BIWEEKLY ADMINISTRATION OF IRINOTECAN (CPT-11) PLUS CISPLATIN WITH AN ANTIDIARRHEAL PROGRAM OF INTESTINAL ALKALIZATION TO REDUCE DIARRHEA IN CANCER PATIENTS

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Abstract

Background: Previously, we reported that the maximum tolerated dose (MTD) of biweekly administration of irinotecan (CPT-11) plus cisplatin (CDDP) was 70 mg/m² plus 30 mg/m², respectively. The same biweekly regimen was combined with intestinal alkalization to address delayed diarrhea in this phase I study.

Methods: CPT-11 plus CDDP were administered biweekly with an antidiarrheal program consisting of sodium bicarbonate and magnesium oxide to patients with various malignancies. CDDP dosing was fixed at 30 mg/m² and dose escalation of CPT-11 from 60 mg/m² to 100 mg/m² by a step of 10 mg/m² was used.

Results: A total of 22 patients (Level I (60 mg/m²): 3 patients, Level II (70 mg/m²): 3 patients, Level III (80 mg/m²): 7 patients, Level IV (90 mg/m²): 6 patients, and Level V (100 mg/m²): 3 patients) entered into this study. Of the 22 patients, diarrhea of grade 2 and 3 was observed in 3 patients and 1 patient (5%), respectively. At Level IV, 2 patients experienced grade 3 neutropenia, and one of the 2 patients coincidentally had grade 3 thrombocytopenia and grade 3 diarrhea. At Level V, there were no patients with dose limiting toxicities, but 2 of the 3 patients could not be dosed more than three times. Of the 22 patients, 19 patients were assessed for response. One and 12 patients had partial response and stable disease, respectively, resulting in a disease control rate of 68%.

Conclusion: Intestinal alkalization could prevent CPT-11-induced diarrhea and increase MTD of biweekly 100 mg/m² of CPT-11 with CDDP 30 mg/m² administration.

Key Words: phase I, CPT-11, diarrhea, transport, biochemical modulation

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Introduction

A combination chemotherapy of CPT-11 and cisplatin (CDDP) showed a synergistic effect *in vitro*¹⁾. And it is used for patients with many malignancies²⁻⁴⁾. For example, untreated patients with extensive small cell lung cancer (SCLC) showed an improvement in overall survival when treated with CPT-11 and CDDP compared with patients treated with CDDP/etoposide in a randomized phase III study²⁾. In a phase II study for gastric cancer, when CDDP 80 mg/m² on day 1 was combined with CPT-11 70 mg/m² on days 1 and 15 in 4 weeks, the response rate was 48%⁴⁾. However, this two-drug com-

bination had a high frequency of grade 3 and 4 diarrhea and neutropenia²⁻⁴⁾, resulting in lower dose delivered than planned dose. Both delayed diarrhea, which typically presented 5 days after and beyond the initial CPT-11 administration, and neutropenia are recognized as dose-limiting toxicities (DLT) of CPT-11 plus CDDP.

A maximal synergistic effect on tumor cells has been observed by the simultaneous combination of CDDP and CPT-11 *in vitro*¹⁾. We confirmed that the cytotoxicity of CDDP is dependent on the area under the concentration-time curve (AUC)⁵⁾, indicating that if the AUC per month was maintained, the anti-tumor activity of CDDP was *not* weakened by the divided administration of the maximal dose. Phase I studies for the weekly administration of CPT-11 concurrently with divided CDDP was reported by us⁵⁾ and Salts B et al.⁶⁾. On the other hand, in 2005, we reported a phase I study investigating the biweekly administration of CPT-11 plus CDDP, using patients

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with gastrointestinal cancers^{8,9}. The dose of CPT-11 was increased while fixing the dose of CDDP at 30 mg/m², and the maximum tolerated dose (MTD) of CPT-11 was found to be 70 mg/m². The dose limiting toxicities were identified to be both leucopenia and delayed diarrhea.

To overcome these side-effects, the metabolic pathway of CPT-11 in the liver has been investigated. CPT-11 is metabolized to an active form, 7-ethyl-10-hydroxycamptothecin (SN-38), by carboxyl esterase¹⁰, and SN-38 is deactivated to SN-38 glucuronide (SN38-Glu) by UDP-glucuronosyltransferase (UGT) in the liver¹¹. The UGT gene has a polymorphism of its gene, and gene analysis of UGT-1A1 can predict leucopenia¹². However, the prediction delayed diarrhea by UGT-1A1 polymorphism has shown difficulties. Thus, delayed diarrhea remains problematic in clinical practice¹³.

We have designed an anti-diarrheal program for CPT-11 designated as oral alkalization (OA) and control of defecation (CD)¹⁴, which is now widely termed *intestinal alkalization*. To develop a practical and well tolerated regimen using the biweekly administration of CPT-11 plus CDDP, this two drug regimen was combined with intestinal alkalization. This phase I study investigated whether the MTD of CPT-11 plus CDDP observed in our previous study mentioned above may be increased by intestinal alkalization.

Patients and Methods

The protocol employed in this study followed that of our previous study⁹ except for adding the intestinal alkalization. This study was performed in accordance with the Helsinki Declaration (amended in 2003) of the World Medical Association, and the protocol was approved by the institutional review board of each participating institution.

Patients entered

Prior to their participation in the study, patients admitted to 8 institutions were examined to ensure that they met the following criteria: (a) histologic or cytologic diagnosis of lung cancer, gastrointestinal cancer, gynecological cancer or breast cancer, with an indication for CPT-11 treatment in Japan, (b) more than 4 weeks after the previous therapy or no previous chemotherapy, (c) performance status (PS) of 2 or better on the Eastern Cooperative Oncology Group scale, (d) age from 20 to 75 years old, (e) adequate bone marrow function (white blood cell (WBC) count $\geq 4,000/\text{mm}^3$, plt $\geq 100,000/\text{mm}^3$, Hb ≥ 9.0 g/dl), (f) adequate hepatic function (T-Bil ≤ 1.5 mg/dl, aminotransferases less than twice the upper limit of normal), (g) adequate renal function (S-Cr ≤ 1.5 mg/dl), (h) no diarrhea and no ileus, (i) no interstitial pneumonitis, 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 (Fig. 1)

Based on the MTD of our previous phase I study of biweekly CPT-11 plus CDDP without the intestinal alkalization⁹, the starting doses of CPT-11 and CDDP were set at 60 mg/m² and 30 mg/m², respectively, on days 1 and 15 in 4 weeks. CDDP dosing was fixed at 30 mg/m², and dose escalation of CPT-11 was performed from 60 mg/m² to 100 mg/m² in steps of 10 mg/m² (Level I: 60 mg/m², Level II: 70 mg/m², Level III: 80 mg/m², Level IV: 90 mg/m², and Level V: 100 mg/m²).

Initially, CPT-11 was administered in 500 ml normal saline as a 90-min i.v. infusion. Then CDDP was given during a 60-min period. Patients with no evidence of disease progression were treated at least 2 cycles. In the present study, the intestinal alkalization was employed to prevent late diarrhea¹⁴. Coinciding with day one of CPT-11 infusion and for four days thereafter, the following was 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). The dose of magnesium oxide was increased or decreased with the occurrence of constipation or diarrhea, respectively. 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.

Granulocyte colony-stimulating factor (G-CSF) was administered when grade 4 leukopenia ($<1,000/\text{mm}^3$) and/or neutropenia ($<500/\text{mm}^3$) were observed. Erythropoietin was not used. Delayed diarrhea was treated with a high dose of loperamide according to previous reports¹¹. Persistent or grade 3 or greater diarrhea, despite loperamide therapy, warranted the use of intravenous hyperalimentation for fluid management.

Fig. 1. Treatment Schedule

CPT-11 plus CDDP were administered biweekly with an anti-diarrheal program, OA and CD, consisting of sodium bicarbonate and magnesium oxide. CDDP dosing was fixed at 30 mg/m² and dose escalation of CPT-11 from 60 mg/m² to 100 mg/m² by increments of 10 mg/m² was performed. (Level I: 60 mg/m², Level II: 70 mg/m², Level III: 80 mg/m², Level IV: 90 mg/m², and Level V: 100 mg/m²)

Evaluation

Patients underwent staging evaluation before entry of this study, and the staging procedures followed those of the tumor-node-metastasis (TNM) system. Tumor response was classified in accordance with World Health Organization criteria. 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.

Dose limiting toxicities (DLT) were defined as Grade 4 hematologic toxicity or Grade 3 non-hematologic toxicity except for emesis and alopecia. During the course of treatment, the dose of CPT-11 and CDDP was withheld when leukopenia ($<3,000/\text{mm}^3$) and/or diarrhea in excess of grade 1 was present on the day of planned administration. Administration delay over 1 week was also judged as DLT. Maximum tolerated dose (MTD) was defined at the dose which produces more than 50% patients with DLT. Namely, if the first 3 patients experienced no DLT, dose escalation was made; if the first 3 patients experienced DLT, the dose was MTD; if 1 or 2 patients experienced DLT, additional 3 patients were treated by the same dose. If 1 or 2 patients of the total 6 patients experienced DLT, dose escalation was made, but if ≥ 3 patients of the total 6 patients experienced DLT, the dose was judge to be MTD.

Results

Twenty three patients participated in the trial. One patient dropped out of the study because of the patient's refusal prior to treatment. The characteristics of the 22 patients are shown in **Table 1**. Three patients were women and 19 were men, and the median age was 61 years. Most of the patients had a good PS, but 2 patients were PS 2. Primary sites of malignancy were the lung: 11 patients, the stomach: 2 patients, the large intestine: 6 patients, and the uterine and ovary: 2 patients.

Twenty two patients were assessable for toxicity. **Table 2** and **3** shows hematologic toxicity and non-hematologic toxicity, respectively. The leukocyte count nadir usually occurred around day 21. However, grade 4 leukopenia and neutropenia occurred in none of the patients. Thrombocytopenia occurred less frequently than leukopenia and was less severe. Thrombocytopenia of grade 3 or more was observed in level IV. No patient required platelet transfusion. Grade ≥ 2 diarrhea was observed in 4 patients (18%) of the 22 patients, but grade 3 diarrhea occurred only in 1 patient (5%), who required i.v. hydration and recovered within seven days. Four patients experienced grade 3 nausea or vomiting (18%), indicating that nausea and vomiting were modest with

Table 1. Patient characteristics

Male/female	19 / 3 pts
Median age	61
(Range)	(38-72)
Performance status	
0	10 pts
1	10 pts
2	2 pts
Cancer type	
NSCLC [#]	9 pts
SCLC ^{##}	2 pts
Gastric cancer	3 pts
Colonic cancer	6 pts
Gynecological cancer	2 pts
Previous therapy	
No	4 pts
Yes	18 pts
Chemotherapy	18 pts
Radiation therapy	7 pts
Operation	9 pts
Others	1 pt

[#] NSCLC: non-small cell lung cancer

^{##} SCLC : small cell lung cancer

this regimen. No hepatic, renal and pulmonary toxicities related to drug administration were observed in this trial. No treatment-related death was observed.

From the view point of dose escalation of CPT-11, at Levels I and II (CPT-11 60, 70 mg/m^2 and CDDP 30 mg/m^2), no DLT was observed. At level III (CPT-11 80 mg/m^2 and CDDP 30 mg/m^2), one patient ceased the second administration because of disease progression, and, therefore, the total number of level III patients was 7. Administration delay over 3 weeks occurred in one patient of the other 6 patients. At level IV (CPT-11 90 mg/m^2 and CDDP 30 mg/m^2), 2 patients experienced grade 3 neutropenia, and one of the 2 patients had grade 3 thrombocytopenia and grade 3 diarrhea. Furthermore, 2 patients experienced grade 3 emesis. Only one of the 6 patients entered at level IV had DLT, and, therefore, dose escalation was made. At level V (CPT-11 100 mg/m^2 and CDDP 30 mg/m^2), one of the 3 patients experienced grade 3 emesis, indicating that level V was not judged to be MTD according to the study protocol. However, further dose escalation was not made. Two of the 3 patients could not be given more than three biweekly CPT-11 100 mg/m^2 and CDDP 30 mg/m^2 due to emesis. Therefore, biweekly CPT-11 90 mg/m^2 with CDDP 30 mg/m^2 with intestinal alkalization was recommended in clinical practice.

The median administration frequency of CPT-11 and CDDP was 4 times with a range from 1 to 16 times. Four patients had no previous treatment, and the other 18 patients had previous chemotherapy. Of the 22 patients, 19 patients were assessed for response (**Table 4**). One patient and 12 patient had partial response (PR) and stable disease (SD), respectively, resulting in a disease control rate of 68%.

Table 2. Hematologic toxicities (n=22)

Level [#]	n	Leucopenia CTC Grade ^{##}				Neutropenia CTC Grade ^{##}				Anemia CTC Grade ^{##}				Platelet depletion CTC Grade ^{##}			
		1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
I	3	1	1	0	0	2	0	0	0	1	1	0	0	0	0	0	0
II	3	1	1	1	0	0	1	0	0	1	0	0	0	0	0	0	0
III	7	4	1	0	0	1	0	0	0	0	2	0	0	0	1	0	0
IV	6	1	1	1	0	1	0	2	0	1	0	2	0	0	0	1	0
V	3	0	1	0	0	0	0	0	0	1	1	0	0	0	0	0	0

[#] CDDP 30 mg/m² plus CPT-11 at a dose of Level I: 60 mg/m², Level II: 70 mg/m², Level III: 80 mg/m², Level IV: 90 mg/m², or Level V: 100 mg/m²

^{##} CTC Grade: the NCI Common Toxicity Criteria (version 2.0)

Table 3. Non-hematologic toxicities (n=22)

Level [#]	n	Diarrhea CTC Grade ^{##}				Emesis CTC Grade ^{##}				Appetite loss CTC Grade ^{##}				Abdominal pain CTC Grade ^{##}			
		1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
I	3	1	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0
II	3	1	0	0	0	0	1	1	0	1	0	1	0	0	0	0	0
III	7	2	2	0	0	2	0	0	0	1	1	0	0	0	0	0	0
IV	6	1	1	1	0	2	0	2	0	2	0	2	0	0	0	0	0
V	3	1	0	0	0	1	2	1	0	0	2	1	0	0	0	0	0

[#] CDDP 30 mg/m² plus CPT-11 at a dose of Level I: 60 mg/m², Level II: 70 mg/m², Level III: 80 mg/m², Level IV: 90 mg/m², or Level V: 100 mg/m²

^{##} CTC Grade: the NCI Common Toxicity Criteria (version 2.0)

Table 4. Dosing and Response Rate

Dosing																	
		Times given		Median													
				Range													
Response [#]																	
Overall		CR		PR		SD		PD		NE		Disease control rate					
		0		1		12		6		3		13 / 19 (68 %)					

[#] CR: complete response, PR: partial response, SD: stable disease and PD: progressive disease was classified in accordance with World Health Organization criteria.

Discussion

The Food and Drug Administration (FDA) recommends to test for UGT1A1 polymorphisms before the administration of CPT-11. This gene analysis can predict leucopenia, but in terms of prediction of diarrhea¹³, the FDA recognizes that the assay has difficulty. To explain this, a two-compartment model constructed by the liver and the intestine to metabolizing CPT-11 has been considered (**Fig. 2**). The liver compartment, as described in the Introduction, has UGT as a key enzyme^{11, 12}. In the intestinal compartment¹⁵, CPT-11, SN-38 and SN-38G are secreted into bile by hepatocytes with subsequent excretion into the intestine^{16, 17}. It was reported that SN-38G is transformed to active SN-38 by bacterial beta-glucuronidase¹⁸. In reports from us and other researchers, damage in the small intestine was observed in humans^{7, 19} where *little* bacteria exist and, therefore, another key of CPT-induced diarrhea was considered.

We found that the intestinal absorption of CPT-11 and SN-38 was characteristic of that of weakly basic drugs²⁰.

At acid pH in the intestinal lumen, non-ionic lactone forms of CPT-11 and SN-38 are passively transported, and their uptake rates are very rapid. On the other hand, the respective anionic carboxylate forms are actively and slowly absorbed at basic pH. Non-ionic SN-38 lactone is more cytotoxic than anionic SN-38 carboxylate, and the uptake rate of SN-38 correlated with its cytotoxicity of intestinal epithelium model *in vitro*²⁰, indicating that elevating pH in the intestinal lumen might result in a reduced cytotoxic effect on the intestinal epithelium. And, *in vivo*, hamster's damaged diarrhea was found to be reduced by sodium bicarbonate²⁷.

We have designed an anti-diarrheal program for CPT-11 designated as the OA and CD, which is also called *intestinal alkalization*. Its rationale was constructed on the intestinal compartment in metabolizing CPT-11 mentioned above (**Fig. 2**). The rationale in designing intestinal alkalization was to reduce absorption of active SN-38 lactone by intestinal cells, which should in turn reduce epithelial damage and its impact on subsequent delayed diarrhea (US patented). The intestinal alkalization consisted of an oral administration of sodium bicarbonate

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