Weekly Administration of Irinotecan (CPT-11) plus Cisplatin for Non-small Cell Lung Cancer

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Abstract. *Background: Weekly administration of irinotecan plus cisplatin was evaluated for untreated patients with non-small cell lung cancer (NSCLC). Patients and Methods: Sixty mg/m^2 of irinotecan plus 30 mg/m^2 of cisplatin were administered on days 1, 8 and 15 every 4 weeks. Patients with no evidence of disease progression were treated with at least two cycles (8 weeks). Of the 39 patients, 29 were provided an antidiarrheal program consisting of sodium bicarbonate and magnesium oxide. Results: There were 13 partial responses and an overall response rate of 33.3% [95% CI: 20%-50%]. The median time to progression and survival were 64 days and 12.8 months, respectively. Grade 4 neutropenia occurred in 15.4% of the patients, and Grade 3 and 4 diarrhea was observed in 12.8% and 2.6%, respectively. The incidence of leukopenia of grade 3-4 was significantly lower in patients provided with the antidiarrheal program due to lack of decrease in the lymphocyte count. Conclusion: This phase II study indicated that weekly irinotecan plus cisplatin administration was a promising treatment for untreated NSCLC.*

Irinotecan (CPT-11), a topoisomerase I inhibitor, in combination with cisplatin (CDDP) administration for previously untreated patients with extensive small cell lung cancer (SCLC) resulted in improvement in overall survival, compared with CDDP/etoposide in a randomized phase III study (1). CPT-11 plus CDDP was also active for refractory or relapsed SCLC, after treatment with etoposide in combination with a platinum compound of either CDDP or carboplatin (2). In terms of published results on the use of CPT-11 for non-small cell lung cancer (NSCLC), CPT-11 alone at 100 mg/m^2 on days 1, 8 and 15 within 4-week periods was shown to be active, with a response rate of 34.3% in a phase II study (3). In another phase II study, when 80 mg/m^2 of CDDP on day 1 was combined with 60 mg/m^2 of CPT-11 on days 1, 8 and 15 within 4-week periods, the response rate increased (4) and a randomized phase III study, the Four-Arm Cooperative Study (FACS), compared CPT-11 plus CDDP by this regimen to gemcitabine plus CDDP, paclitaxel plus carboplatin or vinorelbine plus CDDP (5). Regarding to survival time, the FACS showed the same efficacy for CPT-11 plus CDDP [median survival time (MST): 14.2 months] as gemcitabine plus CDDP (MST: 14.8 months), paclitaxel plus carboplatin (MST: 12.3 months), or vinorelbine plus CDDP (MST: 11.4 months) (5).

The maximum synergistic effect on tumor cells was observed by the simultaneous combination of CDDP and CPT-11 *in vitro* (6). We confirmed that the cytotoxicity of CDDP is dependent on the area under the concentration-time curve (AUC) (7), indicating that if the AUC per month was maintained, anti-tumor activity of CDDP was not weakened by divided administration of the maximal dose. In 1998, two phase I studies of weekly administration of irinotecan plus CDDP were performed, one by Saltz *et al.* (8) and another one by our group (9). Saltz *et al.* increased

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the dose of irinotecan, while fixing the dose of cisplatin at 30 mg/m^2 and investigated the pharmacokinetics of irinotecan. In our study the cisplatin dose was increased and the dose of irinotecan was fixed at 60 mg/m^2 and the theoretical validity of dividing the maximum dose of cisplatin was addressed and the pharmacokinetics of cisplatin were clarified. Regardless of the differences in the study design, the treatments in the two studies were similar, *i.e.* the former group concluded that the recommended dose of cisplatin and irinotecan was 30 mg/m^2 and 65 mg/m^2, respectively, on a weekly schedule for 4 out of 6 weeks. Similarly, we reported that the MTD was 33 mg/m^2 of cisplatin and 60 mg/m^2 of irinotecan on a weekly schedule for 3 out of 4 weeks (8, 9).

Recently, a phase II study of weekly administration of CPT-11 plus CDDP for refractory or relapsed SCLC was conducted by our group (2). The treatment schedule was 60 mg/m^2 of CPT-11 plus 30 mg/m^2 of CDDP on days 1, 8 and 15 within 4 weeks. The results indicated that this regimen was both safe and promising. The current study, employing the same treatment schedule, was conducted in chemotherapy-naïve patients with NSCLC.

Patients and Methods

Patients. This study was performed in accordance with the Helsinki Declaration (1964, amended in 1975 and 1983) of the World Medical Association. Prior to their participation in the study, patients admitted to the six institutions of the East Japan Chesters Group (EJCG), were examined to ensure that they met the following criteria: (a) histological or cytological diagnosis of NSCLC, (b) no previous therapy, (c) measurable disease, (d) performance status (PS) of 2 or above on the Eastern Cooperative Oncology Group scale; (e) adequate bone marrow function (white blood cell (WBC) count≥4,000/mm^3, plt≥100,000/mm^3, Hb≥9.5 g/dl); (f) adequate hepatic function (T-Bil≤1.5 mg/dl, transaminases less than twice the upper limit of normal); (g) adequate renal function (S-Cr≤1.5 mg/dl); (h) age 15-75 years; (i) no brain metastasis and (j) no medical problems severe enough to prevent compliance with the study requirements. All patients provided informed consent before enrollment in the study, according to institutional guidelines.

Treatment schedule. Based on the experience with our phase I study of weekly CPT-11 plus CDDP (9), the doses of CPT-11 and CDDP were set at 60 mg/m^2 and 30 mg/m^2, respectively, on days 1, 8, and 15 every 4 weeks. Initially, CPT-11 was administered in 500 ml normal saline as a 90-min *i.v.* infusion. CDDP was then given over a 60-min period. Patients with no evidence of disease progression were treated with at least 2 cycles.

For prevention of emesis, 5-hydroxytryptamine-3-receptor antagonist and dexamethasone were given *i.v.,* prior to the administration of CPT-11 and CDDP. To avoid CDDP-induced renal damage, *d.i.v.* hydration with a total of 1,500 ml was performed.

During performance of this study, it was shown that an antidiarrheal program would prevent CPT-11-induced side-effects (10). Therefore, from the eleventh patient, the antidiarrheal program of oral alkalization (OA) and control of defecation (CD) were employed (10). Coinciding with day one of CPT-11 infusion and for four days thereafter, the following were administered: sodium bicarbonate powder, 2.0 g/day t.i.d. (between meals) and magnesium oxide powder, 1.5 g/day, t.i.d. (after meals). Each dose was to be accompanied by a glass of basic water (pH>7). The dose of magnesium oxide was increased or decreased at the time of constipation or diarrhea, respectively.

During the course of treatment, the doses of CPT-11 and CDDP were withheld on the day it was due in the presence of leukopenia (<3,000/mm^3) and/or diarrhea in excess of grade 1. In the previous phase I study (9), the nadir WBC count was found to be significantly correlated to the ratio of WBC on day 8, to that on day 1 ($r=0.603$, $p=0.0081$). Therefore, the doses of CPT-11 and CDDP were also withheld on day 8, when the WBC count had dropped by more than 30%, compared to day 1.

Granulocyte colony-stimulating factor (G-CSF) was administered when grade 4 leukopenia (<1,000/mm^3) and/or neutropenia (<500/mm^3) were observed. Erythropoietin was not used. Delayed diarrhea, which typically presented 6 days after and beyond the initial CPT-11 administration, was treated with a high dose of loperamide, according to previous reports (11). Persistent, grade 3 or greater diarrhea, despite loperamide therapy, warranted the use of *i.v.* hyperalimentation for fluid management.

Evaluation. Patients underwent staging evaluation by physical examination, chest X-ray, bone scintiscan, computed tomography of the head, chest and abdomen, and fiberoptic bronchoscopy. Staging procedures followed those of the tumor-node-metastasis system.

Prior to the first course, each patient was subjected to chest X-rays and chest CT. The former was assessed at least once every two weeks after the initial evaluation and the latter was planned to be checked once every two months. Tumor response was extramurally reviewed and classified in accordance with World Health Organization criteria. A complete response (CR) was defined as the disappearance of all clinical and radiological evidence of tumor, for at least 4 weeks; a partial response (PR) was defined as a decrease of 50% or more in the sum of products of the longest perpendicular diameters of all measurable lesions, for at least 4 weeks; and progressive disease (PD) was defined as an increase of more than 25% in the sum of products of the longest perpendicular diameters of all measurable lesions or the appearance of new lesions. All other circumstances were considered to indicate stable disease (SD). The time-to-progression (TTP) and survival curves were drawn using the Kaplan-Meier method, and the median survival time was calculated from the day of the first treatment until the death or the last follow-up.

Also, before the first course, a complete blood cell count (CBC), serum chemistry for renal and hepatic function, electrolyte analysis, and urinalysis were performed. These studies were repeated at least once a week after the initial evaluation. The NCI Common Toxicity Criteria was used to grade organ system damage.

Statistical analysis. Sample size, calculated by the response rate, was determined to be 38 patients, to evaluate this phase II study. A 50% response rate was chosen as the desirable target level and a 20% response rate was considered uninteresting. Our design had a power in excess of 90% and a less than 10% type I error. Bayesian data monitoring of the response rate for an early interruption of the study was performed throughout the study (12).

Table I. *Patient characteristics (n=39).*

Male/female	31/8 pts
Median age	64 years old
(Range)	(43-75)
Performance status	
0-1	37 pts
2	2 pts
Stage	
IIIB	11 pts
IV	28 pts
Histology	
Adenocarcinoma	26 pts
Squamous cell carcinoma	9 pts
Adenosquamous	2 pts
Large cell carcinoma	1 pt
Unclassified	1 pt
Antidiarrheal program of OA and CD	
Without OA and CD	10 pts
With OA and CD	29 pts
Courses given	
1	8 pts
2	24 pts
3	6 pts
4	1 pt

OA: oral alkalization; CD: control of defecation.

Table II. *Response rate (n=39).*

Response		CR	PR	SD	PD	NE	Response rate
Histology							
Adenocarcinoma	(n=26)	0	9	12	5	0	34.6%
Squamous	(n=9)	0	3	4	1	1	33.3%
Adenosquamous	(n=2)	0	1	1	0	0	50.0%
Large	(n=1)	0	0	0	1	0	0.0%
Unclassified	(n=1)	0	0	1	0	0	0.0%
Antidiarrheal program +/–							
Without OA & CD	(n=10)	0	2	6	2	0	20.0%
With OA & CD	(n=29)	0	11	12	5	1	37.9%
Overall	(n=39)	0	13	18	7	1	33.3%

Of the 39 patients, there were 13 partial responses and an overall response rate of 33.3% (95% confidence interval, 20%-50%) was obtained.
CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; NE: not evaluable (see Patients and Methods).

Results

Between January 1997 and June 2001, 39 patients participated in the trial. The characteristics of the patients are shown in Table I. Eight of the patients were women and 31 were men and the mean age was 64 years. Eleven and 28 patients exhibited stage IIIB and stage IV disease, respectively. Most of the patients had a good performance status (PS), but two of them were PS 2.

Twenty-six out of the 39 patients (67%) received the full schedule of therapy (CDDP+CPT-11 three times/course) in the first course and the others received two times administration, either on days 1 and 8 or days 1 and 15, because of myelosuppression or diarrhea. The average administration frequency of 60 mg/m^2 CPT-11 and 30 mg/m^2 CDDP was 5.2 times in the average of 2.0 courses, calculating that the average administration was 2.6 times/course. Dose intensities of CPT-11 and CDDP were 156 mg/m^2/course and 78 mg/m^2/course, respectively. The first 10 patients, who did not receive the antidiarrheal regimen, were given 1.8 courses of CPT-11 plus CDDP at dose intensities of 150 mg/m^2/course and 75 mg/m^2/course, respectively. The remaining 29 patients, who received the antidiarrheal regimen, were given 2.1 courses of combined therapy of CPT-11 plus CDDP at dose intensities of 158 mg/m^2/course and 79 mg/m^2/course, respectively. Specifically, patients without the antidiarrheal program were given total doses of CPT-11 and CDDP of 270 mg/m^2 and 135 mg/m^2, respectively, and those with the antidiarrheal program were administered with CPT-11 and CDDP at doses of 332 mg/m^2 and 166 mg/m^2, respectively.

All 39 patients were assessed for response (Table 2). Thirteen patients had PR and 18, and seven had SD or PD, respectively. The overall response rate was 33.3% [95% CI: 20%-50%]. When data were analyzed according to whether or not subjects received the antidiarrheal program, there was no statistical difference in the overall response rate. However, among the ten patients without the antidiarrheal program, two (20%) PRs were observed, while among the 29 patients on this program, 11 (37.9%) PRs were observed. The median TTP of all patients was 64 days (Figure 1A), for the first ten patients it was 58 days and for the remaining 29 patients it was 73 days (Figure 1B). There was a significant difference in TTP between those who did and did not receive the antidiarrheal program (log-rank test: $p<0.05$).

The median survival time (MST) for all patients was 12.8 months, and the 1-year survival rate in patients was 55% [95% CI: 38%-70%] (Figure 2).

All 39 eligible patients were assessable for toxicity (Table III). Leukopenia was the major toxicity. The leukocyte count nadir usually occurred around day 21. Grade 4 leukopenia and neutropenia occurred in two patients (5.1%) and six patients (15.4%), respectively. No treatment-related death was observed. Thrombocytopenia occurred less frequently than leukopenia and was less severe. Thrombocytopenia of grade 3 or more was

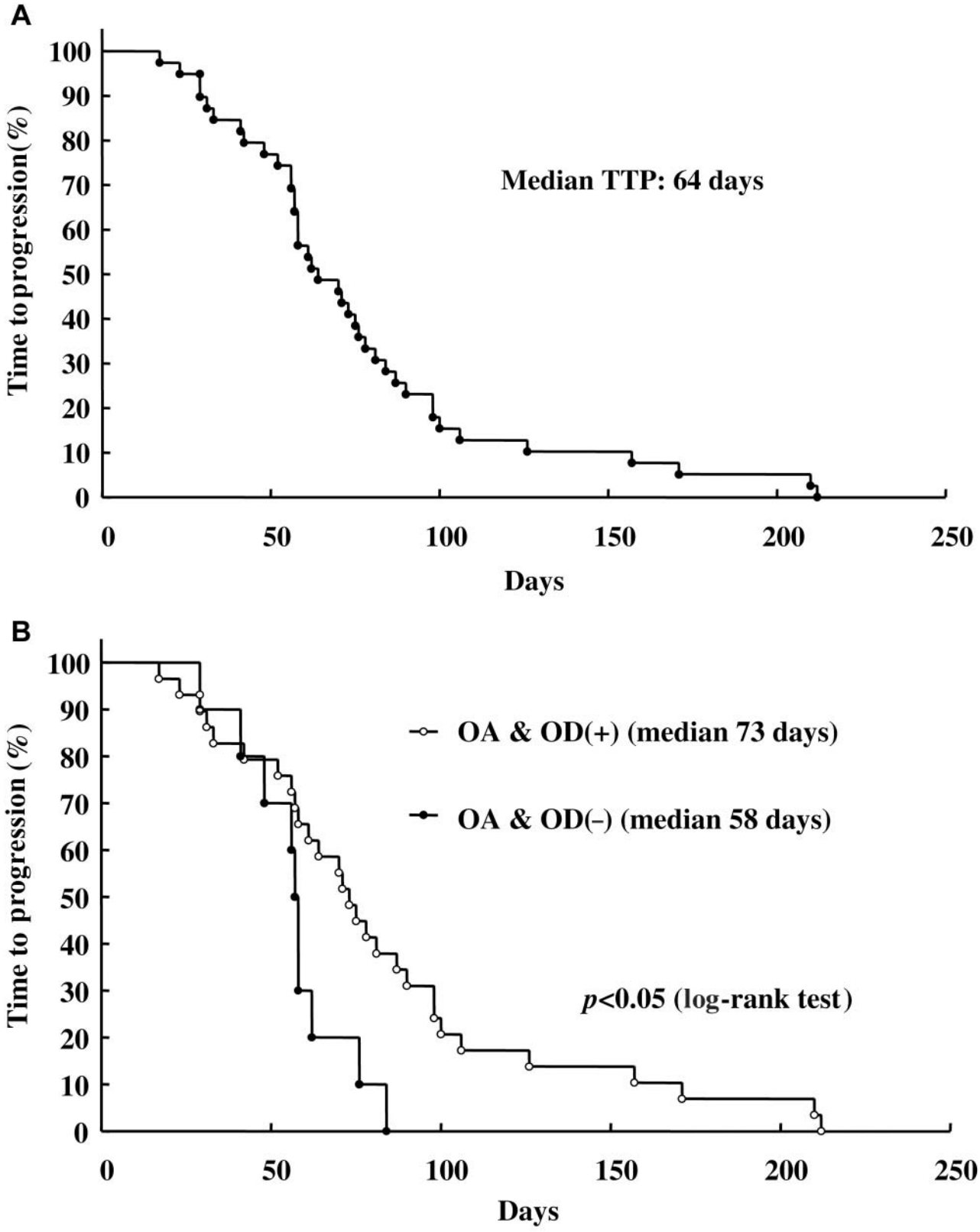

Figure 1. *a) Time to progression (TTP) of all 39 patients. b) TTP of the 29 patients treated by the antidiarrheal program of OA and CD and the 10 patients without the program.*

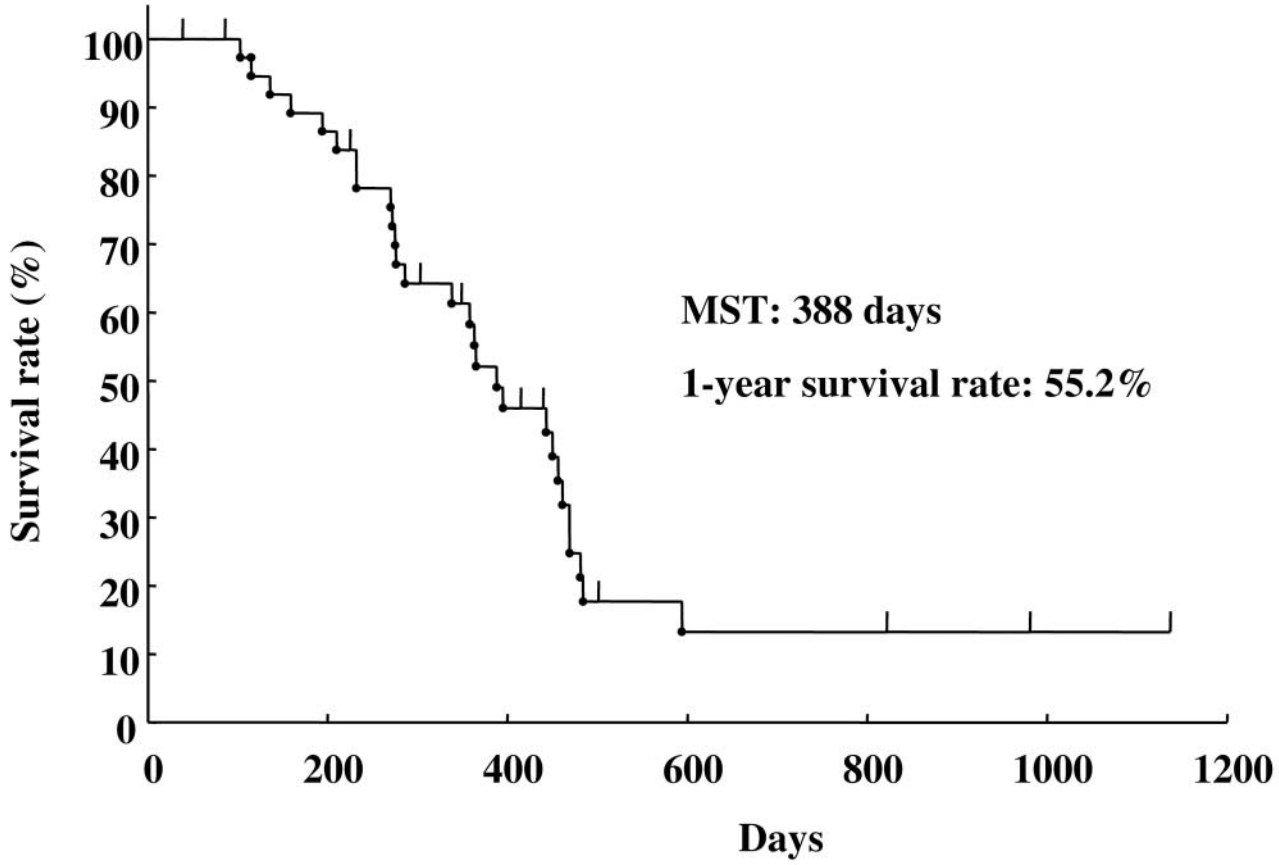

Figure 2. *Median survival time (MST) of all 39 patients after starting weekly CPT-11 plus CDDP.*

observed in one patient (2.6%). No patient required platelet transfusion.

Grade 3 diarrhea was observed in only five patients (12.8%) and grade 4 diarrhea occurred in one patient (2.6%). Although these patients required *i.v.* hydration, they recovered within four to seven days. Of the six patients experiencing diarrhea of grade 3 or higher, three had grades 3 and 4 leukopenia, coincidentally. Although six patients experienced grade 3 nausea or vomiting (15.4%), the other 33 patients experienced nausea of grade 2 or less or no nausea at all, indicating that nausea and vomiting were mild with this regimen. No hepatic, renal and pulmonary toxicities, related to drug administration, were observed in this trial.

Comparing the presence or absence of the antidiarrheal program, the incidence of leukopenia at more than grade 3 was significantly lower in patients receiving the antidiarrheal program (Table IV). This was due to no decrease in lymphocyte count. Anemia, emesis and diarrhea had tendency to be less severe in patients on the antidiarrheal program.

Table III. *Toxicities (n=39).*

	No. of patients with					
CTC grade	1	2	3	4	≥3 (%)	4 (%)
Hematological toxicity						
Leukopenia	9	14	8	2	25.6	5.1
Neutropenia	3	12	12	6	46.2	15.4
Thrombocytopenia	6	5	1	0	2.6	0.0
Anemia	9	9	6	1	17.9	2.6
Other toxicities						
Diarrhea	9	9	5	1	15.4	2.6
Nausea and vomiting	13	8	6	-	15.4	-

Discussion

From the response rate (Table II), survival time and 1-year survival rate (Figure 2), the results of this study indicate that treatment by weekly administrations of CPT-11 plus cisplatin was active in chemotherapy-naïve patients with NSCLC. The

Table IV. *Toxicities with or without antidiarrheal program of OA and CD.*

CTC grade		No. of patients with 1	2	3	4	≥3 (%)	4 (%)
Leukopenia							
Without OA & CD	(n=10)	2	1	4	2	60.0*	20.0
With OA & CD	(n=29)	7	13	4	0	13.8*	0.0
Neutropenia							
Without OA & CD	(n=10)	1	3	3	2	50.0	20.0
With OA & CD	(n=29)	2	9	9	4	44.8	13.8
Thrombocytopenia							
Without OA & CD	(n=10)	1	3	0	0	0.0	0.0
With OA & CD	(n=29)	5	2	1	0	3.4	0.0
Anemia							
Without OA & CD	(n=10)	2	1	3	0	30.0	0.0
With OA & CD	(n=29)	7	8	3	1	13.8	3.4
Diarrhea							
Without OA & CD	(n=10)	2	3	2	1	30.0	10.0
With OA & CD	(n=29)	7	6	3	0	10.3	0.0
Nausea and vomiting							
Without OA & CD	(n=10)	3	3	2	-	20.0	-
With OA & CD	(n=29)	10	5	4	-	13.8	-

OA: oral alkalization; CD: control of defecation.
*$p=0.004$

randomized phase III study designated, as FACS showed that quality of life (QOL) profiles differed depending on the regimen (5). With the single administration of CDDP combined with CPT-11 in the FACS, half of the patients experienced diarrhea at grade 2 or more and half also experienced vomiting at grade 2 or more, which might have reduced the patients' QOL. Our weekly administrations of CPT-11 plus cisplatin together with the antidiarrheal program provided a practical and well-tolerated regimen (grade 2-3 vomiting: 31%, grade 2-4 diarrhea: 31%) (Table IV).

CPT-11 is a water-soluble semi-synthetic derivative of camptothecin and is metabolized to 7-ethyl-10-hydroxy-camptothecin (SN-38) by carboxyl esterase, mainly in the liver (13). The non-ionic lactone form of SN-38 is the active compound, and the molecular target of SN-38 has been identified as DNA topoisomerase I, a nuclear enzyme implicated in DNA replication and transcription (14). The mechanism of topoisomerase I inhibition involves the formation of a reversible enzyme-drug-DNA ternary complex. Active SN-38 is deactivated to SN38-Glu by conjugation in the liver and is secreted into bile by hepatocytes, with subsequent excretion into the intestine (15, 16). We found that the intestinal absorption of CPT-11 and SN-38 was characteristic of that, with weakly basic drugs (17). At acidic pH, non-ionic lactone forms of CPT-11 and SN-38 were passively transported, and their uptake rates were rapid. On the other hand, the respective anionic carboxylate forms were actively and slowly absorbed at basic pH (17). The uptake rate of SN-38 also correlated with its cytotoxicity (17), indicating that acidic pH in the intestinal lumen might result in a more significant cytotoxic effect of SN-38, on the intestinal epithelium.

In our case-controlled clinical study, we designed an anti-diarrheal program for CPT-11, designated as oral alkalization and control of defecation (OA and CD) (10). The rationale in designing OA and CD was to prevent absorption of active SN-38 lactone by intestinal cells, which should in turn reduce epithelial damage and its impact on subsequent delayed diarrhea. The OA and CD consisted of oral administration of sodium bicarbonate, magnesium oxide and basic water. The three agents have a basic pH and are known to directly mediate alkalization of the intestinal lumen. Sodium bicarbonate also mediates alkalization of bile in the gallbladder. Magnesium oxide demonstrates a laxative action, which should shorten the dwelling time of CPT-11 and SN-38 within the intestine. As a result of the case-control study, the OA and CD induced dose-intensity of CPT-11 and reduced the incidence of delayed diarrhea, nausea, vomiting, myelotoxicity and consumption of loperamide (10).

Sargent *et al.* recommended caution with the use of CPT-11 with fluorouracil and leucovorin for colorectal cancer (18). Deaths occurred within 60 days after initiation of treatment had several characteristics in common: dehydration (resulting from diarrhea, nausea, and vomiting), neutropenia, and sepsis, leading to death. Interpatient variability in CPT-11-induced side-effects is considered to be a major deterrent to clinical use. Therefore, we employed the OA and CD, beginning with the eleventh patient in this study. The weekly administration of CPT-11 plus CDDP with OA and CD was found to be safe for both untreated patients with NSCLC in this phase II study (Table IV) and patients with refractory or relapsed SCLC in the previously reported phase II study (2). The weekly administration of CPT-11 plus CDDP with OA and CD did not reduce activity in either of the phase II studies (2). TTP was significantly longer in NSCLC patients receiving OA and CD than in those not treated (Figure 1). With the use of OA and CD, the lower toxicity might enable administration of the total dose of CPT-11 plus CDDP, resulting in longer TTP.

In conclusion, it is indicated that weekly CPT-11 plus CDDP is a promising treatment for untreated patients with NSCLC, especially when combined with the antidiarrheal regimen of OA and CD. The mildness of side-effects permits administration in an outpatient setting.

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