Cancer Chemother Pharmacol (2011) 67:717–722
DOI 10.1007/s00280-010-1539-y

CLINICAL TRIAL REPORT

A phase I study of S-1 and irinotecan combination therapy in previously treated advanced non-small cell lung cancer patients

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Received: 30 July 2010 / Accepted: 24 November 2010 / Published online: 9 December 2010

Abstract
Background This phase I study was conducted to evaluate the feasibility and to determine the recommended doses of the combination therapy of S-1 and irinotecan (CPT-11) in patients with advanced non-small cell lung cancer (NSCLC) as second-line treatment.
Methods Patients with NSCLC who were previously treated with one chemotherapy regimen and had a performance status of 0 or 1 were eligible. CPT-11 was administered at 60 mg/m^2 (level 1), 80 mg/m^2 (level 2) on days 1 and 8, and oral S-1 was administered at 80 mg/day for body surface area (BSA) less than 1.25 m^2, 100 mg/day for BSA 1.25–1.5 m^2, and 120 mg/day for BSA more than 1.5 m^2 on days 1–14 every 3 weeks. The dose-limiting toxicity (DLT) was defined as grade 4 leukocytopenia or neutropenia, grade $\geq$3 neutropenia with fever over 38°C, grade $\geq$3 thrombocytopenia, or grade $\geq$3 major nonhematological toxicities.
Results Nine patients were enrolled in the study. None of 3 patients enrolled in level 1 had any DLT. Of 6 patients in level 2, 2 patients had grade 3 diarrhea and one had grade 3 interstitial pneumonia. Level 1 was declared as the recommended dose.
Conclusion The feasibility of the combination therapy of S-1 and CPT-11 was shown in the second-line setting for the treatment of advanced NSCLC. The recommended dose of CPT-11 was 60 mg/m^2 combined with standard dose of S-1 for phase II trials of pretreated advanced NSCLC patients.

Keywords S-1 · Irinotecan · Non-small cell lung cancer · Second line · Phase I trial

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Introduction

Lung cancer remains the most common cause of cancer death worldwide [1]. In Japan, lung cancer has the highest cancer mortality rate by site. In 2008, 48,610 men and 18,239 women died from lung cancer [2], and survival rates were 52.1 and 19.5% for 1 and 5 years, respectively [3]. Approximately 80% of lung cancers result from the non-small cell histology, and most patients show locally advanced or metastatic disease at diagnosis.

In advanced-stage non-small cell lung cancer (NSCLC), doublet combinations of platinum compounds are reference regimens for the first-line treatment. Approximately one-third of patients obtain an objective response with the first-line chemotherapy, and another 20–30% achieve temporary disease stabilization [4, 5]. After failure of the first-line chemotherapy, many patients still have a good performance status and remain to be candidates to receive further chemotherapy. Docetaxel and pemetrexed are recognized as standard regimens for NSCLC patients with failure of the first-line treatment [6]. Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs), erlotinib and gefitinib, are also options for second-line chemotherapy of NSCLC patients [7, 8]. Even though response rates (RR) of these treatments were reported to be up to 10% in unselected NSCLC, better treatment options will be needed.

S-1 (Taiho Pharmaceutical Co., Ltd, Tokyo, Japan), an orally administered fluoropyrimidine antitumor agent, is composed of a mixture of tegafur, 5-chloro-2,4-dihydroxypyridine (CDHP), a reversible inhibitor of dihydropyrimidine dehydrogenase (DPD), and potassium oxonate at a molar ratio of 1:0.4:1. Tegafur, an oral prodrug of 5-fluorouracil (5-FU), is gradually converted to 5-FU and rapidly catabolized by DPD in the liver. In a phase II trial of S-1 monotherapy, 59 advanced NSCLC patients without previous history of chemotherapy were orally administered S-1 at approximately 80 mg/m^2/day for 28 days, followed by a 2-week drug-free period. The RR and median survival time (MST) were 22% and 10.2 months, respectively [9]. In the study of S-1 for previously treated patients with advanced NSCLC, the RR and MST were 12.5% and 8.2 months, respectively [10]. S-1 is suggested as an easily administrable agent, which has new possibilities in the therapeutic strategy of advanced NSCLC. Recently, the combination of S-1 plus carboplatin showed comparable efficacy in the first-line NSCLC treatment compared with carboplatin plus paclitaxel [11]. Although S-1 has not been approved in Europe and United States, the clinical development is underway such as phase II trial with NSCLC in United States [12] and large global phase III trial with gastric cancer [13]. Through these trials, S-1 has been gradually recognized globally and internationally.

Irinotecan (CPT-11) is an inhibitor of DNA topoisomerase I. In a phase III trial of CPT-11 monotherapy for untreated non-small lung cancer patients, the RR was 20.5% [14]. The combination of this drug and platinum agent is considered as one of the standard regimens in the first-line treatment of NSCLC.

Preclinical studies of human cancer cell lines and tumor xenografts have suggested that the combination of CPT-11 and 5-FU has additive-to-synergistic antitumor activity [15, 16]. The combination of CPT-11 and S-1, which contains a prodrug of 5-FU, is also expected to have synergistic antitumor activity. Thus, both CPT-11 and S-1 have moderate activity against NSCLC as a single agent, and the combination of these agents have been reported to possess marked synergistic effects and tolerability in several gastrointestinal cancers [17–23]. So the combination of CPT-11 and S-1 will be a promising alternative for the second-line treatment of NSCLC patients. However, we still have limited evidence for the way to use S-1. We need to evaluate and find the ideal method of using S-1 and irinotecan in aspects of safety and efficacy in those patients. So, we planned the current phase I study.

The purpose of this trial is to determine the dose-limiting toxicity (DLT) and the recommended dose (RD) of CPT-11 that could be administered in combination with S-1 for patients with previously treated NSCLC. Secondary objectives include toxicity and tolerability of this combination therapy.

Patients and methods

Patient eligibility

Patients with histologically or cytologically confirmed advanced NSCLC who were previously treated with one chemotherapy regimen except EGFR-TKIs were eligible for enrollment in the study. Additional eligibility criteria included measurable lesions with Response Evaluation Criteria In Solid Tumors (RECIST) [24]; a minimum age of 20; a maximum age of 75; Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1; adequate organ functions defined as white blood cell (WBC) count $\geq$4,000 and $\leq$12,000/mm^3, absolute neutrophil count (ANC) $\geq$2,000 mm^3, platelet count $\geq$100,000/mm^3, hemoglobin $\geq$9.5 g/dl, aspartate aminotransferase (AST) $\leq$100 IU/l, alanine aminotransferase (ALT) $\leq$100 IU/l, bilirubin $\leq$1.5 mg/dl, creatinine $\leq$1.2 mg/dl, and a partial pressure of arterial oxygen $\geq$70 torr (if the reason of hypoxemia is the primary disease, $\geq$60 torr); and life expectancy more than 3 months. Main exclusion criteria included patients with active infections, massive pleural or pericardial effusion or ascites, which require drainage, obvious interstitial pneumonia, diarrhea, intestinal paralysis or intestinal obstruction, clinically significant heart disease, other significant complications, pregnancy or lactation, active concomitant malignancy, symptomatic brain metastasis, administration of flucytosine or atazanavir sulfate, drug allergy and clinically significant mental disease. The study protocol was approved by the institutional review board. All patients provided written, witnessed, and informed consent before study entry.

Dose-limiting toxicity, dose escalation, and maximum tolerated dose

Toxicity was assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) v3.0. The DLT was defined as grade 4 leukocytopenia or neutropenia, grade $\geq$3 neutropenia with fever over 38°C, grade $\geq$3 thrombocytopenia, or grade $\geq$3 major nonhematological toxicities. Also included in the DLT was the dose causing a patient to delay CPT-11 on day 8 more than 7 days or delay of the second course more than 7 days due to adverse effect. A total of 3–6 patients were to be treated at any given dose of CPT-11. If DLT occurred in none of 3 patients, we proceeded to the next dose level. If DLT occurred in 2 or 3 of 3 patients, we stopped dose escalation and declared that dose level as the MTD. If DLT occurred in one of 3 patients, a total of up to 6 evaluable patients were treated at that dose level and if DLT occurred in 2 or fewer of the 6 patients, we proceeded to the next dose level. If DLT occurred in greater than 2 of 6 patients, we stopped

dose escalation and declared that dose level as the MTD. Doses were not escalated in individual patients. There would be no dose escalation beyond the MTD. The RD for phase II was defined as one dose level below the MTD.

Drug administration and modification

During every 21-day cycle, CPT-11 was administered at 60 mg/m^2 (level 1), 80 mg/m^2 (level 2), or 100 mg/m^2 (level 3) on days 1 and 8, and oral S-1 was administered twice daily after a meal from day 1 to day 14. The dose of S-1 was modified according to body surface area (BSA), that is, 80 mg/day for BSA less than 1.25 m^2, 100 mg/day for BSA 1.25–1.5 m^2, 120 mg/day for BSA more than 1.5 m^2. CPT-11 and S-1 were administered only when the following criteria were satisfied: WBC count $\geq$4,000/mm^3, platelet count $\geq$100,000/mm^3, and absence of diarrhea and grade $\geq$3 other nonhematological toxicities except for nausea and alopecia. The administration of CPT-11 and S-1 was delayed until the criteria are satisfied for the maximum of 7 days.

The dose of CPT-11 in cycle 2 was reduced by 20 mg/m^2, if WBC was <1,000/mm^3, platelet count <50,000/mm^3, diarrhea of grade 3 or greater was occurred during cycle 1. The dose of S-1 in cycle 2 was reduced as follows: 120 to 100 mg/day, 100 to 80 mg/day, 80 to 50 mg/day, if WBC count was <1,000/mm^3, platelet count <50,000/mm^3, creatinine $\geq$1.21 mg/dl, diarrhea, stomatitis, or eruption of grade 3 or greater is occurred during cycle 1.

Granulocyte colony-stimulating factor (G-CSF) is allowed only when ANC is under 1,000/mm^3 with fever over 38°C, or ANC is under 500/mm^3. Patients were allowed to receive premedication, including antiemetics and glucocorticoid.

The treatment was discontinued in the face of documented disease progression, nonhematological toxicities of grade 4, creatinine $\geq$1.51 mg/dl, grade $\geq$3 elevation of AST or ALT, consent withdrawal, or other changes in patient condition rendering further treatment unacceptable or unsafe in the judgment of the investigator.

Pretreatment evaluation and treatment assessment

Measurements of tumors were performed at baseline by chest X-ray, computed tomography (CT) scans, magnetic resonance imaging (MRI) scans, and bone scintigraphy within 2 weeks of protocol initiation. During treatment, complete blood count (CBC) and blood chemistry were monitored at least weekly. Radiographic evaluation was performed to assess response to treatment every 6 weeks. The response was defined according to the RECIST criteria.

Results

Patient characteristics

Between September 2006 and January 2008, a total of 9 patients were enrolled in the study (Table 1). Histological analysis revealed that 4 patients had adenocarcinoma, 4 had squamous cell carcinoma, and one had adenosquamous carcinoma. Seven patients (78%) had smoking history. All patients had been treated previously with platinum-based chemotherapy regimens. The median number of cycles of the previous regimens was 4 (range 1–7). The best response of the previous regimens was partial response (PR) in 5 patients, and stable disease (SD) in 2 patients. The median interval from the end of the previous regimens to the start of protocol was 2 months (range 0–12).

Toxicity and efficacy

Three patients were administered CPT-11 at 60 mg/m^2 (level 1) and S-1 at 80 mg/m^2/day. Six patients were

Table 1 Patient characteristics

	No. of patients
Total enrolled	9
Median age (range)	60 years (55–71 years)
Gender	
Male	8
Female	1
ECOG performance status	
0	5
1	4
Histology	
Adenocarcinoma	4
Squamous cell carcinoma	4
Adenosquamous carcinoma	1
Stage	
IIIB	6
IV	3
Previous treatment	
CDDP + DTX	5
CBDCA + DTX	3
CBDCA + PTX	1
Response to previous treatment	
PR	5
SD	2
PD	2

CDDP cisplatin, *DTX* docetaxel, *CBDCA* carboplatin

Stage: according to TNM ver. 6th

administered CPT-11 at 80 mg/m^2 (level 2) and S-1 at 80 mg/m^2/day (Table 2).

None of 3 patients enrolled in level 1 had any DLT. Two patients were administered 4 cycles, and one patient was administered 2 cycles. The adverse events of all patients in level 1 are presented in Table 3. None had ≥grade 3 adverse events.

When 3 patients were administered in level 2, one patient had grade 3 diarrhea (DLT) on day 11. We enrolled 3 more patients in level 2. One of those patients developed grade 3 diarrhea on day 13, and the same patient developed grade 3 rash on the whole body on day 19. Another patient in level 2 had grade 3 interstitial pneumonia during cycle 4. We declared 80 mg/m^2 of CPT-11 as the MTD, because grade 3 nonhematological toxicities (DLT) occurred in 3 of 6 patients. According to these results, level 1 was declared as the RD. Of 6 patients in level 2, the median number of cycles is 3 (range 1–6). The adverse events of all patients in level 2 are presented in Table 4.

Table 2 Dose levels

Level	Irinotecan (mg/m^2)	S-1 (mg/m^2)	No. of patients
1	60	80	3
2	80	80	6
3	100	80	0

Table 3 Maximum patient-specific toxicities: dose level 1 ($n = 3$)

Grade	0	1	2	3	4
Neutropenia	3	0	0	0	0
Anemia	0	2	1	0	0
Thrombocytopenia	3	0	0	0	0
Diarrhea	2	1	0	0	0
Rash	3	0	0	0	0
Nausea	1	2	0	0	0
Anorexia	2	1	0	0	0

Table 4 Maximum patient-specific toxicities: dose level 2 ($n = 6$)

Grade	0	1	2	3	4
Neutropenia	4	1	1	0	0
Anemia	0	5	1	0	0
Thrombocytopenia	4	1	1	0	0
Diarrhea	1	3	0	2[a,b]	0
Rash	5	0	0	1[a,b]	0
Interstitial pneumonia	5	0	0	1[a]	0
Nausea	2	2	2	0	0
Anorexia	2	2	2	0	0

[a] Dose-limiting toxicity

[b] One patient had both G3 diarrhea and G3 rash

Eight patients could be evaluated for response. Two (25%) patients had PR, 3 (37.5%) with SD, and 3 (37.5%) with progressive disease (PD). One patient was not evaluable (NE), because of early removal from the study due to toxicities.

Discussions

We evaluated the feasibility and determined the RD of CPT-11 that could be administered in combination with S-1 for patients with previously treated NSCLC.

The combination therapy of CPT-11 and S-1 was reported in two trials for the treatment of NSCLC, recently [25, 26]. One is phase II trial for chemonaïve NSCLC patients, and the other is phase I trial for previously treated patients. Okamoto et al. [25] performed phase II study of CPT-11 and S-1 doublet for chemonaïve advanced NSCLC. Fifty-six patients were treated with CPT-11 at 150 mg/m^2 on day 1 and S-1 at 80 mg/m^2 on days 1–14 every 3 weeks. No complete responses and 16 PR were observed, giving an overall RR of 28.6%. Median progression-free survival and MST was 4.9 and 15 months, respectively. These results are not inferior to those of platinum doublet therapies and proved this combination to be a candidate for one of new treatment options for NSCLC. This study showed the effectiveness of this combination therapy in the chemonaïve NSCLC patients who were different targets from ours. Although the treatment interval and the dose of S-1 were completely same with ours, those of CPT-11 were different. They administrated CPT-11 at a single dose of 150 mg/m^2, on day1, q3w without splitting, giving higher DI for CPT-11 in their study compared to ours (Table 5). Ishimoto et al. [26] performed phase I study of the same combination therapy for the pretreated NSCLC patients. They showed that the recommended dose of CPT-11 was 70 mg/m^2 on days 1, 8, and 15 with fixed dose of S-1 at 80 mg/m^2 on days 1–14 every 4 weeks. In that study, all patients were also treated previously with platinum-based chemotherapy; however, the recommended dose of CPT-11 and the interval of chemotherapy were different from our study. The DI for CPT-11 in our study is lower, while that for S-1 is higher compared to the previous study by Ishimoto et al. (Table 5). So the main differences of the current study compared to the previous studies are the target patients and the doses of both drugs.

On the other hand, several studies have already been reported for the treatment of chemonaïve advanced gastric and colorectal carcinoma with CPT-11 and S-1 combination therapy. They varied in schedule and doses of the agents. CPT-11 was given either by splitting doses weekly or biweekly or by a single dose triweekly, while S-1 was

Table 5 Clinical trials with CPT-11 + S-1

Author (Refs.)	Clinical trial	Diseases	CPT-11			S-1		
			Dose	Interval	Planned DI (mg/m^2/week)	Dose	Interval	Planned DI (mg/m^2/day)
Okamoto et al. [25]	Phase II	1st line NSCLC	150 mg/m^2 day 1	q3w	50	80 mg/m^2 days 1–14	q3w	53.3
Ishimoto et al. [26]	Phase I	≥2nd line NSCLC	70 mg/m^2 days 1, 8, 15	q4w	52.5	80 mg/m^2 days 1–14	q4W	40
Uedo et al. [19]	Phase II	1st line gastric ca	80 mg/m^2 days 1, 15	q5w	32	80 mg/m^2 days 1–21	q5W	48
Inokuchi et al. [20]	Phase I/II	1st line gastric ca	80 mg/m^2 days 1, 8	q4w	40	80 mg/m^2 days 1–14	q4W	40
Yamada et al. [18]	Phase I	1st line gastric ca	150 mg/m^2 day 1	q3w	50	80 mg/m^2 days 1–14	q3w	53.3
Katsube et al. [21]	Phase I/II	1st line gastric ca	80 mg/m^2 days 1, 8	q3w	53.3	80 mg/m^2 days 1–14	q3w	53.3
Goto et al. [17]	Phase II	1st line CRC	150 mg/m^2 day 1	q3w	50	80 mg/m^2 days 1–14	q3w	53.3
Tsunoda et al. [22]	Phase II	1st line CRC	80 mg/m^2 days 1, 15	q5w	32	80 mg/m^2 days 1–21	q5W	48
Shiozawa et al. [23]	Phase I	1st line CRC	120 mg/m^2 days 1, 15	q4w	60	80 mg/m^2 days 1–14	q4W	40
Current study	Phase I	2nd line NSCLC	60 mg/m^2 days 1, 8	q3w	40	80 mg/m^2 days 1–14	q3w	53.3

given daily dose of 80 mg/m^2 for 2–3 weeks, every 3–5 weeks (Table 5). According to all the trials reported for the lung and gastrointestinal cancers, adequate as well as supposed maximum planned DI for CPT-11 and S-1 in combination seem to be 50–53.3 mg/m^2/week and 53.3 mg/m^2/day, respectively, for the first-line setting. In the present trial, DI of recommended dose for CPT-11 was 40 mg/m^2/week and that for S-1 was 53.3 mg/m^2/day. Considering this trial was planned for the pretreated NSCLC patients, it is quite reasonable that lower DI of CPT-11 compared to the above-planned DI was recommended when supposed maximum dose of S-1 was administered. Inversely, reduced dose of S-1 may be an alternative option when maximum CPT-11 is administered in the second-line setting like Ishimoto et al. reported.

The most frequent DLT was diarrhea. Diarrhea is a major common adverse event induced by both CPT-11 and S-1. According to the previous report that diarrhea induced by S-1 mostly occurred on day 15 [27], we administered CPT-11 on days 1 and 8 to avoid overlap of common toxicity. Even though we experienced G3 diarrhea in two patients (33.3%) in level 2 (CPT-11: 80 mg/m^2), there was relatively high incidence compared to previous reports (7.7–8.9%) [25, 26]. This might be due to difference of patients' status of UGT1A1 genotype that is thought to be related to CPT-11-induced adverse event, background of patients (such as second-line setting in this trial), or difference of the usage of anti-diarrhea medication. Despite high percentage of diarrhea in the level 2, none of the 3 patients had severe diarrhea in level 1 (CPT-11: 60 mg/m^2). As severe diarrhea was also reported at higher dose of CPT-11 in the previous study for pretreated NSCLC patients [26], combined use of S-1 might exaggerate the incidence of diarrhea induced by CPT-11, especially in the second-line treatment. Further careful monitoring with adequate supportive care for the diarrhea will be needed in following phase II trial.

In this study, we showed the feasibility of the combination therapy of S-1 and CPT-11 in the second-line setting. The recommended dose of CPT-11 was 60 mg/m^2 on days 1 and 8 combined with standard dose of S-1 on days 1–14 every 3 weeks for phase II trials of pretreated advanced NSCLC patients. Combination of CPT-11 and S-1 may be of great value in the outpatient setting because of easily administrable regimen. Our following phase II trial is currently undergoing to define the efficacy of this combination therapy.

Acknowledgments The authors would like to thank deceased Professor A. Ishizaka for his great contribution on this study.

Conflicts of interest The authors declare that they have no conflict of interest.

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