Cancer Chemother Pharmacol (2007) 60:267–274
DOI 10.1007/s00280-006-0369-4

ORIGINAL ARTICLE

Phase II study of biweekly administration of docetaxel and irinotecan in patients with refractory or relapsed advanced non-small cell lung cancer

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Received: 17 August 2006 / Accepted: 23 October 2006 / Published online: 2 February 2007

Abstract We examined the safety and efficacy of the combination of docetaxel and irinotecan administered biweekly in patients with refractory or relapsed advanced non-small cell lung cancer (NSCLC). Patients with previously treated NSCLC of stage III or IV were eligible if they had a performance status of 2 or less, were 75 years or younger, and had adequate organ function. From May 2003 through February 2006, 35 patients (27 men and 8 women; median age 64 years; age range 41–75 years) were enrolled. Patients were treated every 4 weeks with docetaxel (33 mg/m^2 on days 2 and 16) plus irinotecan (50 mg/m^2 on days 1 and 15). None of the 35 patients achieved a complete response, but five achieved a partial response, for an overall response rate of 14.3% (95% confidence interval, 4.8–30.3%). The median survival time was 8 months (range 2–29 months). The median time to progression was 3 months (range 1–12 months). Grade 3 to 4 hematologic toxicities included leukopenia in 48.6% of patients, neutropenia in 54.3%, and anemia in 25.7%. No patients had grade 3 to 4 diarrhea or nausea and vomiting. Although one patient had grade 3 drug-induced interstitial pneumonia, all side effects were manageable, and there were no treatment-related deaths. In conclusion, the combination of docetaxel and irinotecan administered biweekly is a safe and effective treatment for refractory or relapsed NSCLC. However, the search for even more active regimens should be continued.

Keywords Docetaxel · Irinotecan · Refractory or relapsed · Second-line chemotherapy · Non-small cell lung cancer

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Introduction

Almost all patients with advanced non-small cell lung cancer (NSCLC) relapse after first-line chemotherapy and require second-line chemotherapy. Additionally, these patients may require treatment for tumor-related symptoms. Thus, second-line chemotherapy has been increasingly recognized as an important treatment for patients with refractory or relapsed NSCLC.

Docetaxel promotes microtubule assembly and inhibits depolymerization to free tubulin, which results in the arrest of the cell cycle in the M phase [22]. In two phase III trials in patients with NSCLC previously treated with a platinum-based regimen, 75 mg/m^2 of docetaxel administered every 3 weeks resulted in a survival benefit over either best supportive care, or vinorelbine or ifosfamide [5, 25]. The results were overall response rates of 7.1 and 6.7%, with time to progression (TTP) of 10.6 and 8.5 weeks, MSTs of 7.5 and 5.7 months, and 1-year survival rates of 37 and 32%, respectively [5, 25]. As a result of these two randomized trials, docetaxel is currently approved as a standard treatment for recurrent NSCLC.

Irinotecan is a water-soluble camptothecin analog with strong antitumor activity [14]. Irinotecan is a prodrug that is transformed by a carboxylesterase to its active metabolite, SN-38 (7-ethyl-10-hydroxy-camptothecin), which inhibits topoisomerase I, a nuclear enzyme involved in such key nuclear processes as DNA replication [13]. Inhibition of topoisomerase I leads to single-strand DNA breaks and to the death of cancer cells. Irinotecan achieved a response of 16% in patients with advanced NSCLC previously treated with platinum-based agents and taxanes [23].

Preclinical studies have demonstrated that the sequential administration of docetaxel and irinotecan results in at least supra-additive cytotoxicity against human lung cancer cell lines in vitro [19]. In human tumor-derived cell lines, topoisomerase I inhibitors show synergistic effects with subsequently administered docetaxel [28]. Furthermore, the antitumor spectrum of docetaxel was completely different from that of irinotecan in an in vitro study using human lung cancer cell lines [16]. Moreover, no pharmacokinetic interactions have been found between irinotecan and docetaxel [3, 17].

Doses recommended by Masuda et al. [17] for phase II studies in patients with NSCLC are 50 mg/m^2 of irinotecan (days 1, 8, and 15) and 50 mg/m^2 of docetaxel (day 2) administered every 28 days. However, in the phase I trial leading to the recommended dosages, leukopenia or diarrhea or both on day 15 often led to doses being omitted. Therefore, in our phase II study we treated 15 patients with 50 mg/m^2 of irinotecan (days 1, 8) and 50 mg/m^2 of docetaxel (day 2) every 21 days [12]. However, doses of irinotecan were omitted on day 8 in 74% of patients, most often because of neutropenia. For this reason, we decided to modify the treatment schedule as follows: docetaxel (33 mg/m^2) was given on days 2 and 16, and irinotecan (50 mg/m^2) was given on days 1 and 15 every 4 weeks. The calculated dose intensity of docetaxel was approximately 16.5 mg/m^2/week in both treatment schedules. Additionally, Yoshioka et al. [34] have recommended doses of 35 mg/m^2 of docetaxel and 50 mg/m^2 of irinotecan every 2 weeks for patients with inoperable or recurrent gastric cancer.

We performed a study of biweekly administration of a combination of docetaxel 33 mg/m^2 and irinotecan 50 mg/m^2 in patients with refractory or relapsed advanced NSCLC. The aim of the present phase II study was to assess the antitumor activity and toxicity of this regimen in patients with refractory or relapsed advanced NSCLC.

Patients and methods

Eligibility criteria

Patients with refractory or relapsed NSCLC were enrolled. The criteria for study entry were as follows: (1) histologically or cytologically confirmed NSCLC; (2) stage III or IV disease; (3) age 75 years or less; (4) Eastern Cooperative Oncology Group performance status (PS) of 2 or less; (5) measurable or assessable lesions; (6) life expectancy of at least 8 weeks; (7) adequate bone marrow function (white blood cell [WBC] count from 4,000/μl to 12,000/μl, neutrophil count of 2,000/μl or more, platelet count of 1,00,000/μl or more, and hemoglobin level of 9 g/dl or more), hepatic function (total serum bilirubin level less than the upper limit of the normal range, levels of aspartate aminotransferase and alanine aminotransferase less than or equal to twice the upper limits of the normal ranges), and renal function (serum creatinine level less than 1.5 mg/dl, creatinine clearance rate of 50 ml/min or more), and arterial oxygen pressure of 60 mmHg or more; and (8) written informed consent. Patients were excluded if they had massive pleural effusion, pericardial effusion, or ascites, pulmonary fibrosis, uncontrolled diabetes mellitus, severe heart disease, active infection, ileus, diarrhea, symptomatic brain metastasis, or an active second malignancy.

Treatment schedule

Irinotecan (50 mg/m^2) was diluted in 500 ml of normal saline immediately before injection and given as an intravenous drip infusion in 90 min on days 1 and 15. Docetaxel (33 mg/m^2) was diluted in 500 ml of normal saline and given as an intravenous drip infusion in 60 min on days 2 and 16. This regimen was repeated every 4 weeks for a total of 2–4 courses. Chemotherapy was discontinued if the treatment outcome was progressive disease or if intolerable toxicity developed at any time. If there was no change after two courses, subsequent therapy was left to the discretion of the physician in charge of the patient. If two or more weeks passed after the scheduled start of the next cycle until these criteria were satisfied, the patient left the study at that time but was still included in the analysis. Palliative radiotherapy was permitted to control persistent pain associated with bone metastasis.

Administration of docetaxel and irinotecan were omitted and treatment was delayed 1 week if the WBC count was less than 2,000/μl, if the platelet count was less than 75,000/μl, or if the patient had diarrhea of grade 2 or higher. The docetaxel and irinotecan doses

were reduced by 20% of the initial doses if the patient had grade 4 leukopenia or neutropenia lasting 3 days or longer, grade 4 thrombocytopenia, neutropenic fever during grade 4 neutropenia, or diarrhea of grade 3 or higher. Chemotherapy was discontinued for grade 3 or higher nonhematologoic toxicity, except for alopecia, nausea/vomiting, fever, and diarrhea. All patients received premedication with dexamethasone to delay or prevent the onset of edema by docetaxel. The antiemetic medication ondansetron was given prophylactically to all patients. High-dose loperamide therapy was used to manage diarrhea induced by irinotecan. If grade 4 leukopenia or neutropenia occurred after chemotherapy, granulocyte colony-stimulating factor (G-CSF) was administered until the WBC and neutrophil counts had returned to the normal range.

Evaluation

Evaluation before treatment included a baseline history and physical examination, complete blood count with differential, routine chemistry profiles, chest radiography, computed tomography (CT) of the chest and abdomen, magnetic resonance or CT of the brain, and radionucleotide bone scan. Complete blood counts with differential and routine chemistry profiles were determined at least twice a week during chemotherapy. Chest radiography was performed once per week during chemotherapy. Electrocardiograms were obtained before and after chemotherapy.

Tumor measurements were performed after second cycle and fourth cycle. Tumor response was classified according to World Health Organization criteria [33]. Toxicities were assessed and graded according to the National Cancer Institute Common Toxicity Criteria version 2.0. All patients who received at least two cycles of chemotherapy were assessable for response, and all patients who received at least one cycle of chemotherapy were assessable for toxicity and survival.

Statistical methods

TTP was defined as the period from the start of this treatment to the identifiable time for progression. Survival time was measured from the start of the present treatment until death or last follow-up. The Kaplan–Meier method was used to calculate survival curves.

The trial was designed as a phase II study, with response rate as the main endpoint. We chose a 30% response rate as a desirable target level and a 10% response rate as undesirable. The study design had a power of greater than 90% to detect a response with an error of less than 5%. Therefore, we required 22 assessable patients in the first stage and 11 in the second stage, according to the Simon's minimax design. We decided to stop the study if fewer than three patients responded in the first stage.

Results

Patients characteristics

From May 2003 through February 2006, 35 patients were considered eligible (Table 1). Toxicity and survival could be assessed in all 35 eligible patients, and response could be assessed in 33 patients. Two patients could not be evaluated for response because they had not received two courses of chemotherapy owing to their general condition having rapidly deteriorated after receiving chemotherapy. These patients were considered nonresponders. The PS was 0 in 2 patients, 1 in 15 patients, and 2 in 18 patients (51.4%). All patients had received a platinum-containing regimen as first-line chemotherapy: 12 patients had received cisplatin and vinorelbine, 11 patients had received nedaplatin, which is a second-generation platinum derivative that appears to have some abilities and a toxicity profile similar to those of carboplatin, and paclitaxel, 10 patients had received nedaplatin and gemcitabine, 1 patient had received cisplatin and etoposide, and 1 patient had received carboplatin and paclitaxel. Eight (23%) of these 35 patients had previously received two regimens of other chemotherapy. With front-line chemotherapy, 12 patients had a partial response, 9 had no change, 13 had progressive disease, and 1 was not evaluable. The median time off chemotherapy was 3 months (range 1–37 months).

Table 1 Patient characteristics

Total number of patients	35
Sex (M/F)	27/8
Age (range)	64 (41–75)
Performance status at relapse (0/1/2)	2/15/18
Stage at relapse (IIIA/IIIB/IV)	4/2/29
Histologic type	
Adenocarcinoma	25
Squamous	7
Others	3
Number of prior regimens of chemotherapy (1/2)	27/8
Thoracic radiation therapy (yes /no)	16/19
Whole brain radiation therapy (yes/no)	7/28
Response to previous chemotherapy	
Complete response	0
Partial response	12
No change	9
Progressive disease	13
Not evaluable	1

Treatment response and survival

Five (14.3%) of the 35 patients achieved a partial response, 16 (45.7%) had no change, 12 (34.3%) had progressive disease, and 2 (5.7%) were not evaluable, for an overall response rate of 14.3% (95% confidence interval, 4.8–30.3%; Table 2). There were no differences in response rates between patients who had a PS of 0 or 1 (11.8%) and patients who had a PS of 2 (16.7%, $P = 0.68$).

Survival analysis was performed when the median follow-up time of all evaluable patients was 8 months. At the time of analysis, ten patients (28.6%) were alive and none had been lost to follow-up. The median time to progression was 3 months (range 1–12 months). TTP did not differ significantly between patients who had a PS of 0 or 1 (3 months) and those who had a PS of 2 (2 months, $P = 0.58$). The MST from the start of this regimen was 8 months (range 2–29 months; Fig. 1). The 1-year survival rate from the start of this regimen was 30%. MST did not differ significantly between patients who had a PS of 0 or 1 (9 months) and those who had a PS of 2 (5 months, $P = 0.18$).

Toxicity

A total of 71 courses of chemotherapy were given. The median number of courses given per patients was 2 (range 1–4). The most frequent toxicity was myelosuppression. Table 3 lists the maximum toxicities developing during treatment. Grade 3 to 4 leukopenia developed in 48.6% of all patients (17 of 35 patients), and grade 3 to 4 neutropenia developed in 54.3% of patients (19 of 35 patients). G-CSF was given during 35.2% of courses (25 of 71 courses; median duration of administration, 4 days; range 2–7 days). No patients had grade 3 to 4 thrombocytopenia or received platelet transfusions. Although 25.7% of patients (9 of 35 patients) had grade 3 anemia, only three patients received transfusions of erythrocytes. No patients had severe complications related to myelosuppression.

No patients had grade 3 to 4 diarrhea or nausea and vomiting. However, 5.7% of patients (2 of 35 patients) had grade 3 pulmonary toxicity. One patient had grade 3 drug-induced interstitial pneumonia developed during the second cycle of chemotherapy but recovered after receiving steroid pulse therapy and supplemental oxygen. Although another patient had simultaneous grade 3 hypoxia and grade 3 transient liver dysfunction, chest CT did not reveal radiographic interstitial pneumonia. This hypoxia resolved without treatment when the transient liver dysfunction resolved. Although grade 3 infections developed owing to neutropenia in 5.7% of patients (2 of 35 patients), all patients recovered rapidly after treatment with antibiotics. There were no treatment-related deaths.

Table 2 Response rate

	Number ($n = 35$)	%
Complete response	0	0
Partial response	5	14.3
No change	16	45.7
Progressive disease	12	34.3
Not evaluable	2	5.7

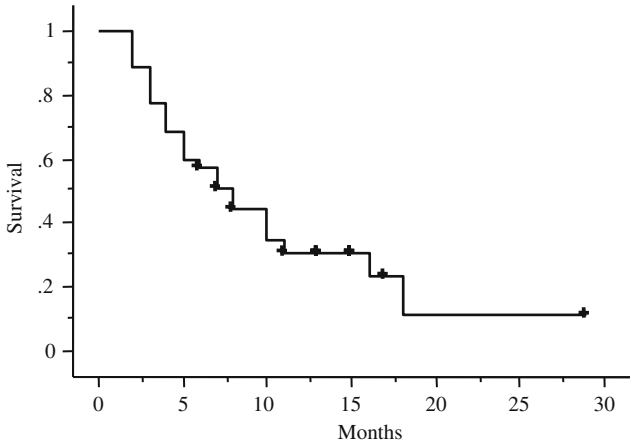

Fig. 1 Overall survival time from the start of treatment

Dose intensity

Doses of both docetaxel and irinotecan were reduced in one patient because of grade 4 neutropenia lasting 3 days and in another patient because of neutropenic fever. During the 71 courses of chemotherapy, 7 (9.9%) doses of both docetaxel and irinotecan were delayed 1 week, usually because of neutropenia. The actual delivered mean individual doses for docetaxel and irinotecan were 15.7 mg/m^2 (95.4% of planned) and 23.9 mg/m^2 (95.4% of planned), respectively.

Discussion

Randomized trials of second-line therapy have demonstrated that docetaxel confers greater survival and clinical benefits and improves quality of life to a greater degree than does best supportive care or monotherapy with vinorelbine or ifosfamide [5, 25]. Thus, docetaxel is currently approved as a treatment for NSCLC refractory to platinum-based agents. However, these trials yielded unsatisfactory results, with response rates of approximately 7%, and MSTs of 5.7 and 7.5 months [5, 25].

Table 3 Toxicity

Toxicity	National Cancer Institute—common toxicity criteria grade				
	1	2	3	4	3 or 4 (%)
Leukopenia	4	8	14	3	48.6
Neutropenia	4	3	7	12	54.3
Thrombocytopenia	1	0	0	0	0
Anemia	7	14	9	0	25.7
Nausea	9	1	0	0	0
Vomiting	2	0	0	0	0
Diarrhea	12	3	0	0	0
Infection	2	1	2	0	5.7
Elevation of serum creatinine	2	0	0	0	0
Elevation of aminotransferases	8	2	1	0	2.9
Electrolyte	2	0	0	0	0
Pulmonary	0	0	2	0	5.7
Arthralgia	0	0	0	0	0
Fatigue or asthenia	6	4	0	0	0
Peripheral neuropathy	2	0	0	0	0

Therefore, research should focus on the development of regimens that are less toxic and more effective for relapsed or refractory NSCLC.

When docetaxel was administered every 3 weeks at a dose of 75–100 mg/m^2, grade 3 or 4 neutropenia developed in more than 80% of patients, and febrile neutropenia frequently led to hospitalization [6, 7]. Both in vitro and in vivo studies have suggested that docetaxel is a schedule-independent drug [2, 31]. In a phase I study, severe myelosuppression was not observed with weekly docetaxel, despite the cumulative dose being much higher than with every 3 weeks schedule [9]. Moreover, the rates of nonhematologic toxicities, such as fatigue, neuropathy, peripheral edema, and alopecia, were also reduced with weekly docetaxel [10]. In a recent phase III study in previous treated NSCLC patients, weekly docetaxel of 35 mg/m^2 demonstrated similar efficacy and better tolerability than 3-weekly docetaxel of 75 mg/m^2 [27]. On the other hand, in a phase II trial of biweekly docetaxel of 50 mg/m^2 as second-line treatment in patients with NSCLC, grade 3 or 4 neutropenia developed in only 16% of patients [30].

Various dosages of docetaxel and irinotecan have been evaluated and recommended [1, 3, 17, 18]. For phase II studies in patients with NSCLC Adjei et al. [1] have recommended doses of irinotecan and docetaxel of 160 mg/m^2 and 65 mg/m^2, respectively, on day 1 every 3 weeks. Couteau et al. [3] have recommended dosages of 275 mg/m^2 of irinotecan and 60 mg/m^2 of docetaxel on day 1 every 3 weeks. However, with these dosages 85% of patients had grade 4 neutropenia, and 22.5% of patients had sepsis. Because quality of life is important for patients receiving second-line chemotherapy, severe toxicity is not acceptable. Therefore, we administered 33 mg/m^2 of docetaxel (days 2 and 16) and 50 mg/m^2 of irinotecan (days 1 and 15) every 4 weeks. In our study, the actual delivered mean individual doses of docetaxel and irinotecan were 15.7 mg/m^2 (95.4% of planned) and 23.9 mg/m^2 (95.4% of planned), respectively.

Several phase II trials of docetaxel using weekly, biweekly, or every 3 weeks schedules in the second-line treatment of NSCLC have achieved overall response rates ranging from 10% to 23%, with MSTs of 4–9.7 months and 1-year survival rates of 8–44% [6, 7, 15, 21, 24, 29, 30]. Table 4 summarizes recent phase II second-line trials of NSCLC. On the other hand, several studies have assessed the combination of docetaxel and irinotecan in the second-line treatment of NSCLC. In these studies, overall response rates have ranged from 6 to 10%, MSTs have ranged from 7.4 to 8 months, and 1-year survival rates have ranged from 24 to 30% [4, 8]. In the present study, the overall response rate was 14.3%, with a MST of 8 months and a 1-year survival rate of 30%. Additionally, there were no differences in response rates or survival rates between patients who had a PS of 0 or 1 and patients who had a PS of 2. These results compare favorably with those of most published trials in the second-line treatment of NSCLC. However, comparing our results with those of other studies of second-line treatment is difficult because of the inclusion of patients with different prognostic factors. In our study the median time off chemotherapy was 3 month, suggesting that patients were likely to have chemoresistant disease.

The most frequent toxicity in the present study was myelosuppression. Grade 3 to 4 hematologic toxicities included neutropenia in 54.3% of patients, thrombocytopenia in 0%, and anemia in 25.7%. These rates of

Table 4 Second-line phase II trials-literature summary

References	Regimen	Response rate (%)	MST (months)	1-year survival rate (%)
Fossela [6]	Docetaxel 100 mg/m^2, q 3 weeks	21	9.7	44
Gandara [7]	Docetaxel 100 mg/m^2, q 3 weeks	16	7	25
Lilenbaum [15]	Docetaxel 36 mg/m^2, weekly	10	8	31
Petrioli [21]	Docetaxel 25 mg/m^2, weekly	23	7	8
Serke [24]	Docetaxel 35 mg/m^2, weekly	11	5.3	23
Valerio [29]	Docetaxel 35 mg/m^2, weekly	12.5	NR	NR
Vazquez [30]	Docetaxel 50 mg/m^2, biweekly	20	4	23
Font [4]	Docetaxel 25 mg/m^2, d 1,8,15, q 4 weeks Irinotecan 70 mg/m^2, d 1,8,15, q 4 weeks	6	8	30
Grossi [8]	Docetaxel 65 mg/m^2,q 3 weeks Irinotecan 160 mg/m^2, q 3 weeks	10	7.4	24
Pectasides [20]	Arm A: Docetaxel 75 mg/m^2, q 3 weeks	14	6.4	34
	Arm B: Docetaxel 30 mg/m^2, d 1,8, q 3 weeks Irinotecan 60 mg/m^2, d 1,8, q 3 weeks	20	6.5	37
Wachters [32]	Arm A: Docetaxel 75 mg/m^2, q 3 weeks	16	7.4	26
	Arm B: Docetaxel 60 mg/m^2, q 3 weeks Irinotecan 200 mg/m^2, q 3 weeks	10	6.2	30

q every, *d* days, *NR* not reported

toxicity compare favorably with those in most recently published trials of second-line treatment of NSCLC. In recent phase II or III trials of second-line chemotherapy for NSCLC, rates of grade 3 to 4 neutropenia, thrombocytopenia, and anemia have ranged from 0 to 85, 0 to 17, and 0 to 23%, respectively [4–8, 15, 20, 21, 24, 25, 29, 32]. Diarrhea is another common dose-limiting toxicity of irinotecan treatment [1, 4, 8, 17]. Font et al. [4] have reported grade 3 to 4 diarrhea in 25% of patients, respectively. Grossi et al. [8] have reported grade 3 to 4 diarrhea and neutropenic fever in 32% and 22% of patients. However, in our study, no patients had grade 3 to 4 diarrhea. Furthermore, only 2 patients (5.7%) had grade 3 neutropenic fever. Although grade 3 drug-induced interstitial pneumonia developed in one patient, it resolved with steroid pulse therapy. All side effects were manageable, and there were no treatment-related deaths.

Two recent randomized phase II trials of second-line treatment in NSCLC have compared the combination of docetaxel and irinotecan with 75 mg/m^2 of docetaxel alone (Table 4) [20, 32]. The addition of irinotecan to docetaxel did not improve significantly the response rate, MST, or 1-year survival rate in either study, although time to progression was prolonged. However, the regimens had different toxicity profiles. Leukopenia, nail changes, myalgia, and arthralgia occurred more frequently with docetaxel alone. Thrombocytopenia and diarrhea were more common with the combination of docetaxel and irinotecan [32]. Toxicities occurring with docetaxel alone might be related to the higher doses administered. In our study, no patients had grade 3 to 4 nail changes, myalgia, or arthralgia related to docetaxel. Moreover, no patients had grade 3 to 4 thrombocytopenia or diarrhea. Therefore, our biweekly regimen is an acceptable option for patients with refractory or relapsed NSCLC.

A randomized trial in previously treated patients with NSCLC has demonstrated that erlotinib, an oral tyrosine kinase inhibitor of epidermal growth factor receptor, prolongs survival and decreases symptoms as compared with placebo [26]. Moreover, treatment with pemetrexed, a novel multitargeted antifolate, resulted in clinically equivalent efficacy outcomes, but with significantly fewer side effects compared with docetaxel in the second-line treatment of patients with NSCLC [11]. Therefore, these drugs should be considered a standard treatment option for second-line NSCLC.

In conclusion, to our knowledge the present phase II study is the first to examine the combination of biweekly docetaxel and irinotecan for refractory or relapsed advanced NSCLC. Biweekly administration of the combination of docetaxel and irinotecan is a safe and effective treatment for refractory or relapsed NSCLC and is, therefore, an acceptable option in this setting. However, our results were not superior to those of other recent trials. In the future, the search for even more active regimens, including new cytotoxic and target-specific agents, should be continued.

References

1. Adjei AA, Klein CE, Kastrissios H, Goldberg RM, Alberts SR, Pitot HC, Sloan JA, Reid JM, Hanson LJ, Atherton P, Rubin J, Erlichman C (2000) Phase I and pharmacokinetic study of irinotecan and docetaxel in patients with advanced

solid tumors: preliminary evidence of clinical activity. J Clin Oncol 18:1116–1123
2. Bissery MC, Guenard D, Gueritte-Voegelein F, Lavelle F (1991) Experimental antitumor activity of taxotere (RP 56976, NSC 628503), a taxol analogue. Cancer Res 51:4845–4852
3. Couteau C, Risse ML, Ducreux M, Lefresne-Soulas F, Riva A, Lebecq A, Ruffie P, Rougier P, Lokiec F, Bruno R, Armand JP (2000) Phase I and pharmacokinetic study of docetaxel and irinotecan in patients with advanced solid tumors. J Clin Oncol 18:3545–3552
4. Font A, Sanchez JM, Taron M, Martinez-Balibrea E, Sanchez JJ, Manzano JL, Margeli M, Richardet M, Barnadas A, Abad A, Rosell R (2003) Weekly regimen of irinotecan/docetaxel in previously treated non-small cell lung cancer patients and correlation with uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1) polymorphism. Invest New Drugs 21:435–443
5. 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. J Clin Oncol 18:2354–2362
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 13:645–651
7. 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: results of a phase II multicenter trials. J Clin Oncol 18:131–135
8. Grossi F, Fasola G, Rossetto C, Spizzo R, Meduri S, Sibau A, Vigevani E, Tumolo S, Adami G, Sacco C, Recchia L, Rizzato S, Ceschia T, Belvedere O (2006) Phase II study of irinotecan and docetaxel in patients with previously treated non-small-cell lung cancer: an alpe-adria thoracic oncology multidisciplinary group study (ATOM 007). Lung Cancer 52:89–92
9. Hainsworth JD, Burris III HA, Erland JB, Thomas M, Greco A (1998) Phase I trial of docetaxel administered by weekly infusion in patients with advanced refractory cancer. J Clin Oncol 16:2164–2168
10. Hainsworth JD, Burris III HA, Litchy S, Morrissey LH, Barton JH, Bradof JE, Greco FA (2000) Weekly docetaxel in the treatment of elderly patients with advanced non-small cell lung carcinoma. Cancer 89:328–333
11. Hanna N, Shepherd FA, Fossela FV, Pereira JR, Marinis FD, von Pawel J, Gatzemeier U, Tsao TCY, Pless M, Muller T, Lim HL, Desch C, Szondy K, Gervais R, Manegold C, Paul S, Paoletti P, Einhorn L, Bunn Jr PA (2004) Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. J Clin Oncol 22:1589–1597
12. Hirose T, Horichi N, Ohmori T, Ando K, Ishida H, Hosaka T, Shirai T, Okuda K, Ohnishi T, Adachi M (2004) Docetaxel and irinotecan in patients with refractory or relapse non-small cell lung cancer. JJLC 44:541 [abstract]
13. Hsiang YH, Hertzberg R, Hecht S, Liu LF (1985) Camptothecin induces protein-linked DNA breaks via mammalian DNA topoisomerase I. J Biol Chem 260:14873–14878
14. Kunimoto T, Nitta K, Tanaka T, Uehara N, Baba H, Takeuchi M, Yokokura T, Sawada S, Miyasaka T, Mutai M (1987) Antitumor activity of 7-ethyl-10-[4-(1-piperidino)-1-piperidino] carbonyloxy-camptothecin, a novel water-soluble derivative of camptothecin, against murine tumors. Cancer Res 47:5944–5947
15. Lilenbaum RC, Schwartz MA, Seigel L, Belette F, Blaustein A, Wittlin FN, Davila E (2001) Phase II trial of weekly docetaxel in second-line therapy for non-small cell lung carcinoma. Cancer 92:2158–2163
16. Matsushita A, Tabata M, Ueoka H, Kiura K, Shibayama T, Aoe K, Kohara H, Harada M (1999) Establishment of a drug sensitivity panel using human lung cancer cell lines. Acta Med Okayama 53:67–75
17. Masuda N, Negoro S, Kudoh S, Sugiura T, Nakagawa K, Saka H, Takada M, Niitani H, Fukuoka M (2000) Phase I and pharmacologic study of docetaxel and irinotecan in advanced non-small-cell lung cancer. J Clin Oncol 18:2996–3003
18. Nogami N, Harita S, Ueoka H, Yonei T, Kiura K, Kamei H, Tabata M, Segawa Y, Gemba K, Tanimoto M (2004) Phase I study of docetaxel and irinotecan in patients with advanced non-small-cell lung cancer. Lung Cancer 45:85–91
19. Okishio K, Kudoh S, Hirata K (1995) Schedule dependent additive effect of docetaxel and irinotecan in vitro. Proc Jpn J Cancer Res 86:619 [abstract]
20. Pectasides D, Pectasides M, Farmakis D, Kostopoulou V, Nikolaou M, Gaglia A, Koumpou M, Mylonakis N, Xiros N, Economopoulos T, Raptis SA (2005) Comparison of docetaxel and docetaxel-irinotecan combination as second-line chemotherapy in advanced non-small-cell lung cancer: a randomized phase II trial. Ann Oncol 16:294–299
21. Petrioli R, Pozzessere D, Messinese S, Sabatino M, Ceciarini F, Marsili S, Correale P, Fiaschi AI, Voltolini L, Gotti G, Francini G (2003) Weekly low-dose docetaxel in advanced non-small cell lung cancer previously treated with two chemotherapy regimens. Lung Cancer 39:85–89
22. Ringel I, Horwitz SB (1991) Studies with RP 56976 (Taxotere): a semisynthetic analogue of Taxol. J Natl Cancer Inst 83:288–291
23. Sanchez R, Esteban E, Palacio I, Fernandez Y, Muniz I, Vieitez JM, Fra J, Blay P, Villanueva N, Una E, Mareque B, Estrada E, Buesa JM, Lacave AJ (2003) Activity of weekly irinotecan (CPT-11) in patients with advanced non-small cell lung cancer pretreated with platinum and taxanes. Invest New Drugs 21:459–463
24. Serke M, Schoenfeld N, Loddenkemper R (2004) Weekly docetaxel as second-line chemotherapy in advanced non-small cell lung cancer: phase II trial. Anticancer Res 24:1211–1216
25. Shepherd FA, Dancey J, Ramlau R, Mattson K, Gralla R, Rourke MO, 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 18:2095–2103
26. Shepherd FA, Pereira JR, Ciuleanu T, Tan EH, Hirsh V, Thongprasert S, Campos D, Maoleekoonpiroj S, Smylie M, Martins R, van Kooten M, Dediu M, Findlay B, Tu D,Johnston D, Bezjak A, Clark G, Santabarbara P, Seymour L (2005) Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med 353:123–132
27. Shuette W, Nagel S, Blankenburg T, Lautenschlaeger C, Hans K, Schmidt EW, Dittrich I, Schweisfurth H, Weikersthal LFV, Raghavachar A, Reisig A, Serke M (2005) Phase III study of second-line chemotherapy for advanced non-small-cell lung cancer with weekly compared with 3-weekly docetaxel. J Clin Oncol 23:8389–8395
28. Taron M, Plasencia C, Abad A, Martin C, Guillot M (2000) Cytotoxic effects of topotecan combined with various active G2/M-phase anticancer drugs in human tumor-derived cell lines. Invest New Drugs 18:139–147

29. Valerio MR, Russo A, Latteri MA, Modica G, Gulotta G, Armata MG, Bajardi E, Cicero G, Pantuso G, Grassi N, Agosta G, Gebbia N (2001) Weekly docetaxel as II line therapy in non-small cell lung cancer: an interim analysis of a phase II study. Lung Cancer 34:S31–S35
30. Vazquez S, Grande C, Amenedo M, Firvida JL, Lazaro M, Alonso G, Cureil T, Huidobro G, Mel JR, Ramos M (2004) Biweekly docetaxel as second-line chemotherapy of patients with advanced non-small cell lung cancer: a phase II study of the Galician Lung Cancer Group (GGCP 006-00). Anticancer Drugs 15:489–494
31. Verweij J, Clavel M, Chevalier B (1994) Paclitaxel (Taxol) and docetaxel (Taxotere): not simply two of a kind. Ann Oncol 5:495–505
32. Wachters FM, Groen HJM, Biesma B, Schramel FMNH, Postmus PE, Stigt JA, Smit EF (2005) A randomized phase II trial of docetaxel vs docetaxel and irinotecan in patients with stage IIIB-IV non-small-cell lung cancer who failed first-line treatment. Br J Cancer 17:15–20
33. World Health Organization: WHO handbook for reporting results of cancer treatment. WHO offset publication no.48. Geneva, Switzerland: World Health Organization, 1979
34. Yoshioka T, Sakata Y, Terashima M, Sekikawa K, Gamoh M, Mitachi Y, Saitoh S, Kanamaru R (2003) Biweekly administration regimen of docetaxel combined with CPT-11 in patients with inoperable or recurrent gastric cancer. Gastric Cancer 6:153–158