Is Irinotecan Plus Docetaxel Useful as Second-Line Therapy in Advanced Non-small Cell Lung Cancer?

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Introduction: The ability of doublet therapy in the second-line setting in patients with platinum-refractory non-small cell lung cancer (NSCLC) has not yet been proven. In this setting, docetaxel (D) has shown efficacy and irinotecan (I) has only recently been introduced. This study was initiated to explore the activity and tolerability of three D + I regimens in platinum pretreated NSCLC patients.

Methods: From March 2003 to June 2006, 65 patients (age range, 39–71 years; 83% male) with relapsed stage III/IV NSCLC were randomly assigned to receive either I 160 mg/m^2 plus D 60 mg/m^2 on day 1 every 21 days (arm A), I 80 mg/m^2 on days 1,8 plus D 60 mg/m^2 on day 1 every 21 days (arm B), or I 60 mg/m^2 plus D 30 mg/m^2 on days 1, 8, 15, and 22 every 42 days (arm C), for a maximum of 18 weeks.

Results: Per protocol analysis (47 of 65) overall response rates were 5.6% (A), 6.7% (B), and 7.1% (C). Median times to progression were 3.4, 4.0, and 4.3 months, respectively. Overall survival was 8.9 (A), 8.3 (B), and 9.4 (C) months. G3/4 neutropenia was more frequent in arms A (42%) and B (55%) whereas G3/4 nonhematologic toxicity was similarly prevalent in all arms, although diarrhea occurred in 47% of arm C patients.

Conclusions: Single-agent treatment with D or the multitarget antifolate pemetrexed or erlotinib remain the best choices and investigational studies, following first-line therapy, are required.

Key Words: Docetaxel, Irinotecan, Second-line chemotherapy, Non-small cell lung cancer, Phase II, Randomized trial.

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Approximately 30% of patients with non-small cell lung cancer (NSCLC) have locally advanced disease at diagnosis; 45% of these patients have metastases; after receiving first-line chemotherapy, patients have a 40 to 50% likelihood of survival at 1 year.[1] A considerable proportion of patients with disease progression after first-line treatment has good performance status and may benefit from second-line treatment. However, until the year 2000, in the absence of active second-line chemotherapy, best supportive care or investigational trials were the only options available to these patients. At that time, based on two phase III randomized trials,[2,3] docetaxel became the standard second-line treatment for NSCLC.[4] Notwithstanding a low response rate, trials based on treatment with docetaxel reported an improvement in survival and quality of life, compared with best supportive care[2] and to ifosfamide or vinorelbine.[3] However, at the standard dose (75 mg/m^2 every 21 days), docetaxel is associated with a significant rate of hematologic toxicity and neutropenic fever.[5]

In a phase III study,[6] the multitarget antifolate agent pemetrexed demonstrated clinically equivalent therapeutic outcomes but a more favorable hematologic toxicity profile compared with docetaxel. Pemetrexed has thus been proposed as the best available single agent for treating NSCLC in the second-line setting, even though response rate is less than 10%.[6]

More recently erlotinib, an inhibitor of tyrosine kinase epidermal growth factor receptor, has demonstrated superiority in terms of overall survival and time to progression compared with best supportive care in pretreated patients with NSCLC.[7] To date, docetaxel, pemetrexed, and erlotinib are considered equivalent options in a nonselected second-line setting.

Irinotecan, a topoisomerase I inhibitor, has shown promising activity as first-line treatment in advanced NSCLC, both as a single agent[8–10] and in combination with platinum compounds.[11–13] In preclinical studies, irinotecan has demonstrated a broad spectrum of antitumor activity.[14–16] The maximum tolerated dose of irinotecan given as a single agent was determined in phase I studies, where late diarrhea and neutropenia were dose-limiting toxicities. Phase II studies of irinotecan as a single agent for NSCLC reported response rates of 15 to 34% and median survival times of 6 to 10 months. Toxicities resulting from the recommended dosage of irinotecan (350 mg/m^2 given every 3 weeks as a 30- to 90-minute infusion) included diarrhea (any grade) in 87% of

patients, grade 3/4 neutropenia in 45%, fatigue in 20%, and nausea and vomiting in 20%.[16]

Preclinical studies of irinotecan in combination with taxanes revealed additive or synergistic effects[17] that may be schedule-dependent. Moreover, a phase I study showed that irinotecan can be safely administered in combination with docetaxel,[18] and a 3-week schedule of administration of irinotecan (160 mg/m^2) plus docetaxel (65 mg/m^2) was recommended for further phase II investigation. Other studies indicated feasibility with weekly schedules or dosing on days 1 and 8 every 21 days.[19–21]

Based on these results, we undertook a phase II, randomized, three-arm study to explore the activity and tolerability of three different irinotecan-docetaxel regimens as second-line therapy in patients with NSCLC. We also sought to determine a schedule of administration that would produce optimal activity and toxicity profiles. Our decision to study a combination therapy is based on evidence that irinotecan and docetaxel differ from platinum compounds in their mechanisms of action and resistance, apparently do not have overlapping toxicity, and produce potentially synergistic activity that may amplify the response rate obtained with single-agent therapy.

METHODS

Study Population

Patients meeting all the following criteria were enrolled: cytologically proven recurrent or metastatic NSCLC after previous first line chemotherapy course containing cisplatin or carboplatin, at least 1 measurable lesion according to Response Evaluation Criteria in Solid Tumors (RECIST),[22] interval of more than 4 weeks from the last chemotherapy application, with all toxic effects completely resolved. Patients with only previous adjuvant chemotherapy were not allowed. Additional inclusion criteria were a performance status of 0 to 1 according to the Eastern Cooperative Oncology Group scale,[23] life expectancy $\geq$12 weeks, and adequate bone marrow reserve (neutrophil count $\geq$2000/μl, platelet count $\geq$100,000/μl, and hemoglobin $\geq$10 g/dl), as well as adequate kidney, liver, and cardiac function. Previous radiotherapy was allowed only if the extent of bone marrow involvement was $\leq$10%, treatment stopped at least 4 weeks before study entry, and assessable disease was outside the radiation field.

Patients with a history or presence of brain or meningeal metastases, prior malignancy, contraindications to use of atropine sulfate, peripheral neuropathy more than grade 2 according to National Cancer Institute Common Toxicity Criteria criteria,[24] or serious systemic disorder were excluded from the study. Women of childbearing potential were required to use an approved form of contraception over the study period.

Written informed consent was obtained from all patients before inclusion. The study protocol was approved by the Ethics Committees of all participating centers.

Study Design

This is a prospective, three-arm, randomized, multicenter, phase II trial. Patients were first stratified according to response obtained with front-line chemotherapy, i.e., as responsive (previous complete or partial response) or unresponsive (previous stabilization or progressive disease), and by participating center.

Patients were randomly assigned to receive irinotecan 160 mg/m^2 intravenously (IV) and docetaxel at 60 mg/m^2 IV on day 1 every 21 days (arm A); irinotecan 80 mg/m^2 on days 1 and 8 and docetaxel 60 mg/m^2 on day 1, repeated every 21 days (arm B); or irinotecan 60 mg/m^2 and docetaxel 30 mg/m^2 on days 1, 8, 15, and 22 every 6 weeks (arm C). All treatments were administered as a 60-minute infusion in 250 ml normal saline, except in arm C, where docetaxel 30 mg/m^2 was administered over 30 minutes.

Patients received ondansetron 8 mg and dexamethasone 8 mg, intravenously, and atropine sulfate 0.25 mg subcutaneously, as premedication for irinotecan infusion. Patients in arms A and B also received oral methylprednisolone 16 mg the evening before docetaxel infusion, 48 mg the day of infusion, and 32 mg the day after infusion. In arm C, patients received oral methylprednisolone 16 mg the day before and 32 mg the day of docetaxel infusion.

Most chemotherapy infusions were administered on an outpatient basis. Treatment was considered complete after six cycles in arms A and B and after three cycles in arm C, for a total of 18 weeks of treatment in each arm. Patients could be withdrawn from the study if disease progression, unacceptable toxicity, withdrawal of consent, physician decision, or need for palliative external beam radiotherapy occurred.

Toxicity was graded according to National Cancer Institute Common Toxicity Criteria criteria[24] and assessed on day 1 in arm A, on days 1 and 8 in arm B, and weekly in arm C by means of physical examination, direct questions, and measurement of hematologic and biochemical variables. If neutrophil count was $<$1500/μl or platelet count was $<$100,000/μl, a 1-week delay was required in arm A; in arm B day 8 and in arm C weekly infusion were omitted. In addition to the delay, for grade 4 neutropenia or thrombocytopenia, or febrile neutropenia, docetaxel and irinotecan doses were stepped down as follows: irinotecan, to 130 mg/m^2 (arm A), 65 mg/m^2 (arm B), or 50 mg/m^2 (arm C); docetaxel, to 50 mg/m^2 (arms A and B) or 25 mg/m^2 (arm C). Chemotherapy was stopped 2 weeks after the previous cycle if neutrophil counts had not recovered. If further episodes of grade 4 neutropenia or thrombocytopenia occurred after dose reduction, chemotherapy was stopped. Irinotecan and docetaxel doses were also reduced for grade 3/4 diarrhea. Patients with diarrhea were immediately prescribed oral loperamide. For diarrhea persisting for more than 48 hours, prophylactic oral fluoroquinolone was given, and patients were hospitalized for rehydration. The docetaxel dose was also reduced for grade 3 mucositis or grade 2/3 neurologic toxicity.

Use of granulocyte-colony stimulating factor (G-CSF) was not allowed during treatment except in patients with febrile neutropenia or grade-4 neutropenia according to American Society of Clinical Oncology guidelines.[25] Supportive treatments, including blood transfusion, erythropoietin, antibiotics, antiemetics, and analgesics, were administered when considered appropriate by the investigators.

Medical history was taken and physical examination performed 1 week before randomization (baseline), before each infusion, and at the end of treatment. Electrocardiography was performed within 14 days before randomization. Hematologic and biochemical analyses were performed 7 days before randomization and repeated before each cycle. Complete blood counts were furthermore monitored weekly while patients were on study. Brain, chest, and upper abdomen computed tomography, and bone scan were performed at least 28 days before randomization. Computed tomography was performed every 6 weeks thereafter to assess tumor response according to RECIST.[22] Duration of response was determined from the date of randomization until disease progression. Post treatment response evaluation were performed every 2 months for at least 12 months or until death.

Data Analysis

Primary study endpoints were efficacy, as determined by objective response rate (complete plus partial response) according to RECIST,[22] and safety, as determined by severe toxicity (grade 3/4 according to the NCIC-CTC criteria).[24] Secondary endpoints were time to progression, time to treatment failure, and survival time (see below for definition).

All endpoints were assessed in patients in arm A and B completing at least two cycles of chemotherapy, or at least one cycle in arm C, in patients without protocol violation (evaluable population) and in all randomly assigned patients.

Statistical Methodology

Sample size estimation was done according to the Briant & Day approach,[26] by assessing each treatment independently. This approach is an extension of the two-stage design proposed by Simon,[27] in that it jointly considers both efficacy and tolerability. To have adequate power to assess treatment efficacy, 21 patients were required to be accrued into each arm at the first stage. Treatment arms with less than three objective responses or with excessive toxicity (defined as containing fewer than 14 patients free of grade 3/4 toxicity) were considered inadequate for evaluation of activity. The second step required 46 patients per arm, for a total of 138 patients. In the second step, treatment arms with fewer than eight responses or with excessive toxicity (defined as fewer than 32 patients free of grade 3/4 toxicity) were also considered inadequate for evaluation of activity.

Input parameters used to determine sample size originated from probability of accepting poor response $\alpha_r \leq 0.10$, probability of accepting toxic treatment $\alpha_t \leq 0.10$, probability of rejecting good treatment $\beta \leq 0.10$, unacceptable response probability $p_{r0} = 0.10$, acceptable response probability $p_{r1} =$

TABLE 1. Demographic and Clinical Characteristics of the Study Population at Time of Randomization ($n = 65$)

	Arm A ($n = 24$)	Arm B ($n = 22$)	Arm C ($n = 19$)
Age (yr, mean ± SD, range)	58.3 ± 8.1 (39–70)	58.7 ± 8.0 (40–68)	60.7 ± 7.3 (42–71)
Male (*n*, %)	21 (87.5)	17 (77.3)	12 (84.2)
Weight (kg, mean ± SD)	75.1 ± 13.7	73.6 ± 12.1	68.9 ± 8.1
Height (cm, mean ± SD)	170.4 ± 5.5	168.0 ± 11.6	165.5 ± 7.2
Concomitant diseases (*n*, %)	14 (58.3)	9 (40.9)	11 (57.9)
Concomitant drug treatments (*n*, %)	24 (100.0)	22 (100.0)	19 (100.0)
ECOG performance status (*n*, %)			
0	13 (54.2)	12 (54.5)	9 (47.4)
1	11 (45.8)	10 (45.5)	10 (52.6)
Histologic type (*n,* %)			
Adenocarcinoma	18 (75.0)	13 (59.1)	10 (52.6)
Squamous-cell carcinoma	5 (20.8)	8 (36.4)	7 (36.9)
Others	1 (4.2)	1 (4.5)	2 (10.5)
Extent of disease (*n*, %)			
Stage IV	17 (70.8)	17 (77.3)	11 (57.9)
Other	7 (29.2)	5 (22.7)	8 (42.1)
No. of disease sites (*n*, %)			
≤2	15 (62.5)	10 (45.5)	9 (47.4)
>2	9 (37.5)	12 (54.5)	10 (52.6)
Previous first-line chemotherapy (*n*, %)			
Cisplatin or carboplatin or oxaliplatin + gemcitabine	19 (79.2)	15 (68.2)	12 (63.2)
Cisplatin + vinorelbine	2 (8.3)	4 (18.2)	4 (21.1)
Others	3 (12.5)	3 (13.6)	3 (15.7)
Previous response to chemotherapy (*n*, %)	13 (54.2)	9 (40.9)	11 (57.9)
Previous surgery for neoplasia (*n*, %)	6 (25.0)	10 (45.5)	8 (42.1)
Previous radiotherapy (*n*, %)	5 (20.8)	7 (31.8)	8 (42.1)

ECOG, Eastern Cooperative Oncology Group.

0.30, unacceptable toxicity probability $p_{t0} = 0.40$, and acceptable toxicity probability $p_{t1} = 0.20$.

Proportions of patients with objective response or unacceptable toxicity were estimated with corresponding 95% confidence intervals. Survival for each treatment, calculated from date of randomization to date of death or most recent follow-up examination, was represented using Kaplan-Meier curves. The same approach was employed for describing time to progression (measured from randomized treatment assignment to the first date of documented progression or death) and time to treatment failure (measured from date of initial treatment to documented progression, withdrawal from study treatment, administration of other antitumor therapy, or death for any cause).

RESULTS

Patient and Treatment Characteristics

Sixty-five patients (24 in arm A, 22 in Arm B, 19 in arm C; age range, 39–71 years; 83% male) were enrolled between March 2003 and June 2006. Baseline patient characteristics are summarized in Table 1. All patients had received first-line platinum-based chemotherapy and were well balanced for previous response and number of metastatic sites, with 51% previously responding to treatment and 52% having two or fewer disease sites. Patients had a performance status of 0 (52%) or 1 (48%). The most common histologic NSCLC type was adenocarcinoma (63%); 69% of patients had stage IV disease at study entry. All patients were taking concomitant medications at time of randomization, and concomitant diseases (mainly diabetes, dyslipidemia, and hypertension) were present in 52% of patients.

Response, Survival, and Time to Progression

Forty-seven of the 65 randomized patients were evaluable for efficacy: 7 patients were excluded from analysis because of protocol violations, 3 did not have postbaseline assessments, and 8 did not complete the minimum period of treatment. Response analysis results are summarized in Table 2. No complete responses were observed. In the evaluable population, 1 patient in arm A (5.6%; 95% confidence interval (CI), 0.1% to 27.3%), 1 in arm B (6.7; 95% CI, 0.2% to 31.9%), and 1 in arm C (7.1%; 95 CI, 0.2% to 33.9%) had a partial remission. Overall 6.5% of patients responded to treatment. Disease was stable in 13 (72.2%), 8 (53.3%), and 10 (71.5%) patients in arms A, B, and C, respectively; progression occurred in 4 (22.2%), 6 (40.0%), and 3 (21.4%) patients.

Because of statistical methods and sample size determination criteria, the minimum number of objective responses required (at least three per arm) to designate the combination as active was not achieved. Consequently enrollment was discontinued, and the study was stopped after reaching the first-stage sample size of 21 patients.

Median time to progression was 3.4 months (95% CI, 2.8–4.8) in arm A, 4.0 months (95% CI, 1.7–8.0) in arm B, and 4.3 months (95% CI, 2.2–7.5) in arm C (Figure 1); median time to treatment failure was 2.8 months (95% CI, 1.5–3.6), 4.0 months (95% CI, 1.5–7.9), and 2.6 months (95% CI, 1.7–4.4). Overall survival was 8.9 months (95% CI, 6.0–12.3) for arm A, 8.3 months (95% CI, 5.9–12.9) for arm B, and 9.4 months (95% CI, 6.5–13.4) for arm C (Figure 2).

For the 31 patients with stable disease, 27 (87.1%) had received previous platinum-based first-line chemotherapy, of whom 15 (55.6%) had a documented response. Previous response did not influence the probability of a response to

TABLE 2. Objective Response Rate to Treatment in Patients Evaluable for Efficacy ($n = 47$)

	Arm A ($n = 18$) n (%)	Arm B ($n = 15$) n (%)	Arm C ($n = 14$) n (%)
Complete remission	—	—	—
Partial remission	1 (5.6)	1 (6.7)	1 (7.1)
Stable disease	13 (72.2)	8 (53.3)	10 (71.5)
Progressive disease	4 (22.2)	6 (40.0)	3 (21.4)

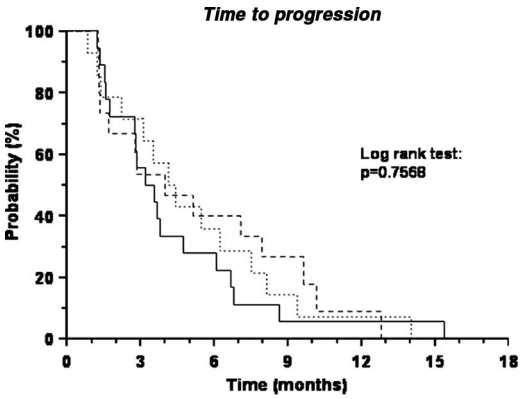

FIGURE 1. Kaplan-Meier curves for time to progression for the evaluable population ($n = 47$). Data are shown for arms A (continuous line, $n = 18$), B (dashed line, $n = 15$), and C (dotted line, $n = 14$). Results of the log-rank test are also reported.

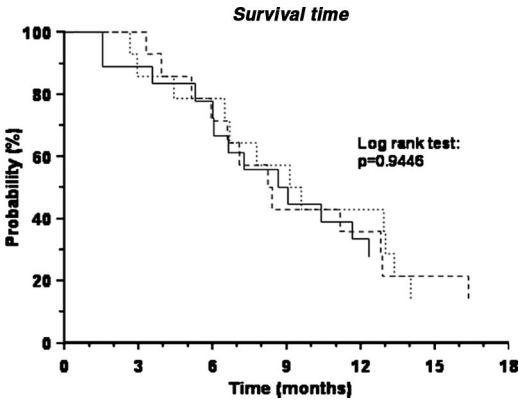

FIGURE 2. Kaplan-Meier survival curves for the evaluable population ($n = 47$). Data are shown for arms A (continuous line, $n = 18$), (dashed line, $n = 15$) and C (dotted line, $n = 14$). Results of the log-rank test are also reported.

TABLE 3. Efficacy Results in Randomized Patients ($n = 65$)

	Arm A ($n = 24$) n (%) (95% CI)	Arm B ($n = 22$) n (%) (95% CI)	Arm C ($n = 19$) n (%) (95% CI)
Complete remission + partial remission	1 (4.2) (0.1–21.1)	1 (4.5) (0.1–22.8)	1 (5.3) (0.1–26.0)
Stable disease	18 (75.0)	10 (45.5)	10 (52.6)
	Median (95% CI)	**Median (95% CI)**	**Median (95% CI)**
Time to progression (mo)	3.8 (2.8–6.5)	3.5 (1.7–7.1)	3.5 (1.9–6.3)
Time to treatment failure (mo)	2.6 (1.6–3.3)	2.6 (1.5–7.0)	2.2 (1.1–3.0)
Survival (mo)	8.9 (6.8–NC)	8.3 (6.0–12.2)	9.6 (6.5–13.4)

CI = confidence interval; NC = Non-Computable.

second-line chemotherapy in any arm. The results for all randomly assigned patients were similar to those for evaluable patients (Table 3).

Toxicity

In all randomly assigned patients, rates of grade 3/4 toxicity occurred in 14 patients in arm A (58.3%; 95% CI, 36.6–77.9%), 14 in arm B (63.6%; 95% CI, 40.7–82.8%), and 12 in arm C (63.2%; 95% CI, 38.4–83.7%).

With regard to hematologic toxicity, grade 3/4 neutropenia was the most common, occurring in 38.5% of patients (particularly in arms A and B), followed by grade 3/4 leukopenia (9.2%) and anemia (3.1%) (Table 4). Grade 1/2 hematologic toxicities were less common than grade 3/4 hematologic toxicities (Table 5).

TABLE 4. Grade 3/4 Toxicity in Randomized Patients ($n = 65$)

	Arm A ($n = 24$) n	Arm B ($n = 22$) n	Arm C ($n = 19$) n	Total ($n = 65$) n (%)
Neutropenia	10	12	3	25 (38.5)
Leukopenia	2	3	1	6 (9.2)
Anemia	2	0	0	2 (3.1)
Diarrhea	4	5	9	18 (27.7)
Nausea or vomiting	5	0	1	6 (9.2)
Fatigue	3	0	3	6 (9.2)
Fever	2	1	1	4 (6.2)
Alopecia	0	1	1	2 (3.1)

TABLE 5. Grade 1/2 Toxicity in Randomized Patients ($n = 65$)

	Arm A ($n = 24$) n	Arm B ($n = 22$) n	Arm C ($n = 19$) n	Total ($n = 65$) n (%)
Neutropenia	0	2	2	4 (6.2)
Leukopenia	1	0	0	1 (1.5)
Anemia	2	0	1	3 (4.6)
Diarrhea	10	8	7	25 (38.5)
Nausea or vomiting	12	5	14	31 (47.7)
Asthenia or fatigue	1	6	3	10 (15.4)
Fever	2	3	3	8 (12.3)
Alopecia	10	6	2	18 (27.7)

Grade 3/4 diarrhea was the most common nonhematologic drug-related adverse event, occurring in 18 patients (27.7%), mainly in arm C. Nausea or vomiting was reported by 37 patients (56.9%), but only 6 patients (9.2%) experienced it at grade 3/4. Other common drug related adverse events were fatigue, fever, and alopecia (Tables 4 and 5). Grade 3 alopecia was rare, occurring in 2 patients (3.1%); grade 1/2 alopecia was more frequent (27.7%), with greater incidence in patients in arm A.

One death occurred in arm C due to treatment-related toxicity (diarrhea with dehydration, followed by hypotension and hypovolemic shock).

DISCUSSION

Platinum-based doublet regimens administered in the first line improved overall survival and quality of life in patients with advanced NSCLC. Many trials have been conducted to assess the efficacy of second-line chemotherapy; to date, only monotherapy with docetaxel[2–4] or pemetrexed,[6] and more recently with erlotinib,[7] has improved survival in these patients.

Since 2000, docetaxel became the treatment paradigm in which only best supportive care was recommended for patients who relapsed after first-line platinum-based chemotherapy. In the study by Shepherd et al.,[2] patients receiving docetaxel, demonstrated improved overall survival at 1 year compared with best supportive care (37% versus 11%, respectively). However, docetaxel administered at a dosage of 100 mg/m^2 was associated to significant toxicity and five deaths related to adverse events occurred. A dosage of 75 mg/m^2 was therefore recommended for clinical use. In a second phase III trial, Fossella et al.[3] compared patients receiving docetaxel (75 mg/m^2 or 100 mg/m^2) with those in the control arm, receiving vinorelbine or ifosfamide. The response rate observed with docetaxel, even though limited, was superior (6.7% and 10.8% for the two dose regimens respectively) to the one obtained in the control arm (0.8%). In addition, as shown in a previous phase III trial,[28] a 1-year survival rate of 32% observed in patients receiving docetaxel reached statistical significance, with an improvement of 10% over that of patients receiving vinorelbine or ifosfamide.

Results from previous trials of single-agent chemotherapy prompted us to design this phase II study with three different schedules of docetaxel administration in combina-

tion with irinotecan, a new agent in the second-line treatment of NSCLC that has shown promising results in monotherapy or combination therapy for patients with advanced disease as first-line chemotherapy.[11–13] Although a number of phase I trials explored the use of docetaxel combined with irinotecan,[20,21,29,30] their varying schedules, sequences of infusion, and toxicity profiles did not produce a clear indication of the optimal combination regimen to employ in clinical practice. Moreover, the safety and efficacy of this combination in various schedules has not been so far investigated in a phase II study.

This is the first randomized trial exploring the activity and safety of three dosages and schedules of irinotecan and docetaxel used as combination therapy in second-line setting in patients with advanced NSCLC. In all three treatment arms, when provided as scheduled, patients received infusional docetaxel followed by infusional irinotecan. In patients in whom irinotecan was administered before docetaxel, activity of the cytochrome P450 3A4 system may have been induced, thereby lessening the exposure to docetaxel. However, previous studies conducted to explore this effect did not show an increase in docetaxel clearance, and clinical pharmacokinetic activity was maintained.[29,30] With regard to efficacy, docetaxel combined with irinotecan produced a very low response rate in our study: only three partial remissions were confirmed overall in the population evaluable for efficacy (6.5%). Stable disease was observed in 65% of the entire patient population, with a median time to progression of 3 to 4 months and a median survival time of 8 to 9 months. Although time to progression tended to be higher for patients in arm B (irinotecan 80 mg/m^2 on day 1 and 8 plus docetaxel 60 mg/m^2 on day 1, every 21 weeks), no statistical conclusions can be made as this trial was not powered to observe a significant statistical differences between the treatment arms.

Overall toxicity was moderate in all treatment arms. As in other trials, diarrhea frequently occurred after treatment with docetaxel and irinotecan[31–33] and, in the majority of patients, was resolved after treatment with high-dose loperamide. Nevertheless, the incidence of severe diarrhea (grade 3/4) tended to be higher in arm C (47.4% versus 19.6% in the other 2 arms combined). Indeed, one patient died in arm C due to grade 4 diarrhea and dehydration complicated by electrolyte alterations and consequent fatal dysrhythmia. Among hematologic toxicities, neutropenia occurred most frequently; arm C showed a lower incidence of neutropenia (15.8%) compared with the other two arms (41.7% in arm A and 54.5% in arm B). A slightly higher incidence of anemia was seen in arm A. In conclusion weekly administration of irinotecan and docetaxel (arm C) seemed to be better tolerated as hematological toxicities respect to gastrointestinal adverse events; these findings reflect the tolerability profile showed by single agent administration with a possible worsening due to doublet therapy.

Despite the inability to complete a comparison for efficacy due to trial premature closure, however, it is interesting to note that time to progression in our study is similar to the one obtained in other phase II studies[31,32] and comparable to results obtained in large phase III trials exploring second-line chemotherapy in advanced NSCLC.[2–7] Nevertheless, compared with recently published studies involving both first- and second-line chemotherapy applying the same regimens, our study had lower overall activity (as determined by best response) and, in arm C, a higher number of episodes of severe diarrhea.

There are no plausible explanations for this lack of activity, although another phase II study[32] demonstrated a similar (10%) response rate with the combination of docetaxel 60 mg/m^2 and irinotecan 200 mg/m^2 on day 1 every 21 days plus G-CSF administered prophylactically from day 2 to day 12. Recently, two other phase II trials explored the activity and safety of this combination,[34,35] with results similar to those of previous studies. In one study, 40 patients received irinotecan 160 mg/m^2 followed by docetaxel 65 mg/m^2 on day 1 every 21 days; an overall response rate of 10% was observed. The most common grade 3/4 adverse events were neutropenia (62%), neutropenic fever (22%), and diarrhea (32%). In a second study, 35 patients received irinotecan 50 mg/m^2 plus docetaxel 33 mg/m^2 bi-weekly and achieved a response rate of 14%, with grade 3/4 neutropenia observed in 54% of patients. In another phase II trial, docetaxel 80 mg/m^2 and irinotecan 200 mg/m^2 (administered on day 1 every 21 days) plus G-CSF administered prophylactically from day 2 to 9 was employed in the first-line setting.[36] In this study, the objective response rate was 23%, with a median survival time of 10.8 months and 1-year-survival rate of 42.2%. The activity of this regimen suggests that this nonplatinum-based chemotherapy is relatively active as first-line treatment and could be administered to patients with contraindications to cisplatin. It is also probable that the objective response rate and the clinical benefit are related more to dosing of irinotecan and docetaxel than to different sequences of infusion. The use of prophylactic G-CSF is probably important in the improved safety of this combination even if it is difficult to enhance the activity especially when this combination is administered in second-line setting in which NSCLC shows an intrinsic resistance to chemotherapy.

The combination of docetaxel and irinotecan produced predictable and generally manageable toxicities. However, patients in arm C demonstrated an unacceptable incidence of grade 3/4 diarrhea, likely related to the dose intensity of both drugs.

Even if the results are similar compared with literature, the originality of our study was a rigorous attempt to better understand if the activity of the combination was influenced by different schedule using an infusion sequence between docetaxel and irinotecan driven by previous pharmacokinetics knowledge.

In conclusion, in our study, the combination docetaxel plus irinotecan in pretreated patients with NSCLC demonstrated a lack of activity and a toxicity profile less favorable than has been observed in previous phase II and III trials using docetaxel alone. Even if time to progression and overall survival with this combination were similar to that observed with other second-line regimens, docetaxel or pemetrexed monochemotherapy and erlotinib remain the standard second-line treatments in platinum refractory patients. Therefore,

studies of regimens combining drugs with newer mechanisms of action are warranted in platinum-refractory, advanced NSCLC patients.

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REFERENCES

1. Scagliotti GV, De Marinis F, Rinaldi M, et al. Phase III randomized trial comparing three platinum based doublets in advanced non-small-cell lung cancer. *J Clin Oncol* 2002;20:4285–4291.
2. Shepherd FA, Dancey J, Dancey J, et al. 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* 2000;18:2095–2103.
3. Fossella FV, DeVore R, Kerr RN, et al. 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* 2000;18:2354–2362.
4. Pfister DG, Johnson DH, Azzoli CG, et al. American Society of Clinical Oncology treatment of unresectable non-small-cell lung cancer guideline: update 2003. *J Clin Oncol* 2004;22:330–353.
5. Ardizzoni A, Tiseo M. Second-line chemotherapy in the treatment of advanced non-small cell lung cancer (NSCLC). *J Chemother* 2004; 16(Suppl 4):104–107.
6. Hanna N, Shepherd FA, Fossella FV, et al. Randomized Phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. *J Clin Oncol* 2004;22: 1589–1597.
7. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al. Erlotinib in previously treated non-small-cell lung cancer. *N Engl J Med* 2005;353: 123–132.
8. Noble J, Ellis PM, Mackay JA, et al. Second-line or subsequent systemic therapy for recurrent or progressive non-small cell lung cancer: a systematic review and practice guideline. *J Thorac Oncol* 2006;1:1042–1058.
9. Bonomi PD. Therapeutic advances in second-line treatment of advanced non-small-cell lung cancer. *Clin Lung Cancer* 2004;6:154–161.
10. Shepherd FA. Second-line chemotherapy for non-small-cell lung cancer. *Expert Rev Anticancer Ther* 2003;3:435–442.
11. Fukuoka M, Niitani H, Suzuki A, et al. A phase II study of CPT-11, a new derivative of campthotecin, for previously untreated non-small-cell lung cancer. *J Clin Oncol* 1992;10:16–20.
12. Ueoka H, Tanimoto M, Kiura K, et al. Fractionated administration of irinotecan and cisplatin for treatment of non-small-cell lung cancer: a phase II study of Okayama Lung Cancer Study Group. *Br J Cancer* 2001;85:9–13.
13. Negoro S, Masuda N, Takada Y, et al. CPT-11 Lung Cancer Study Group West: randomised phase III trial of irinotecan combined with cisplatin for advanced non-small-cell ling cancer. *Br J Cancer* 2003;88: 335–341.
14. Bissery MC, Vrignaud P, Lavelle F, et al. Experimental antitumour activity and pharmacokinetics of the camptothecin analog irinotecan (CPT11) in mice. *Anticancer Drugs* 1996;7:437–460.
15. Abigerges D, Chabot GG, Armand JP, et al. Phase I and pharmacologic studies of camptothecin analog irinotecan administered every 3 weeks in cancer patients. *J Clin Oncol* 1997;13:210–221.
16. Kelly K. Current role of irinotecan in the treatment of non-small-cell lung cancer. *Oncology (Williston Park)* 2002;16:1153–1162.
17. Pei XH, Nakanishi Y, Takayama K, et al. Effect of CPT11 in combination with other anticancer agents in lung cancer cells. *Anticancer Drugs* 1997;8:231–237.
18. Nogami N, Harita S, Ueoka H, et al. Phase I study of docetaxel and irinotecan in patients with advanced non-small-cell lung cancer. *Lung Cancer* 2004;45:85–91.
19. Adjei AA, Klein CE, Kastrissios H, et al. Phase I and pharmacokinetic study of irinotecan and docetaxel in patients with advanced solid tumours. *J Clin Oncol* 2000;18:1116–1123.
20. Font A, Sanchez JM, Rosell R, et al. Phase I study of weekly CPT-11 (irinotecan)/docetaxel in patients with advanced solid tumors. *Lung Cancer* 2002;37:213–218.
21. Bleickardt E, Argiris A, Rich R, et al. Phase I dose escalation trial of weekly docetaxel plus irinotecan in patients with advanced cancer. *Cancer Biol Ther* 2002;1:646–651.
22. Therasse P, Arbuck SG, Eisenhauer EA, et al. Guidelines to Evaluate the Response to Treatment in Solid Tumors. *J Natl Cancer Inst* 2000;92: 205–216.
23. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982;5: 649–655.
24. Appendix A: grading toxicity. In Wittes RE (Ed), Manual of Oncology Therapeutics. Philadelphia, PA: JB Lippincott, 1991:445–448.
25. Ozer H, Armitage JO, Bennett CL, et al. American Society of Clinical Oncology. 2000 update of recommendations for the use of hematopoietic colony-stimulating factors: evidence-based, clinical practice guidelines. American Society of Clinical Oncology Growth Factors Expert Panel. *J Clin Oncol* 2000;18:3558–3585.
26. Briant J, Day R. Incorporating toxicity considerations into design of two-stage phase II clinical trials. *Biometrics* 1995;51:1372–1383.
27. Simon R. Optimal two-stage designs for phase II clinical trials. *Control Clin Trials* 1989;10:1–10.
28. Ornstein DL, Nervi AM, Rigas JR. Docetaxel (Taxotere) in combination chemotherapy and in association with thoracic radiotherapy for the treatment of non-small-cell lung cancer. Thoracic Oncology Program. *Ann Oncol* 1999;10(Suppl 5):S35–S40.
29. Couteau C, Risse ML, Ducreux M, et al. Phase I and pharmacokinetic study of docetaxel and irinotecan in patients with advanced solid tumors. *J Clin Oncol* 2000;18:3545–3452.
30. Masuda N, Negoro S, Kudoh S, et al. Phase I and pharmacologic study of docetaxel and irinotecan in advanced non-small-cell lung cancer. *J Clin Oncol* 2000;18:2996–3003.
31. Pectasides D, Pectasides M, Farmakis D, et al. Comparison of docetaxel-irinotecan combination as second-line chemotherapy in advanced non-small-cell lung cancer: a randomized phase II trial. *Ann Oncol* 2005;16: 294–299.
32. Wachters FM, Groen HJ, Biesma B, et al. A randomised 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* 2005;92:15–20.
33. Yamamoto N, Fukuoka M, Negoro SI, et al. Randomised phase II study of docetaxel/cisplatin vs docetaxel/irinotecan in advanced non-small-cell lung cancer: a West Japan Thoracic Oncology Group Study (WJTOG9803). *Br J Cancer* 2004;90:87–92.
34. Grossi F, Fasola G, Rossetto C, et al. 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* 2006;52:89–92.
35. Hirose T, Shirai T, Ishida H, et al. Phase II study of biweekly administration of docetaxel and irinotecan in patients with refractory or relapsed advanced non-small cell lung cancer. *Cancer Chemother Pharmacol* 2007;60:267–274.
36. Ziotopoulos P, Androulakis N, Mylonaki E, et al. Front-line treatment of advanced non-small cell lung cancer with irinotecan and docetaxel: a multicentre phase II study. *Lung Cancer* 2005;50:115–122.

