

A Phase II Study of Weekly Irinotecan and Capecitabine in Patients with Previously Treated Non-Small Cell Lung Cancer

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ABSTRACT

Purpose: Irinotecan and capecitabine have synergistic antitumor activity with distinct mechanisms of action but without overlapping major toxicity. We conducted a Phase II study to evaluate the efficacy of weekly irinotecan plus capecitabine in patients with previously treated non-small cell lung cancer (NSCLC).

Experimental Design: Eligible patients had received at least one prior chemotherapy regimen. The treatment consisted of irinotecan (90–100 mg/m² i.v.) on days 1 and 8 plus capecitabine (1000 mg/m² p.o. b.i.d.) on days 1–14 of a 21-day cycle. Treatment was given until disease progression or unacceptable toxicity

Results: Thirty-seven patients with median age of 59 years were enrolled. Eighteen (49%) patients had received one prior regimen, and 19 (51%) patients had received two or more prior regimens. The Initial 5 patients received 100 mg/m² irinotecan with grade 3 diarrhea seen in 3 of 5 patients, and subsequent 32 patients received 90 mg/m² irinotecan. Four (11.4%) of 35 evaluable patients had partial response and 12 (34.3%) had stable disease. There was no complete response. All responses were noted in patients who had received one prior regimen (4 of 18, 22%), but there was no response among the patients who had received two or more regimens. Median duration of response was 5.6 months (range, 5–8.7 months). At a median follow-up of 6 months, median survival was 7.4 months (95% confidence interval, 3.6–9.0). Grade 3 or 4 toxicities were neutropenia (12%), anemia (13%), and diarrhea (12%) at the dose level of 90 mg/m².

Conclusions: Weekly irinotecan plus capecitabine had favorable antitumor activity and toxicity profile as a second-line treatment for recurrent NSCLC. This regimen may

provide an additional treatment option for patients with advanced NSCLC.

INTRODUCTION

Current first-line treatment for advanced NSCLC¹ is generally platinum-based combination chemotherapy. Because most patients have received prior platinum-containing regimens, second-line treatment with other platinum-containing regimen carries the risk of cumulative toxicity and cross-resistance (1). More recently, several new agents have shown higher response rates as single first-line treatment, including paclitaxel, docetaxel, gemcitabine, vinorelbine, and irinotecan (2). Furthermore, noncross resistance between new agents and cisplatin provides the rationale for second-line treatment with noncisplatin-containing regimens of new agents (3–5).

Irinotecan is a semisynthetic chemotherapeutic agent derived from the natural alkaloid camptothecin and belongs to topoisomerase-I interactive compounds (6, 7). Irinotecan demonstrated a broad spectrum of efficacy against various solid tumors. Of special interest, considerable activity against 5-FU refractory colorectal cancer has led to an extensive evaluation of irinotecan and 5-FU combination (8–10). Irinotecan has demonstrated lack of cross-resistance and synergistic antitumor activity with 5-FU in patients with chemotherapy-naïve and 5-FU-pretreated metastatic colorectal cancer (8–10). Consequently, the combination of irinotecan and 5-FU has been approved as first-line therapy for patients with metastatic colorectal cancer and it generated a great interest in irinotecan plus capecitabine combination.

Capecitabine (Xeloda) is an oral fluoropyrimidine, which was rationally designed to generate 5-FU preferentially in tumor cells by TP and have shown comparable efficacy when compared with bolus 5-FU (11). In two large randomized trials, a superior therapeutic index was reported for capecitabine as compared with bolus 5-FU/Leucovorin in patients with metastatic colorectal cancer (12, 13). Higher expression of TP in tumor cells than in normal cells has been accounted for the tumor selectivity of capecitabine (11).

The synergistic antitumor activity of irinotecan and 5-FU may be through a prolonged inhibition of thymidylate synthase, which is involved in biosynthesis of DNA and considered as the main intracellular target of 5-FU, and increased incorporation of 5-FU metabolites into DNA (14). Irinotecan plus capecitabine combination also showed synergistic antitumor activity in pre-

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¹ The abbreviations used are: NSCLC, non-small cell lung cancer; 5-FU, 5-fluorouracil; TP, thymidine phosphorylase; PS, performance status; ECOG, Eastern Cooperative Oncology Group; NCI-CTC, National Cancer Institute Common Toxicity Criteria; HFS, hand-foot syndrome; SD, stable disease; CR, complete response; PR, partial response; PD, progressive disease; CI, confidence interval; DI, dose intensity.

clinical and clinical studies (15, 16). Recently, preclinical evidence indicates that irinotecan up-regulates TP expression (15), which may provide the basis for the synergistic antitumor activity of irinotecan and capecitabine combination.

On the basis of the synergistic antitumor activity with distinct mechanisms of action but without overlapping major toxicity, we conducted this Phase II study of weekly irinotecan plus capecitabine to evaluate the efficacy and toxicity profile in patients with advanced NSCLC who had PD after one or more chemotherapy regimens. The dose schedule of this study was based on two Phase II trials of irinotecan/capecitabine in advanced colorectal cancer in which 100–120 mg/m² irinotecan was given on days 1 and 8 with 1000 mg/m² capecitabine twice daily for 2 weeks every 3 weeks (15, 16).

MATERIALS AND METHODS

Eligibility. Eligible patients were required to have locally advanced or metastatic NSCLC that failed one or more prior chemotherapy regimens and at least one bidimensionally measurable lesion. Before study entry, a minimum of 21 days must have elapsed after any prior chemotherapy. ECOG PS of 0–2 was required, as was adequate bone marrow (absolute granulocyte count of $\geq 2.0 \times 10^9$ cells/ \geq and platelet count of $\geq 100 \times 10^9$ cells/liter), hepatic (total bilirubin level within normal limits, alkaline phosphatase level ≤ 5 times the upper limit of normal, and serum transaminase ≤ 1.5 times the upper limit of normal), and renal function (serum creatinine level ≤ 2.0 mg/dl or creatinine clearance ≥ 60 ml/min). No restriction was placed on the number of prior chemotherapy regimens, the amount of prior chemotherapy, or the agents used. Patients who had received prior radiation therapy were eligible provided that at least 30 days had elapsed from completion of radiation before study entry. Patients with asymptomatic brain metastases were eligible. Exclusion criteria included prior history of malignancies except basal cell carcinoma of the skin or carcinoma *in situ* of the cervix, active infection, or other serious underlying medical conditions. All patients signed written informed consent. The study was approved by Institutional Review Board of our institution and was conducted in compliance with Institutional Review Board regulations.

Baseline and Treatment Evaluation. All patients underwent a medical history and physical examination. Assessment, including complete blood cell count, renal and liver function tests, urinalysis, performance status evaluation, height and weight determination (including weight loss), were conducted within 2 weeks before enrollment. Chest X-rays, chest and abdominal computed tomography scans, brain magnetic resonance imaging or computed tomography, and radionuclide bone scan were conducted within 4 weeks before enrollment. Complete blood cell count was repeated on days 8 and 15. Before each course, the medical history and physical examination, laboratory assessment, chest X-ray, weight determination, and toxicity evaluation were repeated. Toxicity was graded according to NCI-CTC. HFS was graded 1–3, as defined in previous capecitabine clinical studies (17).

Treatment. Treatment was given in the outpatient setting. Initial 5 patients received 100 mg/m² i.v. irinotecan on days 1 and 8 plus 1000 mg/m² p.o. b.i.d. capecitabine on days

1–14 of a 21-day cycle. At this dose level, 3 of 5 patients developed grade 3 diarrhea. Thereafter, the dose of irinotecan was reduced to 90 mg/m², whereas the dose of capecitabine was kept the same and the treatment was repeated every 3 weeks as toxicity permitted. Irinotecan was diluted in 500 ml of 5% dextrose in water and infused over 90 min. Patients in this study were premedicated with 20 mg i.v. dexamethasone and 8 mg i.v. ondansetron. To prevent irinotecan-related gastrointestinal toxicity, patients were given orally sodium bicarbonate (2.0 g/day), ursodeoxycholic acid (2.0 g/day), magnesium oxide (300 mg/day), and ondansetron (8 mg \times 2/day) for 4 days immediately after irinotecan infusion. To control delayed diarrhea, patients were advised to take 2 mg of loperamide every 4 h after the first episode of diarrhea. Treatment was given until disease progression or unacceptable toxicity.

Dose Modification. Next course of treatment was to begin only when the granulocyte count was $\geq 1,500/\text{mm}^3$, and the platelet count was $\geq 100,000/\text{mm}^3$, and any other treatment-related toxicities were less than or equal to grade 1; otherwise, treatment was withheld for up to 1 week. If the toxicity had not resolved to grade 0–1 at the end of this period, treatment was delayed for 1 additional week.

Planned treatment with capecitabine within a cycle was withheld in the presence of grade 2 nonhematological (except isolated hyperbilirubinemia or alopecia) or grade ≥ 3 hematological toxicity. Capecitabine was resumed at either the original dose level for grade 2 nonhematological toxicity or grade 3 hematological or 25% dose reduction for grade ≥ 3 nonhematological or grade 4 hematological toxicity. For grade 2–3 HFS, capecitabine treatment was withheld until resolution to less than or equal to grade 1 and then restarted at the same dose or at the preceding dose level. Capecitabine treatment was not interrupted for isolated hyperbilirubinemia.

Irinotecan treatment on day 8 was withheld for the presence of grade ≥ 2 hyperbilirubinemia or any other grade ≤ 3 toxicity during the scheduled day of irinotecan administration, and the patient was reevaluated weekly until regress to less than or equal to grade 2. Missed doses of irinotecan were not to be made up. Treatment of next cycle was restarted at the same dose for grade 3 toxicity and reduced by 10 mg/m² for grade 4 toxicity during the preceding cycle.

Response Evaluation. Responses were evaluated every three cycles of cycles using the same evaluation method. Objective tumor responses were evaluated according to the WHO criteria issued in 1979 (18). CR was defined as the disappearance of all known disease for at least 4 weeks with no new lesion appearing. PR referred to an at least 50% decrease in the sum of the products of bidimensional diameters for at least 4 weeks without the appearance of new lesions. SD was defined as failure to observe a PR or CR, with no progressive or new lesions were observed for at least 4 weeks. PD was defined as a $\geq 25\%$ increase in the products of bidimensional diameters of any measurable lesion or the appearance of new lesions. The response status of all of the patients considered to be showing an objective response (CR or PR) was confirmed independently by an external referee.

Posttreatment evaluation was performed every 2 months until death or PD. Treatment after PD was left to the discretion of the investigator.

Statistics. The primary objective of this study was to estimate the objective response rate of irinotecan and capecitabine in patients with advanced stage NSCLC. The sample size was calculated according to Simon's two-stage minimax design (19). A targeted objective response rate of 20% versus an objective response rate of no interest of 5% with a power of 0.90 at a one-side significance level of 0.05 was chosen and accrual of 32 evaluable patients was projected. All patients receiving at least one course of therapy were considered assessable for toxicity, and all eligible patients who received at least one cycle of therapy were included for response evaluation.

Response rate was calculated as the ratio between the number of responders and number of patients assessable for tumor response. Duration of response and survival are estimated using the Kaplan-Meier method (20). Duration of response was calculated for all responders from the date of first treatment until the date that PD was noted. Survival was calculated from the first day of treatment to death. Patients still alive were censored at the last day the patient was known to be alive. CIs were constructed around the Kaplan-Meier estimates using Greenwood's variance formula. 95% CIs for response rate were calculated using methods for exact binomial confidence intervals (SPSS software, version 9.0; SPSS, Inc., Chicago, IL). DI was calculated by using the method of Hryniuk and Bush (21).

RESULTS

Patients' Characteristics. Thirty-seven patients were accrued from December 2001 to January 2003. All patients were eligible for toxicity evaluation, but 2 patients were not evaluable for response evaluation; 1 because of patient's refusal after the first dose of treatment and the other because of sudden death on day 8 of the first cycle. The characteristics of the 37 eligible patients are listed in Table 1. The median age was 59 years (range, 24–78 years). Twenty-seven (73%) patients were male and 23 (62%) patients had adenocarcinoma, which was the most common histology. The majority of patients had stage IV disease (81%) and 24 (65%) patients had ECOG PS of 0 or 1.

Eighteen (49%) patients had received one prior regimen (7-cisplatin-containing regimen, 11-gemcitabine plus vinorelbine), whereas 19 (51%) had received two or more regimens. Best responses to any prior treatment were evaluable in 33 patients, and only 8 (22%) patients had responded to prior treatment. Most of the patients had PD during or shortly after prior therapy, and 28 (76%) patients had treatment free interval of < 3 months since last administration of prior chemotherapy (Table 1).

Treatment Cycle Administered. A total of 98 cycles was administered with the median of 2 (range, 1–9 cycles). Treatment was delayed for a median of 7 days in 22 (22%) of 98 cycles. The most common cause for the delay was neutropenia (8 cycles) and diarrhea (6 cycles). Dose reduction was necessary in additional 13 (13%) cycles, mainly because of diarrhea (6 cycles) and neutropenia (6 cycles). The median DI was 59.4 mg/m²/week (89.1% of planned dose) for irinotecan and 600.3 mg/m²/week (90.0% of planned dose) for capecitabine at the dose level of 100 mg/m² irinotecan. At the dose level of 90 mg/m² irinotecan, the median DI was 55.3 mg/m²/week (92.1%

Table 1 Patient characteristics

	No. of patients	(%)
Patients enrolled	37	(100)
Evaluable for toxicity	37	(100)
Evaluable for response	35	(95)
Sex		
Male	27	(73)
Female	10	(27)
Age, years	59 (range 24–78)	
ECOG performance status		
0	7	(19)
1	17	(46)
2	13	(35)
Histology		
Squamous cell	14	(38)
Adenocarcinoma	23	(62)
Stage		
III B	7	(19)
IV	30	(81)
No. of prior regimens		
1	18	(49)
2	15	(41)
≥3	4	(10)
Prior surgery	9	(24)
Prior chest radiation therapy	3	(8)
Best response to any prior treatments		
PR	8	(22)
SD	9	(24)
PD	16	(43)
Inevaluable ^a	4	(11)
Treatment-free interval		
<3 months	28	(76)
3–6 months	3	(8)
≥6 months	6	(16)

^a Four patients had received prior chemotherapy in a postoperative adjuvant setting without evaluable disease.

of planned dose) for irinotecan and 600.0 mg/m²/week (90.0% of planned dose) for capecitabine.

Tumor Responses and Survival. There were 4 (11.4%) PRs, 12 (34.3%) SDs, and 19 (54.3%) PDs of 35 evaluable patients (Table 2). There was no CR. The overall response rate was 11.4% (95% CI, 0.6–21.4%), and the median duration of response was 5.6 months (range, 5–8.7 months).

The patients who had received one prior regimen showed significantly higher response rate than those who had received two or more prior regimens [4 of 18 (22%) versus 0 of 17 (0%), $P = 0.04$]. So did the patients who had a longer treatment-free interval (*i.e.*, ≥6 months) as compared with the others [3 of 6 (50%) versus 1 of 29 (3%), $P = 0.001$], as well as the patients who had received a cisplatin-containing regimen as the first-line treatment [4 of 7 (57%) versus 0 of 11 (0%), $P = 0.004$].

According to the status of response to prior chemotherapy regimens, all 3 patients who progressed after postoperative adjuvant chemotherapy achieved objective tumor responses. One of 8 responders and none of 24 nonresponders responded to the current irinotecan plus capecitabine regimen. Patient's performance status, stage, and sex had no significant effect on objective tumor responses.

After a median follow-up of 6 months (range, 1.0–14.1 months), the median survival was 7.4 months with 1-year survival rate of 12.4% (95% CI, 0.5–16.9%; Fig. 1).

Table 2 Objective tumor response

Tumor response	No. of patients (N = 35)	(%)
PR	4	(11.4)
SD	12	(34.3)
PD	19	(54.3)

Hematological Toxicity. At the dose level of 100 mg/m² irinotecan, grade 3 or 4 neutropenia occurred in 2 (40%) of 5 patients. At the dose level of 90 mg/m² irinotecan, grade 3 or 4 neutropenia occurred in 4 (13%) of 32 patients, 1 with fever, grade 3 anemia in 4 patients (13%), and grade 3 thrombocytopenia in 1 (3%) of 32 patients (Table 3).

Nonhematologic Toxicity. Most common nonhematological toxicity was diarrhea (Table 3). Overall, 7 (19%) of total 37 patients experienced grade 3 diarrhea. These include 3 (60%) of 5 patients who received 100 mg/m² irinotecan and 4 (13%) of 32 patients who received 90 mg/m² irinotecan. All patients were fully recovered within 1 week after i.v. administration of electrolytes and fluid. Other toxicities at the dose level of 100 mg/m² irinotecan included grade 2 to 3 asthenia in all 5 (100%), nausea/vomiting in 3 (60%), anorexia in 4 (80%), and HFS in 2 (40%) of 5 patients. At the dose level of 90 mg/m² irinotecan, there were grade 2–3 asthenia in 12 (37%), nausea/vomiting in 15 (46%), anorexia in 10 (31%), and HFS in 2 (6%) of 32 patients. There was no treatment-related death in this study.

DISCUSSION

Irinotecan shows good antitumor activity in chemo-naïve NSCLC patients. However, two Japanese studies evaluating its second-line efficacy for NSCLC are conflicting. Negoro *et al.* (22) reported no response in 26 previously treated NSCLC patients. In contrast, Nakai *et al.* (23) have reported 14% (3 of 22) response rate in 22 previously treated NSCLC patients. These data suggest that additional studies are required to better determine the role of irinotecan-based regimens as second-line treatment.

This study evaluated the antitumor activity and toxicity profile of the combination of weekly irinotecan and capecitabine as a salvage treatment in patients with advanced NSCLC. Although docetaxel is considered as a gold standard second-line treatment for recurrent NSCLC, the objective response rate was 6–11% in two representative Phase III trials of docetaxel as a second-line treatment (3, 4). Although higher proportion of patients in our study had received two or more prior regimens than docetaxel studies, the objective response rate of 11.4% of our study is comparable with that of docetaxel. In addition, our study showed more favorable hematological toxicity profile when compared with docetaxel. There was less neutropenia with or without fever, which resulted in fewer hospitalizations and less need for growth factor support. These findings suggest that irinotecan/capecitabine regimen appears to be efficacious as second-line treatment for recurrent NSCLC.

It is unclear what the threshold for activity of interest would be in a second-line treatment setting of NSCLC. Although the objective response rates in large docetaxel trials for patients with relapsed NSCLC were ~10%, we initially planned

to see the target response rate of 20% because this regimen was composed of two active agents. The reasons for the seemingly lower than expected response rate of 11.4% are unknown. However, it can be explained in part by relatively high proportion of patients who had received multiple chemotherapy regimens and short treatment-free interval. In fact, 27 (77%) of 35 evaluable patients received this treatment because of progression within 3 months from the prior chemotherapy. In addition, only 8 (23%) of 35 evaluable patients had shown objective responses to prior treatments, which suggests that our patients population had more refractory diseases.

In general, resistant tumors defined as disease progression within 6 months of the first-line treatment (24). In our study, the majority of patients (77%) were resistant-relapses with treatment-free interval of <3 months. As expected, there was a significant correlation between treatment-free interval and tumor response in our study. Four patients with major tumor responses had treatment-free intervals of 5, 7, 8, and 11 months, respectively, whereas there was no response in patients with treatment free-interval < 3 months. More refractory nature of the disease in our population seems to account for the relatively low overall response rate.

In our study, all responses were observed in patients who had received one prior chemotherapy of cisplatin-containing regimen as the first-line treatment but not in patients who had received gemcitabine/vinorelbine. It is unclear whether or not the prior use of gemcitabine/vinorelbine combination might have adversely affected the overall response rate because of possible cross-resistance between the two regimens of newer agents. Rather, the more refractory nature of the disease of the patients who had received prior gemcitabine/vinorelbine treatment may account for no response in those patients. In fact, 10 (91%) of the 11 patients who had received gemcitabine/vinorelbine chemotherapy as the first-line treatment, received irinotecan/capecitabine because of disease progression within 3 months after the prior chemotherapy, whereas 3 (43%) of the 7 patients who had received cisplatin-containing chemotherapy as the first-line treatment did so within 3 months from prior chemotherapy.

Besides irinotecan (15), other chemotherapeutic agents

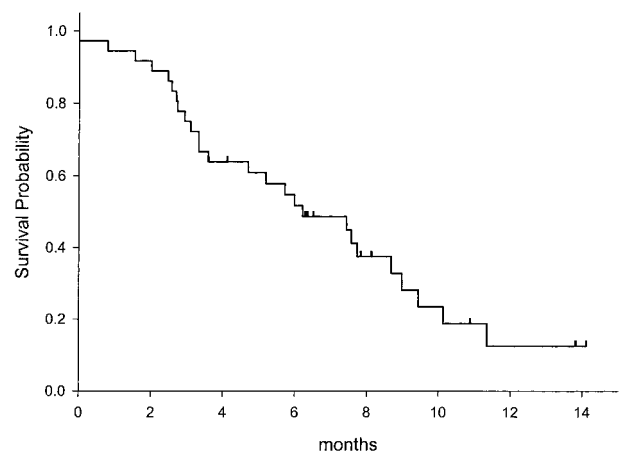


Fig. 1 Overall survival.

Table 3 Hematological and nonhematological toxicities

A. Dose level of irinotecan (100 mg/m ²) by patient (n = 5)											
Toxicity	NCI-CTC grade										
	0		1		2		3		4		
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	
Hematological											
Neutropenia	2	(40)	0	(0)	1	(20)	1	(20)	1	(20)	
Anemia	0	(0)	1	(20)	4	(80)	0	(0)	0	(0)	
Thrombocytopenia	4	(80)	1	(20)	0	(0)	0	(0)	0	(0)	
Nonhematological											
Diarrhea	2	(40)	0	(0)	0	(0)	3	(60)	0	(0)	
Nausea/vomiting	0	(0)	2	(40)	2	(40)	1	(20)	0	(0)	
Asthenia	0	(0)	0	(0)	5	(100)	0	(0)	0	(0)	
Anorexia	0	(0)	1	(20)	4	(80)	0	(0)	0	(0)	
HFS	3	(60)	0	(0)	2	(40)	0	(0)			
Alopecia	3	(60)	1	(20)	1	(20)					
Stomatitis	3	(60)	2	(40)	0	(0)	0	(0)	0	(0)	
Aspartate aminotransferase/alanine aminotransferase	4	(80)	1	(20)	0	(0)	0	(0)	0	(0)	
B. Dose level of irinotecan (90 mg/m ²) by patient (n = 32)											
Toxicity	NCI-CTC grade										
	0		1		2		3		4		
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	
Hematological											
Neutropenia	12	(38)	8	(25)	8	(25)	3	(9)	1	(3)	
Anemia	2	(6)	16	(50)	10	(31)	4	(13)	0	(0)	
Thrombocytopenia	26	(81)	4	(13)	1	(3)	1	(3)	0	(0)	
Nonhematological											
Diarrhea	15	(47)	7	(22)	6	(19)	4	(12)	0	(0)	
Nausea/vomiting	6	(20)	11	(34)	13	(40)	2	(6)	0	(0)	
Infection	29	(91)	1	(3)	0	(0)	2	(6)	0	(0)	
Anorexia	12	(38)	10	(31)	9	(28)	1	(3)	0	(0)	
Febril neutropenia	31	(97)	0	(0)	0	(0)	1	(3)	0	(0)	
T-bil	31	(97)	0	(0)	0	(0)	1	(3)	0	(0)	
Asthenia	14	(44)	6	(19)	12	(37)	0	(0)	0	(0)	
Alopecia	22	(69)	7	(22)	3	(9)					
HFS	27	(85)	3	(9)	2	(6)	0	(0)			
Stomatitis	26	(81)	5	(16)	1	(3)	0	(0)	0	(0)	
Aspartate aminotransferase/alanine aminotransferase	27	(84)	5	(16)	0	(0)	0	(0)	0	(0)	

such as docetaxel, paclitaxel, mitomycin C, and cyclophosphamide have been reported to up-regulate TP activity in tumor cells, which provides the basis for the synergistic antitumor activity between capecitabine and these agents (25, 26). A Phase III study demonstrated clinically significant synergistic antitumor activity of capecitabine/docetaxel combination over single-agent docetaxel in anthracycline-pretreated patients with advanced breast cancer (27). In a recently completed Phase II study of docetaxel plus capecitabine combination, we reported objective responses in 53% of 39 chemo-naïve patients with advanced NSCLC (28). Given the fact that docetaxel alone has a single-agent activity of 38% at best in chemo-naïve advanced NSCLC (29), capecitabine is believed to have significant antitumor activity against NSCLC. Compared with docetaxel/capecitabine combination, which had significant nonhematological toxicities such as asthenia, HFS, onycholysis, and hyperlaccimation (27–29), irinotecan/capecitabine combination showed favorable toxicity profile in the current study, especially with

irinotecan dose level of 90 mg/m². Irinotecan/capecitabine regimen seems to be better tolerated than docetaxel/capecitabine regimen with same dose of capecitabine.

In case of irinotecan and 5-FU combination, the schedule-dependent interactions with respect to toxicity have been demonstrated. The schedule of irinotecan followed by 5-FU infusion was less toxic than the reversed schedule, and it was explained by a reduced SN-38, the active metabolite of irinotecan, area under the curve level when irinotecan proceeded infusional 5-FU (30). In current study, we preceded irinotecan infusion before capecitabine administration. The better tolerability of irinotecan/capecitabine regimen may be associated with the schedule-dependent interactions between irinotecan and capecitabine.

In conclusion, weekly irinotecan and capecitabine has demonstrated favorable activity as second-line treatment of NSCLC. The toxicity profile of dose level 90 mg/m² irinotecan was much more favorable. This regimen may well be used as a second-line treatment for patients with NSCLC.

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