limiting toxicity (DLT) occurred during the first course, up to six patients were treated at that dose level. DLT was defined as follows: (1) grade 4 leukopenia and/or thrombocytopenia, (2) grade 4 neutropenia that lasted for more than 4 days, (3) grade 3 neutropenic fever, (4) grade 3 or 4 non-hematologic toxicity excluding nausea/vomiting, and (5) omission of the treatment on day 8. Dose escalation was stopped if at least two-thirds of the patients in a given cohort had DLT. MTD was defined as the dose level immediately below that causing DLT in two-thirds of the patients or more.

Study evaluations

Pretreatment evaluations consisted of a complete medical history, determination of PS, physical examination, hematologic and biochemical profiles, electrocardiogram, chest radiograph, bone scan, and CT scan of the chest, ultrasound or CT scan of the abdomen, and MRI or CT scan of the whole brain. Evaluations performed weekly were biochemistry studies, complete blood, platelet, and differential counts, physical examination, determination of PS, and toxicity assessment. Imaging studies were performed to assess objective response after every two treatment courses.

Response and toxicity criteria

WHO response criteria were used [15]. Measurable lesions were defined as $\geq$2 cm in at least one diameter on a CT scan. A complete response (CR) was defined as the complete disappearance of all clinically detectable tumors for at least 4 weeks. A partial response (PR) was defined as at least 50% reduction in the product of the largest perpendicular diameters of one or more clearly measurable

lesions or as a greater than 50% reduction in evaluable malignant disease lasting for more than 4 weeks with no new area of malignant disease. No change (NC) was defined as regression of indicator lesions insufficient to meet the response criteria, a less than 25% increase in any measurable lesion, and no new malignant lesions. Progressive disease (PD) was defined as an increase in any measurable lesion by more than 25% or a new malignant lesion. Toxicity was graded using the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2.0.

Phase II

The recommended dose for the phase II study was determined with the toxicities of all courses in the phase I study taken into account. The eligibility criteria were the same as in the phase I study, but measurable lesions were required. The response and toxicity criteria were also the same as in the phase I study.

According to the minimax two-stage phase II study design of Simon [23], the treatment program was designed to refuse response rates of 5% (P_0) and to provide a significance level of 0.05 with a statistical power of 80% in assessing the activity of the regimen as a 20% response rate (P_1). The upper limit for first-stage drug rejection was no response in the 13 evaluable patients; the upper limit of second-stage rejection was three responses in the 27 evaluable patients. Overall survival time was defined as the interval between enrollment in this study and death or last follow-up visit. Median overall survival was estimated using the Kaplan-Meier analysis method [10].

Table 2 Patient characteristics (values are number of patients, except as indicated)

	Phase I	Phase II
Patients enrolled	13	29
Sex		
Male	9	20
Female	4	9
Age (years)		
Median	57	63
Range	37–74	42–73
PS		
0	0	11
1	13	18
Histologic type		
Adenocarcinoma	10	22
Squamous cell carcinoma	2	6
Large-cell carcinoma	1	1
Stage		
IIIB	4	7
IV	9	22
Prior treatment		
Chemotherapy	3	24
Chemoradiotherapy	10	5
Prior chemotherapy (no. of courses)		
Median	2	3
Range	1–4	1–6

Results

Phase I study

Between October 1999 and May 2000, 13 patients were enrolled in the phase I portion. One patient at level +1 developed a bleeding gastric ulcer on day 6 of the first course. He had also been treated for bleeding gastric ulcer 5 months previously. We concluded that the bleeding gastric ulcer was not associated with the chemotherapy and that the case was not evaluable. Therefore, 12 patients were assessable for toxicity. The baseline characteristics of these patients are listed in Table 2. Ten patients received prior chemotherapy and thoracic radiotherapy.

One of the three patients was unable to receive chemotherapy on day 8 of the first course because of leukopenia (WBC 2800/mm^3) at level 0, and we added three patients at level 0. No DLT was observed in the three additional patients. One of the three patients was unable to receive chemotherapy on day 8 of the first course because of leukopenia (WBC 2700/mm^3) at level +1, and we added four patients at level +1. As described above, one patient developed a bleeding gastric ulcer on day 6 of the first course and was not evaluable. One patient was unable to receive chemotherapy on day 8 of the first course because of leukopenia (WBC 1900/mm^3), and another patient developed grade 3 neutropenic fever. Three out of six patients at level +1 experienced DLTs. We therefore considered level +1 to be the MTD. All four patients with DLTs had received prior chemoradiotherapy. No grade 4 leukopenia, neutropenia, or thrombocytopenia was observed in any of the level 0 or +1 courses. We chose level 0 (gemcitabine 800 mg/m^2 and docetaxel 60 mg/m^2) as the recommended dose for the phase II study.

Phase II study

Between August 2000 and July 2001, 29 patients were enrolled in the phase II study, and the patient characteristics are listed in Table 2. The majority of the patients were male (69%), and the median age was 63 years. The most common histologic subtype was adenocarcinoma (76%). A minority of patients had received prior chemotherapy plus thoracic radiotherapy (17%), and the median number of courses of prior chemotherapy was three (range one to six). Prior chemotherapy regimens contained cisplatin plus vinorelbine ($n=10$), cisplatin, vinorelbine, plus gemcitabine ($n=9$), cisplatin plus docetaxel ($n=5$), cisplatin plus vindesine with or without mitomycin C ($n=3$), cisplatin plus irinotecan ($n=1$), and cisplatin, docetaxel, plus mitomycin C ($n=1$). The response to prior chemotherapy was 1 CR, 12 PR, 14 NC, and 2 PD.

In total, 78 courses were administered. The median number of treatment courses was two (range one to six). Only two patients experienced dose reduction, one because of omission of treatment on day 8 and one because of grade 3 neutropenic fever.

All 29 patients enrolled were eligible. The objective responses included PR in 8 of the 29 patients (28%; 95% CI 11–44%), NC in 12, and PD in 8. There were no CRs.

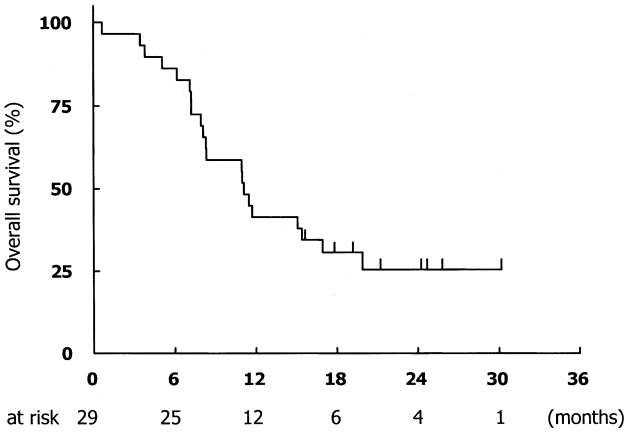

Fig. 1 Overall survival of all patients ($n=29$) in the phase II study was calculated according to the Kaplan-Meier method. The median survival time was 11.1 months, and the 1-year survival rate was 41%. The median follow-up time was 22.7 months

The median number and range of the treatment courses in PR, NC, and PD patients were five (two to six), two (one to five), and two (one to two), respectively. Among the PR or NC patients, 20 received the median three courses of chemotherapy. The prior chemotherapy regimens of eight responders contained cisplatin plus vinorelbine ($n=2$), cisplatin, vinorelbine, plus gemcitabine ($n=2$), cisplatin plus docetaxel ($n=2$), and cisplatin plus vindesine with or without mitomycin C ($n=2$). The response rate in patients who experienced a CR or PR in response to prior chemotherapy was 31% (4/13), whereas the response rate in the NC patients was 29% (4/14). Two patients whose response to prior chemotherapy was PD did not respond to gemcitabine plus docetaxel. One patient could not be evaluated for response because he developed acute interstitial pneumonia after enrollment and did not receive the protocol treatment.

The median follow-up time was 22.7 months. Eight patients were still alive. The median time to disease progression was 4.2 months (95% CI 0.9–7.7 months). The median survival time was 11.1 months (95% CI 9.9–12.4 months), and the 1-year survival rate was 41% (Fig. 1).

Toxicity was evaluated in all 28 patients treated and in all courses. The most common toxicity was hematologic (Table 3). Grade 3 and 4 neutropenia occurred in 43% and 18% of the patients, respectively. Febrile neutropenia occurred in 11% of the patients. There were no toxic deaths. Grade 3 thrombocytopenia occurred in 11% of the patients. Non-hematologic toxicity was generally mild (Table 3). One patient developed a grade 3 rash on day 5 of the first course, and it was concluded that it was gemcitabine-induced dermatitis. The protocol chemotherapy was terminated at the first course. Mild hepatic toxicity was common, but improved immediately.

Discussion

Second-line chemotherapy for recurrent NSCLC after platinum-based chemotherapy has been attracting the attention of investigators. Traditional cytotoxic agents have not been active in a second-line setting after platinum-containing chemotherapy. In a randomized trial, however, docetaxel monotherapy yielded longer survival than the best supportive care in patients with NSCLC previously treated with platinum-based chemotherapy [22], and combination chemotherapy regimens containing docetaxel have been assessed with the aim of enhancing the efficacy of second-line chemotherapy. We conducted a phase I/II trial of gemcitabine and docetaxel in patients with recurrent NSCLC after platinum-based chemotherapy, and the response rate in our phase II trial was 28%, which seemed to be higher than with docetaxel monotherapy. The median survival time was 11.1 months, and the 1-year survival rate was 41% in our phase II trial. The selection criteria such as ECOG PS 0 or 1 could have contributed to this favorable outcome.

Table 3 Maximum toxicity grades (phase II) ($n=29$)

Toxicity	Grade 1		Grade 2		Grade 3		Grade 4	
	No.	%	No.	%	No.	%	No.	%
Leukopenia	4	14	13	46	10	36	1	4
Neutropenia	6	21	5	18	12	43	5	18
Anemia	8	29	15	54	4	14	0	0
Thrombocytopenia	11	39	6	21	3	11	0	0
Nausea	8	29	3	11	1	4	–	–
Vomiting	6	21	1	4	0	0	0	0
Diarrhea	2	7	2	7	0	0	0	0
Infection	2	7	4	14	0	0	0	0
Neutropenic fever	–	–	–	–	3	11	0	0
Fever (no infection)	5	18	3	11	0	0	0	0
Rash	5	18	0	0	1	4	0	0
Neurotoxicity	4	14	0	0	0	0	0	0
AST	12	43	0	0	0	0	0	0
ALT	8	29	2	7	0	0	0	0
Serum creatinine	7	25	0	0	0	0	0	0
Hyponatremia	15	53	–	–	2	7	0	0

Table 4 Results of previous phase II or III trials of combination chemotherapy containing gemcitabine and docetaxel in advanced NSCLC

Reference	Docetaxel		Gemcitabine		G-CSF (days)	Phase	No. of patients		Response rate	
	Dose (mg/m^2)	Day	Dose (mg/m^2)	Day			First-line	Second-line	%	95% CI
12	100	8	1000	1, 8	10–14	II	0	43	33	18.5–46.6
7	30	1, 8	800	1, 8	–	II	0	40	10	NA
26	100	1	800	1, 8, 15	–	II	0	40	33	19–49
4	100	8	1100	1, 8	9–15	III	201	0	30	24.5–36.2
18	85	8	1000	1, 8	–	II	30	6	28	NA
9	100	8	900	1, 8	9–15	II	0	32	16	3.0–28.2
8	80	1	1000	1, 10	2–8	II	34	0	50	32.5–67.5
3	100	8	900	1, 8	9–15	II	41	0	38	24–50
This study	60	8	800	1, 8	–	II	0	29	28	11–44

We considered gemcitabine 800 mg/m^2 on days 1 and 8 and docetaxel 60 mg/m^2 on day 8 to be the recommended dose for the phase II trial. The standard dose of docetaxel in Japan is 60 mg/m^2 [27], lower than in American and European countries (100 mg/m^2). A previous assessment of docetaxel 60 mg/m^2 as second-line chemotherapy in patients with advanced NSCLC showed a response rate of 18% [16], which was comparable with the response rate to the higher docetaxel dose of 100 mg/m^2 found in several phase II trials. Two randomized trials, however, have demonstrated that 75 mg/m^2 of docetaxel yields superior survival to 100 mg/m^2 of docetaxel [2, 22], and that 100 mg/m^2 of docetaxel is not tolerated well. Docetaxel 75 mg/m^2 has been the standard regimen in American and European countries. In a recent Japanese randomized trial, 60 mg/m^2 of docetaxel and 80 mg/m^2 of cisplatin on day 1 every 3 weeks has been shown to yield longer survival and a higher response rate in chemonaive metastatic NSCLC patients than vindesine and cisplatin [13]. Docetaxel 75 mg/m^2 and cisplatin have been used in an ECOG trial [20], and 60 mg/m^2 docetaxel might be as active as 75 mg/m^2.

The findings of several phase II or III trials of combination chemotherapy consisting of gemcitabine and docetaxel in a first- or second-line setting have already been reported (Table 4) [3, 4, 7, 8, 9, 12, 18, 26]. In Greek trials, 100 mg/m^2 of docetaxel with G-CSF support was adopted, but there was no evidence that a higher dose (100 mg/m^2) of docetaxel was more efficacious than lower doses (60–75 mg/m^2). Moreover, G-CSF support was not appropriate in terms of cost. The 800 mg/m^2 dose of gemcitabine on days 1 and 8 in our phase II trial was lower than in previous trials. In our phase I trials, 10 of 13 patients had undergone prior chemotherapy and thoracic radiotherapy. This population had higher hematologic toxicity, which may have resulted in more frequent omission of treatment on day 8 due to leukopenia. Gemcitabine 1000 mg/m^2 on days 1 and 8 (level +1) may be feasible in patients who have never undergone radiotherapy.

A previous phase I trial has demonstrated that gemcitabine 800 mg/m^2 on days 1, 8, and 15 can be safely combined with docetaxel 100 mg/m^2 day 1 of a 28-day cycle [25]. A schedule in which docetaxel was administered on day 15 was also explored but proved not to be feasible because of thrombocytopenia and hepatic dysfunction. In the subsequent phase II trial, gemcitabine dose reductions or omissions were necessary on day 8 in 60% of the courses, and on day 15 in 45% of the courses, mainly because of neutropenia [26]. Since docetaxel-induced neutropenia generally occurs 5 to 8 days after administration, a schedule of docetaxel on day 8 and gemcitabine on days 1 and 8 every 3 weeks has been adopted in most previous trials [3, 4, 9, 12, 18], including our own. Only one patient required omission of gemcitabine on day 8 in our trial, and thrombocytopenia and hepatic dysfunction were also mild. We consider docetaxel on day 8 appropriate.

We allowed previous exposure to gemcitabine or docetaxel if the response was not PD because it was possible that these patients could respond to the combination chemotherapy with gemcitabine and docetaxel. In fact, 4 out of 15 patients who received prior gemcitabine or docetaxel-containing regimens responded to the two-drug combination. There was no correlation between prior chemotherapy regimens and the response to the combination chemotherapy with gemcitabine and docetaxel.

In conclusion, combination chemotherapy consisting of gemcitabine and docetaxel is active and well tolerated in patients with recurrent NSCLC after platinum-based chemotherapy and good PS. The selection criteria could have contributed to the favorable outcome in our trial, and a phase III trial by the Japan Clinical Oncology Group randomizing platinum-treated patients to gemcitabine plus docetaxel or docetaxel is under way.

Acknowledgements This work was supported in part by a grant from the Ministry of Health, Labour and Welfare for the Second Term Comprehensive Strategy for Cancer Control and a Grant-in-Aid for Cancer Research from the Ministry of Health, Labour and Welfare, Japan.

References

1. Crino L, Mosconi AM, Scagliotti G, Selvaggi G, Novello S, Rinaldi M, Della Giulia M, Gridelli C, Rossi A, Calandri C, De Marinis F, Noseda M, Tonato M (1999) Gemcitabine as second-line treatment for advanced non-small-cell lung cancer: a phase II trial. J Clin Oncol 17:2081

2. Fossella FV, DeVore R, Kerr RN, Crawford J, Natale RR, Dunphy F, Kalman L, Miller V, Lee JS, Moore M, Gandara D, Karp D, Vokes E, Kris M, Kim Y, Gamza F, Hammershaimb L (2000) Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small-cell lung cancer previously treated with platinum-containing chemotherapy regimens. The TAX 320 Non-Small Cell Lung Cancer Study Group. J Clin Oncol 18:2354
3. Georgoulias V, Kouroussis C, Androulakis N, Kakolyris S, Dimopoulos MA, Papadakis E, Bouros D, Apostolopoulou F, Papadimitriou C, Agelidou A, Hatzakis K, Kalbakis K, Kotsakis A, Vardakis N, Vlachonicolis J (1999) Front-line treatment of advanced non-small-cell lung cancer with docetaxel and gemcitabine: a multicenter phase II trial. J Clin Oncol 17:914
4. Georgoulias V, Papadakis E, Alexopoulos A, Tsiafaki X, Rapti A, Veslemes M, Palamidas P, Vlachonikolis I (2001) Platinum-based and non-platinum-based chemotherapy in advanced non-small-cell lung cancer: a randomised multicentre trial. Lancet 357:1478
5. Gridelli C, Perrone F, Gallo C, Rossi A, Barletta E, Barzelloni ML, Creazzola S, Gatani T, Fiore F, Guida C, Scognamiglio F (1999) Single-agent gemcitabine as second-line treatment in patients with advanced non small cell lung cancer (NSCLC): a phase II trial. Anticancer Res 19:4535
6. Grilli R, Oxman AD, Julian JA (1993) Chemotherapy for advanced non-small-cell lung cancer: how much benefit is enough? J Clin Oncol 11:1866
7. Hainsworth JD, Burris HA 3rd, Billings FT 3rd, Bradof JE, Baker M, Greco FA (2001) Weekly docetaxel with either gemcitabine or vinorelbine as second-line treatment in patients with advanced nonsmall cell lung carcinoma: phase II trials of the Minnie Pearl Cancer Research Network. Cancer 92:2391
8. Hejna M, Kornek GV, Raderer M, Ulrich-Pur H, Fiebiger WC, Marosi L, Schneeweiss B, Greul R, Scheithauer W (2000) Treatment of patients with advanced nonsmall cell lung carcinoma using docetaxel and gemcitabine plus granulocyte-colony stimulating factor. Cancer 89:516
9. Kakolyris S, Papadakis E, Tsiafaki X, Kalofonos C, Rapti A, Toubis M, Bania E, Kouroussis C, Chainis K, Androulakis N, Agelaki S, Sarra E, Vardakis N, Georgoulias V (2001) Docetaxel in combination with gemcitabine plus rhG-CSF support as second-line treatment in non-small cell lung cancer. A multicenter phase II study. Lung Cancer 32:179
10. Kaplan EL, Meier P (1958) Nonparametric estimation from incomplete observations. J Am Stat Assoc 53:457
11. Kelly K, Crowley J, Bunn PA Jr, Presant CA, Grevstad PK, Moinpour CM, Ramsey SD, Wozniak AJ, Weiss GR, Moore DF, Israel VK, Livingston RB, Gandara DR (2001) Randomized phase III trial of paclitaxel plus carboplatin versus vinorelbine plus cisplatin in the treatment of patients with advanced non-small-cell lung cancer: a Southwest Oncology Group trial. J Clin Oncol 19:3210
12. Kosmas C, Tsavaris N, Vadiaka M, Stavroyianni N, Koutras A, Malamos N, Onyenadum A, Rokana S, Polyzos A, Kalofonos HP (2001) Gemcitabine and docetaxel as second-line chemotherapy for patients with nonsmall cell lung carcinoma who fail prior paclitaxel plus platinum-based regimens. Cancer 92:2902
13. Kubota K, Watanabe K, Kunitoh H, Noda K, Ichinose Y, Katakami N, Sugiura T, Kawahara M, Yokoyama A, Nishiwaki Y, Ohashi Y, Niitani H (2002) Final results of a randomized phase III trial of docetaxel and cisplatin versus vindesine and cisplatin in stage IV non-small cell lung cancer. Proc ASCO 21:296a
14. Marino P, Pampallona S, Preatoni A, Cantoni A, Invernizzi F (1994) Chemotherapy vs supportive care in advanced non-small-cell lung cancer. Results of a meta-analysis of the literature. Chest 106:861
15. Miller AB, Hoogstraten B, Staquet M, Winkler A (1981) Reporting results of cancer treatment. Cancer 47:207
16. Mukohara T, Takeda K, Miyazaki M, Takifuji N, Terakawa K, Negoro S (2001) Japanese experience with second-line chemotherapy with low-dose (60 mg/m^2) docetaxel in patients with advanced non-small-cell lung cancer. Cancer Chemother Pharmacol 48:356
17. Non-small Cell Lung Cancer Collaborative Group (1995) Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials. BMJ 311:899
18. Rebattu P, Quantin X, Ardiet C, Morere JF, Azarian MR, Schuller-Lebeau MP, Pujol JL (2001) Dose-finding, pharmacokinetic and phase II study of docetaxel in combination with gemcitabine in patients with inoperable non-small cell lung cancer. Lung Cancer 33:277
19. Rischin D, Boyer M, Smith J, Millward M, Michael M, Bishop J, Zalcberg J, Davison J, Emmett E, McClure B (2000) A phase I trial of docetaxel and gemcitabine in patients with advanced cancer. Ann Oncol 11:421
20. Schiller JH, Harrington D, Belani CP, Langer C, Sandler A, Krook J, Zhu J, Johnson DH (2002) Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. N Engl J Med 346:92
21. Sculier JP, Lafitte JJ, Berghmans T, Thiriaux J, Lecomte J, Efremidis A, Ninane V, Paesmans M, Mommen P, Klastersky J (2000) A phase II trial testing gemcitabine as second-line chemotherapy for non small cell lung cancer. The European Lung Cancer Working Party. Lung Cancer 29:67
22. Shepherd FA, Dancey J, Ramlau R, Mattson K, Gralla R, O'Rourke M, Levitan N, Gressot L, Vincent M, Burkes R, Coughlin S, Kim Y, Berille J (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
23. Simon R (1989) Optimal two-stage designs for phase II clinical trials. Control Clin Trials 10:1
24. Souquet PJ, Chauvin F, Boissel JP, Cellerino R, Cormier Y, Ganz PA, Kaasa S, Pater JL, Quoix E, Rapp E, et al (1993) Polychemotherapy in advanced non small cell lung cancer: a meta-analysis. Lancet 342:19
25. Spiridonidis CH, Laufman LR, Jones J, Rhodes VA, Wallace K, Nicol S (1998) Phase I study of docetaxel dose escalation in combination with fixed weekly gemcitabine in patients with advanced malignancies. J Clin Oncol 16:3866
26. Spiridonidis CH, Laufman LR, Carman L, Moore T, Blair S, Jones J, George C, Patel T, Roach R, Rupert R, Zangmeister J, Colborn D, Kuebler JP (2001) Second-line chemotherapy for non-small-cell lung cancer with monthly docetaxel and weekly gemcitabine: a phase II trial. Ann Oncol 12:89
27. Taguchi T, Furue H, Niitani H, Ishitani K, Kanamaru R, Hasegawa K, Ariyoshi Y, Noda K, Furuse K, Fukuoka M, et al (1994) Phase I clinical trial of RP 56976 (docetaxel) a new anticancer drug. Gan To Kagaku Ryoho 21:1997
28. van Putten JW, Baas P, Codrington H, Kwa HB, Muller M, Aaronson N, Groen HJ (2001) Activity of single-agent gemcitabine as second-line treatment after previous chemotherapy or radiotherapy in advanced non-small-cell lung cancer. Lung Cancer 33:289