Int. J. Cancer: **92,** 269–275 (2001)

Publication of the International Union Against Cancer

PREVENTION OF IRINOTECAN (CPT-11)-INDUCED DIARRHEA BY ORAL ALKALIZATION COMBINED WITH CONTROL OF DEFECATION IN CANCER PATIENTS

Yuichiro TAKEDA[1,2], Kunihiko KOBAYASHI[2,3]*, Yoshiko AKIYAMA[1], Tomoyuki SOMA[1,2], Satoko HANDA[4], Shouji KUDOH[2,3] and Koichiro KUDO[1,3]

[1]*Department of Respiratory Medicine, International Medical Center of Japan, Tokyo, Japan*
[2]*4th Department of Internal Medicine, Nippon Medical School, Tokyo, Japan*
[3]*East Japan Chesters Group, Department of Respiratory Medicine, Saitama Cancer Center, Saitama, Japan*
[4]*Department of Pharmacology, International Medical Center of Japan, Tokyo, Japan*

It has been reported that 7-ethyl-10-[4-(1-piperidino)-1-piperidino]carbonyloxy-camptothecin (CPT-11) and its active metabolite, 7-ethyl-10-hydroxy-camptothecin (SN-38), have absorption characteristics of weakly basic drugs, suggesting that alkalization of the intestinal lumen might reduce reabsorption and its attendant side effects. Furthermore, stasis of stools containing these compounds is thought to induce damage to the intestinal mucosa. The prevention of CPT-11-induced side effects by oral alkalization (OA) combined with control of defecation (CD) was estimated in a case-control study of lung cancer patients. Coinciding with day 1 of CPT-11 infusion and for 4 days thereafter, OA and CD were practiced utilizing orally administered sodium bicarbonate, magnesium oxide, basic water and ursodeoxycholic acid. OA involved the daily use of all four therapeutics, and CD required doses of up to 4.0 g/day of magnesium oxide and 2 L/day of excess basic water. From three ongoing prospective phase I/II studies, we selected 37 consecutive patients who were treated with CPT-11 in combination with cisplatin in the presence of OA and CD (group B). Thirty-two control subjects who were matched to the background characteristics of the case patients were treated with the same regimen in the absence of OA and CD (group A). Toxicities induced by the CPT-11/cisplatin combination were evaluated and analyzed in group A and group B in a case-control format. The use of OA and CD resulted in significantly higher stool pH ($p < 0.0001$), while reducing the incidence of delayed diarrhea (≥ grade 2: group A 32.3% versus group B 9.4%; $p = 0.005$), nausea ($p = 0.0001$), vomiting ($p = 0.001$) and myelotoxicity, especially granulocytopenia ($p = 0.03$) and lymphocytopenia ($p = 0.034$). In addition, dose intensification was well tolerated in patients receiving OA and CD, allowing dose escalation from 35.6 ± 6.0 to 39.9 ± 5.6 mg/m^2/week ($p < 0.001$). Tumor response rates for non-small cell lung cancer were 59.3% (16/27 patients) in group B compared with 38.5% (10/26 patients) in group A. Multivariate analysis revealed that the risk of CPT-11-induced delayed diarrhea greater than grade 2 was associated with OA and CD (odds ratio for delayed diarrhea, 0.14 with use of OA and CD; 95% confidence interval, 0.05 to 0.4; $p = 0.0002$) and age (odds ratio, 1.08 per increase in age; 95% confidence interval, 1.02 to 1.15; $p = 0.009$). OA and CD appear to be useful in preventing the dose-limiting side effects of CPT-11 noted in clinical practice, mainly nausea, vomiting, granulocytopenia and especially delayed diarrhea. Risk factors statistically associated with delayed diarrhea include advanced age and the use of CPT-11 without OA and CD.

Key words: *alkalization; control of defecation; case-control study; irinotecan (CPT-11); SN-38; damage of intestinal mucosa; prevention of delayed diarrhea*

The topoisomerase I inhibitor irinotecan hydrochloride {7-ethyl-10-[4-(1-piperidino)-1-piperidino]carbonyloxy-camptothecin (CPT-11)}[1] has become one of the more prominent anti-neoplastic drugs in clinical practice today.[2–4] Encouraging response rates have been noted in patients with refractory leukemia, lymphoma and several common solid tumors such as non-small cell lung cancer, small cell lung cancer, colon cancer and gynecologic cancers.[5–8]This success has driven the use of CPT-11 as either a monotherapy or in combination with other agents such as docetaxel, cisplatin (CDDP) and etoposide.[9–11] However, several toxicities including severe delayed diarrhea and leukopenia presently limit the use of CPT-11.[5,10] Some studies have documented success with high-dose loperamide in counter-acting delayed diarrhea when it appeared;[12,13] however, there is still no effective strategy for prevention of this dose-limiting side effect.

CPT-11 is hydrolyzed to active 7-ethyl-10-hydroxy-camptothecin (SN-38) by liver carboxylesterase.[14] A portion of SN-38 undergoes subsequent conjugation to inactive SN-38 β-glucuronide (SN38-Glu) by the hepatic enzyme, UDP-glucuronyltransferase.[15] Recently, it has been discovered that the hepatic cytochrome P-450 3A enzyme metabolizes CPT-11 to 7-ethyl-10-[4-N-(5-aminopentanoic acid)-1-piperidino] carbonyloxy-camptothecin, which has a 500-fold weaker anti-tumor activity than SN-38.[16] CPT-11, SN-38 and SN38-Glu each contain an α-hydroxy-3-lactone ring that undergoes reversible hydrolysis at a rate that is mainly pH dependent.[17] Above physiologic pH, the non-ionic, lactone form is unstable and equilibrium favors hydrolysis of the lactone ring, yielding the ionic, carboxylate form.[17,18] Under acidic conditions, the reverse reaction, *i.e.*, reformation of the lactone ring, is favored.[17,18] All of CPT-11, SN-38 and SN38-Glu are secreted into bile by hepatocytes[19,20] with subsequent excretion into the small intestine.

We have previously shown that both CPT-11 and SN-38 were reabsorbed by hamster intestinal cells and that the nature of the intestinal transport displayed by these compounds suggested absorption characteristics of weakly basic drugs: 1) under acidic pH, the non-ionic form of CPT-11 and SN-38 was transported passively; 2) at neutral/basic pH, the respective ionic form was absorbed actively; and 3) the uptake rate of the respective non-ionic form (lactone) was higher than that of the ionic form (carboxylate).[21] The intestinal transport of these compounds resembled that of short-chain fatty acids, which were weakly basic compounds, reported by Charman *et al.*[22] and Bugaut.[23] Therefore, alkalization of the luminal content should reduce the intestinal uptake of CPT-11 and SN-38. Indeed, respective rates of intestinal uptake for CPT-11 and SN-38 were shown to be pH sensitive under physiologic conditions, with uptake decreasing by more than 65% at pH levels greater than 6.8.[21] Furthermore, the cytotoxic efficacy of SN-38 against HT-29 (a colon carcinoma cell line) cells has been shown to correlate with its uptake into these cells, which is

*Correspondence to: East Japan Chesters Group, Department of Respiratory Medicine, Saitama Cancer Center, Komuro, Ina, 362-0806, Saitama, Japan. E-mail: go1059@cancer-c.pref.saitama.jp

Received 24 May 2000; Revised 3 November 2000; Accepted 20 November 2000

also a pH-dependent process ($r = 0.987$; correlation coefficient obtained by the simple regression method).[21]

Intracellular accumulation of SN-38 has been shown within the intestines of rats[24] and is thought to be responsible for the diarrhea attributed to CPT-11 in nude mice.[25] In addition, disruption of the cecal mucosa has been noted in mice and rats with CPT-11-induced diarrhea.[25–27] Cancer patients with an elevated biliary index, a product of the area ratio of SN-38 to SN38-Glu and the total CPT-11 area under the plasma concentration-time curve, display a greater incidence of diarrhea.[28] Collectively, these findings support a prominent role for SN-38 in mediating both epithelial damage and diarrhea. Moreover, we formerly observed a patient who exhibited constipation upon administration of CPT-11 and found evidence of severe small intestinal injury that was analogous to that seen in the animal models mentioned above.[10] Noted at autopsy in this patient was the presence of pseudomembranous jejuno-ileitis, which appeared under light microscopy to be characterized by disruption of the intestinal epithelium, suggesting that diarrhea induced by intestinal damage could occur in severe cases.

Both our experimental data and prior clinical experience indicated that alkalization of the intestinal lumen and control of defecation are critical to reducing reabsorption, damage of the intestinal epithelium and other side effects associated with CPT-11 administration. We designed this case-control study with lung cancer patients from a single institution to evaluate whether these side effects could be reduced by oral alkalization (OA) combined with control of defecation (CD).

MATERIAL AND METHODS

Patient selection

The patients and control subjects were selected consecutively from three ongoing prospective phase I and II studies utilizing a combination of CPT-11 and CDDP in the Department of Respiratory Medicine at the International Medical Center of Japan.[10] Between June 1997 and November 1998, a total of 69 patients who met the following strict criteria were enrolled in these prospective phase I and II studies: 1) histologic or cytological diagnosis of either small cell lung cancer (SCLC) or non-small cell lung cancer (NSCLC); 2) inoperability at the time of entry into trial, *i.e.*, stage III or IV NSCLC, according to the International Union Against Cancer Classification, or SCLC; 3) no prior therapy or no residual effects of prior treatment (more than 2 months after the previous treatment); 4) age equal to or less than 76 years; 5) performance status of 2 or better on the Eastern Cooperative Oncology Group (ECOG) scale; 6) adequate bone marrow function (leukocyte count $> 4{,}000/\mu l$; platelet count $> 100{,}000/\mu l$; hemoglobin concentration > 9 g/dl), hepatic function (bilirubin < 1.5 mg/dl; transaminases $< 2 \times$ upper limit of that found normally) and renal function (creatinine < 1.5 mg/dl); 7) life expectancy of at least 8 weeks; and 8) informed consent of the patient. We selected 37 consecutive patients who were treated with a combination of CPT-11 and CDDP in the presence of OA and CD (group B). Thirty-two control subjects who were matched to the background characteristics of the case patients were treated with the same regimen in the absence of OA and CD (group A).

Treatment

Nine patients were treated with combined chemotherapy consisting of 60 mg/m^2 CPT-11 and 30 mg/m^2 CDDP on days 1, 8 and 15, with both agents given simultaneously.[10] All the remaining patients were treated with combined chemotherapy consisting of 60 mg/m^2 CDDP on day 1 and 60 to 75 mg/m^2 CPT-11 on days 1 and 8. With both schedules, a standard antiemetic combination of metoclopramide, corticosteroid and a 5-hydroxytryptamine 3 (5-HT3) receptor antagonist were given prophylactically by intravenous infusion prior to the administration of CPT-11. A prophylactic, orally administered 5-HT3-receptor antagonist was continued for 4 days. In all cases, the dose of CPT-11 was withheld on scheduled days in instances of leukopenia ($<3{,}000/\mu l$) and/or diarrhea of grade greater than 1. Granulocyte-colony stimulating factor (G-CSF) was administered when grade 3 toxicities of leukopenia ($<2{,}000/\mu l$) and/or granulocytopenia ($<1{,}000/\mu l$) were observed. Patients who exhibited either disease stabilization or improvement received at least two courses of the same regimen, and patients with obvious evidence of disease progression were removed from the study. Prior to administering each course of chemotherapy, the leukocyte and platelet counts had to exceed $3{,}000/\mu l$ and $100{,}000/\mu l$, respectively. If more than 6 weeks had elapsed from the time of the last treatment to satisfaction of these criteria, the patient was removed from the study.

As these chemotherapeutic regimens included CDDP, it was necessary to hydrate both groups A and B before administering CDDP. This was especially applicable in group B patients, who were required to drink the excessive basic water as part of their controlled defecation therapy (see below). Patients medically unable to load sodium and water because of concomitant illnesses were excluded from this treatment. Additional attention was necessary in controlling defecation in those patients administered high doses of morphine for pain control, as they tended to experience narcotic-related constipation. Patients were treated with OA and CD for prevention of CPT-11-induced delayed diarrhea. The OA and CD treatment began coincident with the first day of CPT-11 and CDDP infusion and was continued for 4 days. OA involved administering sodium bicarbonate and magnesium oxide (0.5 g each, orally) after every meal and before sleep for a total of four doses each per day, ursodeoxycholic acid (UDCA 100 mg, orally) after every meal for a total of three doses per day and basic water (pH greater than 7.2) continuously for a total of 1,500 to 2,000 ml per day (Table I). The magnesium oxide and excessive basic water given to patients in group B also served the purpose of CD. In an effort to prevent constipation and permit defecation at least once a day, patients were given magnesium oxide up to a total of 4.0 g per day and basic water up to a total of 2,000 ml per day. In patients who experienced watery diarrhea during OA and CD, magnesium oxide was discontinued until symptoms resolved, while in cases of soft stool, patients continued per the protocol.

TABLE I – TREATMENT TO PREVENT CPT-11-INDUCED SIDE EFFECTS

Contraindications and precautions
1. Patients who cannot load sodium and water with this treatment (*e.g.*, cardiac failure, renal failure)
2. Patients who use morphine and have had constipation; CPT-11 should be given to patients with regular defecation (more than once a day)

Procedure for oral alkalization and control of defecation
The following oral administration should be started immediately after the decision to use CPT-11 and should continue for 4 days:

Rp. Sodium bicarbonate	2.0 g/day	4×
Ursodeoxycholic acid	300 mg/day	3×
Magnesium oxide	2.0–4.0 g/day	4×
Basic water (pH > 7.2)	1,500–2,000 ml/day for at least 3 days	
5-HT3 receptor antagonist	Regular oral use from 2nd to 4th days	

Special considerations:
1. Magnesium oxide up to 4.0 g/day is regulated to prevent constipation and provide for defecation at least once a day. In case of watery diarrhea, oral administration of magnesium oxide is stopped. In case of soft stool, it must be continued.
2. On the day when CPT-11 is given, elevating the dose of morphine and using loperamide should be avoided.
3. The contraindications and precautions for sodium bicarbonate, magnesium oxide, ursodeoxycholic acid and 5-HT3 receptor antagonist should be kept in mind.

In the case of diarrhea occurring on the day of CPT-11 and CDDP infusion, the symptoms of cholinergic syndrome were controlled with the use of anticholinergic drugs such as butylscopolamine or atropine.[29] Delayed diarrhea, which typically presented 6 days after and beyond the initial CPT-11 administration, was treated with a high dose of loperamide as previously described.[12] Patients with delayed diarrhea were given 2 mg of loperamide on demand after every diarrheal episode. When this approach did not succeed, the patient was managed with 2 mg of loperamide every 4 hours routinely and continued until a 12-hour diarrhea-free interval was achieved. Persistent or grade 3 or greater diarrhea, despite loperamide therapy, warranted the use of intravenous hyperalimentation (IVH) for fluid management.

Determination of stool pH

During chemotherapy, the pH of the stool was determined using stool samples collected by natural defecation from days 1 through 5 after CPT-11 and CDDP administration. Five grams of each stool sample were added to 45 ml of distilled water, mixed well and allowed to stand for more than 30 min at 20°C. After resuspension of the solution, the pH was measured with the HM-14P pH meter (TOA Electronics, Tokyo, Japan).

Evaluation

As part of the staging process, patients were evaluated by physical examination, chest X-ray, bone scintiscan, computed tomography of the head, chest and abdomen and fiberoptic bronchoscopy. Classification was in accordance with the tumor-node-metastasis (TNM) staging system. Prior to receiving CPT-11-containing chemotherapy, each patient was subjected to a complete blood cell count (CBC) with differential (*i.e.*, granulocytes, lymphocytes and platelets) to assess marrow status and serum chemistries, electrolyte analysis and urinalysis to evaluate renal and hepatic function. The CBCs, serum chemistries, electrolyte analyses, urinalyses and chest X-rays were performed at least once a week after the initial evaluation. Tumor response was classified per the World Health Organization criteria, while ECOG common toxicity criteria (CTC) were used to grade organ system damage. For the purpose of this study, we defined the duration of toxicities as the length of time required to return to grade 1 status. For constipation, grade 0 indicated no constipation or constipation lasting 1 day; grade 1 was constipation for 2 days; grade 2 indicated constipation for 3 days; grade 3 indicated constipation for more than 4 days; and grade 4 indicated severe paralytic ileus or mechanical ileus.

Statistical analysis

Differences in patient characteristics between the two groups were examined using Pearson's chi-square test and the unpaired *t*-test.[2] The incidence of hematologic toxicities and non-hematologic toxicities in the two groups were compared using chi-square test or unpaired *t*-test. The unpaired *t*-test was used to detect differences in stool pH between the two groups at the dose of 60 mg/m^2 CPT-11. Variations in response rates to the chemotherapy and in dose intensities between the two groups were analyzed using Fisher's exact test and the unpaired *t*-test, respectively. The logistic regression model was used for both the univariate and multivariate analyses to determine the variables associated with a risk of CPT-11-induced delayed diarrhea greater than grade 2. Cases with more than one missing value were excluded from univariate testing, and only complete datasets were used in the multivariate analysis. Calculations were performed using the Statistical Package for Social Sciences (SPSS) for Macintosh Medical Pack version 6.0. All *p*-values are two-tailed with a p-value < 0.05 considered statistically significant.

RESULTS

Thirty-two patients were treated with a combination of CPT-11 and CDDP in the absence of OA and CD (group A), while 37 received the same chemotherapeutic regimen but with the addition of OA and CD (group B). Patient characteristics are listed in Table II. Of the 69 patients, 18 were female and 51 were male. The mean age was 61.5 years (range, 36 to 76 years). Sixty-one patients had a performance status (PS) of 0 to 1. Forty-six patients had no prior treatment. All patients had primary lung cancers (58 NSCLC, 11 SCLC), with 58 staged as either III-B or IV disease, 9 staged as III-A and 1 each of stage II-A and I-B. Of the nine cases with stage III-A disease, one had SCLC, and the remaining eight had NSCLC with bulky N2 disease. Each of the two patients with either stage I-B or II-A disease had SCLC. There were no statistically significant differences found between clinical characteristics of groups A and B (Table II). In addition, there was no significant difference noted in pretreatment serum bilirubin (total and indirect) between groups A and B.

pH of the stool

The stool pH was determined in both groups using samples collected by natural defecation from days 1 through 5 after CPT-11 and CDDP administration. We examined 9 stool samples collected from four patients in group A (no OA and CD treatment) and 16 samples from five patients in group B (treated with OA and CD). Figure 1 illustrates our observation that stool pH from OA and CD-treated patients (mean pH $\pm$ SD; 9.2 $\pm$ 0.44) was significantly higher than that of stools from control patients (mean pH $\pm$ SD; 7.0 $\pm$ 0.66). These results suggest that our OA and CD program was effective at raising intraluminal pH.

Hematologic toxicity

Hematologic toxicity was evaluated for each course of combination chemotherapy administered (Table III). In total, 150 courses of chemotherapy were given, 65 to group A patients and 85 to group B patients. With respect to leukopenia, there was no signif-

TABLE II – CHARACTERISTICS OF PATIENTS

	Group A[1]	Group B[2]	*p*-value
No. of patients	32	37	
Sex (M/F)	24/8	27/10	0.85[3]
Mean age (yr) (range)	60.4 (44 ~ 76)	62.4 (36 ~ 76)	0.38[4]
Performance status (ECOG)			
0	7	11	
1	23	20	
2	2	6	0.25[3]
Prior therapy			
None	21	25	
Present	11	12	0.86[3]
Operation	2	6	
Radiation	1	1	
Chemotherapy	8	5	
Diagnosis			
Small	5	6	
Non-small	27	31	0.95[3]
Adeno	24	23	
Squamous	3	7	
Large	0	1	
Stage			
IV	28	26	
IIIB	4	11	0.15[3]
IIIB	1	3	
IIIA	2	7	
IIA	0	1	
IB	1	0	
Serum bilirubin level before treatment (mg/dl)			
Total	0.50 $\pm$ 0.16	0.48 $\pm$ 0.20	0.61[4]
Indirect	0.45 $\pm$ 0.17	0.45 $\pm$ 0.18	0.97[4]

[1]Without oral alkinization (OA) and control of defecation (CD).–[2]With OA and CD.–[3]Chi-square test.–[4]Unpaired *t*-test.

icant difference in the incidence of ECOG grade 2 or greater toxicity between the two groups ($p = 0.053$; chi-square test); however, the mean nadir leukocyte count in group A was significantly lower than that in group B ($p = 0.031$; unpaired *t*-test). Although the actual dose intensity of CPT-11 was increased in group B (as described below), grade 3 or 4 leukopenia only occurred in 7.1% of these patients, whereas 23.1% of group A displayed this side effect ($p = 0.0076$; Fisher's exact test). Grade 2 or greater granulocytopenia was observed significantly less often with the use of OA and CD ($p = 0.030$; chi-square test). No significant difference in the mean nadir granulocyte count between the two groups ($p = 0.078$; unpaired *t*-test) was noted. Grade 4 granulocytopenia occurred more often in group A ($p = 0.0297$; Fisher's exact test), which resulted in the only treatment-related death (sepsis) encountered in this group. No treatment-related deaths were observed in group B.

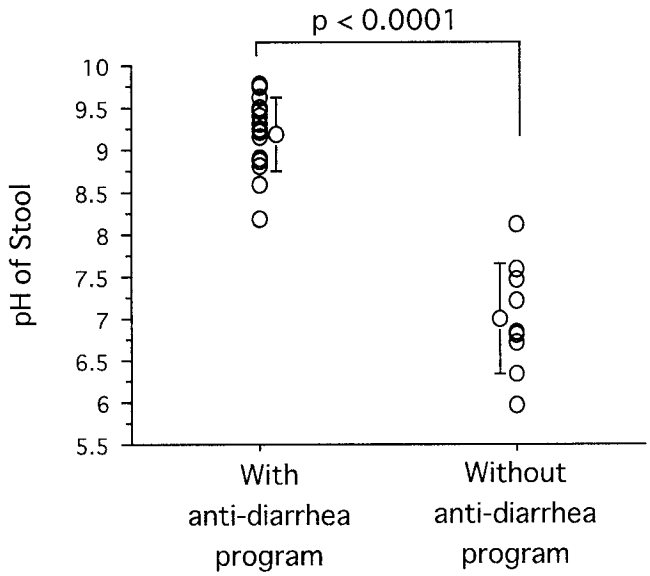

FIGURE 1 – The pH of the stool during chemotherapy with or without OA & CD. All patients were treated with combined chemotherapy consisting of 60 mg/m^2 CDDP on day 1 and 60 mg/m^2 CPT-11 on days 1 and 8. Stool samples were collected by natural defecation from days 1 to day 5 after the admininstration of CPT-11. The pH of the stool samples was examined as described in the Patients and Methods section. A statistically significant difference was found concerning the stool pH from both groups ($P < 0.0001$, Unpaired t-test).

The mean nadir lymphocyte count among group A patients was significantly less than that observed in group B ($p = 0.034$; unpaired *t*-test). Lymphocytopenia less than 500/mm^3 was also seen more often in group A ($p = 0.007$; Fisher's exact test). Furthermore, the duration of lymphocytopenia less than 2,000/mm^3 in group A was longer than that in group B (6.56 ± 5.88 and 4.92 ± 3.96 days, respectively; $p = 0.047$; unpaired *t*-test). Thrombocytopenia of grade 2 or greater was not significantly different between the groups, nor was the mean nadir platelet count. However, thrombocytopenia of grade 3 or greater did occur more often in group A ($p = 0.016$; Fisher's exact test), affecting two patients who then required platelet transfusions. Notably, there was neither grade 3 nor 4 thrombocytopenia in group B. Lastly, there was no significant difference in the incidence of grade 2 or greater anemia between groups; however, anemia greater than grade 3 occurred more often in patients not receiving OA and CD ($p = 0.038$; Fisher's exact test). Together, these findings suggest a reduction in CPT-11-induced hematologic toxicities with the use of OA and CD. The toxicities most effectively controlled include leukopenia, granulocytopenia and lymphocytopenia; however, anemia and thrombocytopenia might occur less often as well with this treatment.

Non-hematologic toxicity

The main non-hematologic side effects encountered in either group were related to gastrointestinal toxicity (Table IV). Appetite loss in group A was more severe than that in group B ($p = 0.007$; chi-square test), with grade 3 or greater toxicity observed in 7.7% of group A patients ($p = 0.0006$, Fisher's exact test). One patient from group A who suffered grade 4 appetite loss for 48 days required IVH for 5 weeks. In both groups, nausea and vomiting were managed by a standard antiemetic combination of metoclopramide, corticosteroids and a 5-HT3 receptor antagonist. The grade of nausea and vomiting in group A patients was significantly greater than that in group B ($p = 0.0001$ and $p = 0.001$, respectively; chi-square test), with grade 3 or greater toxicity observed only in group A. Grade 3 or 4 constipation was observed in 7 of 65 cycles (10.8 %) in group A, while not at all in group B. The incidence of grade 3 or 4 constipation grade in group A was higher than that in group B ($p < 0.0001$; two-sided Fisher's exact test).

Merrouche and coworkers[13] reported that the median time to onset of the first delayed diarrheal episode was 6 days after administration of high CPT-11 dose intensities. Thus, we defined watery diarrhea from the 6th day after the CPT-11 administration as delayed diarrhea. Patients in group A experienced delayed

TABLE III – HEMATOLOGIC TOXICITY

	Group A[1]	Group B[2]	*p*-value
Leukopenia			0.053[3]
ECOG grade 2 (%)	70.8	57.6	
ECOG grade 3 (%)	23.1	7.1	
Nadir (mean ± SD [μl])	2570 ± 960	2899 ± 876	0.031[4]
Granulocytopenia			0.030[3]
ECOG grade 2 (%)	71.4	68.2	
ECOG grade 3 (%)	33.3	34.1	
Nadir (mean ± SD [μl])	1163 ± 581	1329 ± 646	0.078[4]
Lymphocytopenia			
Nadir (mean ± SD [μl])	982 ± 486	1147 ± 449	0.034[4]
Hemoglobin			0.139[3]
ECOG grade 2 (%)	50.8	42.4	
ECOG grade 3 (%)	15.4	5.9	
Nadir (mean ± SD [g/dl])	9.8 ± 1.6	10.2 ± 1.6	0.109[4]
Thrombocytopenia			0.171[3]
ECOG grade 2 (%)	12.3	4.7	
ECOG grade 3 (%)	3.1	0	
Nadir (mean ± SD [×10^4/μl])	16.9 ± 7.8	17.8 ± 5.9	0.462[4]

[1]Without oral alkinization (OA) and control of defecation.–[2]With OA and CD.–[3]Chi-square test.–[4]Unpaired *t*-test; *p*-values less than 0.05 are underlined.

TABLE IV – NONHEMATOLOGIC TOXICITY

	Group A[1]	Group B[2]	*p*-value
Appetite			0.007[3]
ECOG grade 2 (%)	59.9	28.2	
ECOG grade 3 (%)	7.7	1.2	
Nausea			0.0001[3]
ECOG grade 2 (%)	61.5	29.4	
ECOG grade 3 (%)	10.8	0	
Vomiting			0.001[3]
ECOG grade 2 (%)	26.2	7.1	
ECOG grade 3 (%)	1.5	0	
Delayed diarrhea			0.005[3]
ECOG grade 2 (%)	32.3	9.4	
ECOG grade 3 (%)	9.2	0	
Mean consumption of dosages of loperamide (mg/patient/course)	11.0 ± 19.9	3.14 ± 5.56	0.003[4]

[1]Without oral alkinization (OA) and control of defecation (CD).–[2]With OA and CD.–[3]Chi-square test.–[4]Unpaired *t*-test; *p*-values less than 0.01 are underlined.

TABLE V – VARIABILITY OF DOSE INTENSITY

Actual dose intensity (mg/m^2/week)	No. of chemotherapy courses		Total
	Group A[1]	Group B[2]	
25–30	20	2	22
31–35	10	21	31
36–40	25	29	54
41–45	10	20	30
46–50	0	13	13
Total	65	85	150
Average	35.6 ± 6.0	39.9 ± 5.6	$p < 0.0001$*

[1]Without oral alkinization (OA) and control of defecation (CD).–[2]With OA and CD.–*Significant difference between Group A and B (unpaired *t*-test).

diarrhea more frequently than those in group B ($p = 0.005$; chi-square test), with grade 3 to 4 toxicity occurring in 6 of 65 cycles (9.2 %) in group A versus none at all in group B (0 %). The difference in delayed diarrhea greater than grade 3 between the two groups was statistically significant ($p = 0.0014$; Fisher's exact test). The duration of delayed diarrhea in group A was 2.8 times longer than in group B ($p < 0.0001$; unpaired *t*-test). In both groups, delayed diarrhea was treated with a high dose of loperamide. As expected, we found that the amount of loperamide necessary to control the diarrheal episodes of each chemotherapy cycle adequately was related to the severity of delayed diarrhea. The total dose of loperamide given to patients in group A exceeded that given to those in group B ($p = 0.003$; unpaired *t*-test). These results indicate that OA and CD effectively decreased the severity of CPT-11-induced delayed diarrhea.

Actual dose intensity and response

Table V shows the variability in actual dose intensity (ADI) between groups A and B. The ADI value was calculated by the following formula:

T (days) = the duration of therapy as measured from the start of the treatment until recovery to grade 1 leukopenia and thrombocytopenia

W (weeks) = T/7 days

ADI (mg/m^2/week) = actual total administered dose of CPT-11 during each course of chemotherapy (mg/m^2)/W

The ADI of CPT-11 was increased from 35.6 ± 6.0 to 39.9 ± 5.6 mg/m^2/week as a result of adding OA and CD to the treatment regimen. The ADIs of groups A and B were noted to be statistically different ($p < 0.0001$; unpaired *t*-test).

TABLE VI – RESPONSE-RATE ANALYSIS BASED ON HISTOLOGIC TYPES[1]

Histologic type	Responders/evaluative patients (% response rate)		*p*-value[4]
	Group A[2]	Group B[3]	
SCLC	5/5 (100)	6/6 (100)	NS
NSCLC	10/26 (38.5)	16/27 (59.3)	0.173

[1]Abbreviations: SCLC, small cell lung cancer; NSCLC, non-small cell lung cancer; NS, not significant.–[2]Without oral alkinization (OA) and control of defecation.–[3]With OA and CD.–[4]Fisher's exact test.

Although it was not the aim of this study, we formulated a comparison with respect to response rates between groups A and B. Such analyses were performed only on those cases deemed evaluable, as some patients had no measurable lesions to serve as comparisons. Table VI lists the response rates for each group according to histologic classification. In the case of SCLC, each of the 11 eligible patients was evaluated for response. Of the five group A and six group B patients with SCLC, all were considered responders. Five patients with NSCLC (one patient in group A and four patients in group B) could not be evaluated for response secondary to a lack of measurable lesions in these patients. From the remaining set of patients with NSCLC, there were 10 responders out of the 26 patients in group A (a response rate of 38.5%) and 16 responders out of the 27 patients in group B (a response rate of 59.3%) ($p = 0.173$; Fisher's exact test). These data suggest that OA and CD treatment does not significantly alter the response rate following this particular regimen of combination chemotherapy.

Univariate and multivariate analyses of risk factors for delayed diarrhea

Univariate and multivariate logistic regression analyses were used to identify risk factors for delayed diarrhea greater than grade 2 (Table VII). One hundred fifty courses of chemotherapy were evaluated in this analysis. Results are reported as odds ratios, 95% confidence intervals (CIs) and *p*-values. By univariate analysis, age, total bilirubin and OA and CD treatment were found to be significantly associated with delayed diarrhea greater than grade 2 ($p = 0.05$, 0.03 and 0.0008, respectively).

Multivariate analysis related increased age to a significantly higher risk of developing delayed diarrhea greater than grade 2 (odds ratio, 1.08; 95% CI, 1.02 to 1.15; $p = 0.009$). However, this risk was significantly reduced with the use of OA and CD (odds ratio, 0.14; 95% CI, 0.05 to 0.40; $p = 0.0002$). Multivariate analysis indicated that omission of OA and CD from these combined chemotherapy regimens is a stronger risk factor for delayed diarrhea than advanced age.

DISCUSSION

The role of oral alkalization (OA) combined with control of defecation (CD) in reducing the side effects of CPT-11 chemotherapy was evaluated in this clinical study. As mentioned earlier, alkaline conditions within the intestinal lumen have been shown to decrease reabsorption of CPT-11 and its metabolites.[21] In addition, absorption of CPT-11 has been associated with epithelial damage within the intestines of rats and is thought to be the insult responsible for delayed diarrhea.[25–27] Thus, our rationale in designing this study was to prevent absorption by oral alkalization, which should in turn reduce epithelial damage and its impact on subsequent delayed diarrhea. Controlling defecation should prevent constipation, thereby also preventing epithelial disruption and allowing less time for additional absorption. This concept of defecation control so as to prevent reabsorption of CPT-11 and SN-38 is based on our clinical experience.[10,21] Also, the concept of increasing clearance of these metabolites from the body is supported by recent experimental work from our group, which demonstrated similar absorption rates for the lactone forms of CPT-11 and SN-38 among

TABLE VII – RISK FACTORS OF DELAYED DIARRHEA GREATER THAN GRADE 2[1]

Variable	Univariate analysis		Multivariate analysis	
	Odds ratio (95% CI)	*p*-value	Odds ratio (95% CI)	*p*-value
Age	1.04 (0.99–1.09)	0.05	1.08 (1.02–1.15)	0.009
Weekly dose of CPT-11	0.95 (0.88–1.01)	0.12	NE	NE
Diagnosis	1.92 (0.53–6.92)	0.32	NE	NE
OA and CD	0.22 (0.09–0.53)	0.0008	0.14 (0.05–0.40)	0.0002
Indirect bilirubin[2]	12.0 (0.94–152.2)	0.06	NE	NE
Total bilirubin[2]	14.9 (0.90–103.6)	0.03	NE	NE
Pretreatment	0.54 (0.21–1.36)	0.19	NE	NE
Performance status	1.78 (0.88–3.62)	0.06	NE	NE
Sex	1.08 (0.42–2.78)	0.87	NE	NE
Stage	1.21 (0.45–3.25)	0.71	NE	NE

[1]Logistic regression analysis. CI, confidence interval; NE, variables were not entered in the equation; OA, oral alkalization; CD, control of defecation.–[2]Serum total bilirubin and indirect bilirubin level before treatment.

jejunal, ileal, cecal and colonic cells by passive transport.[21] By assisting the body in clearing the insulting agents, we anticipated a decline in the dose-limiting side effect associated with CPT-11 chemotherapy, namely, delayed diarrhea; however, reductions in other known sequelae such as hematologic toxicity were felt to be possible.

The OA and CD regimen implemented in this study involved oral administration of sodium bicarbonate, magnesium oxide, basic water and UDCA. The former three agents have a basic pH and are known to mediate alkalization of both the gastric and intestinal lumens directly. Magnesium oxide is partially absorbed in the stomach, enters the intestinal lumen and demonstrates a laxative action that should shorten the dwelling time of CPT-11 and SN-38 within the intestine. UDCA has been reported to stimulate bile flow associated with a bicarbonate-rich choleresis.[30] UDCA exerts a direct effect on bile duct cells by increasing the intracellular calcium concentration and stimulating Cl^- efflux through the opening of Cl^- channels in the cellular membrane.[31] This is thought to incite biliary Cl^-/HCO_3^- exchange, contributing to increased biliary HCO_3^- concentration and bile flow.[31]Dumont *et al.*[32] demonstrated an increased concentration of HCO_3^- in rat bile with continuous intravenous infusion of UDCA. In a patient with pancreatic cancer undergoing percutaneous transhepatic cholangiographic drainage (PTCD), Tsujii *et al.*[33] reported an increase in biliary HCO_3^- after oral administration of 300 mg/day of UDCA. In observance of these findings, we included UDCA as well as sodium bicarbonate in our OA and CD regimen in an effort to increase biliary pH.

Our study revealed a significant reduction in incidence, severity and duration of CPT-11-induced delayed diarrhea with the use of OA and CD. By multivariate analysis, the lack of OA and CD therapy was associated with the development of delayed diarrhea greater than grade 2. The number of patients suffering severe diarrhea was significantly greater in the group not receiving OA and CD. As mentioned before, SN-38 accumulation within intestinal cells has been shown to result in epithelial damage and associated diarrhea. Therefore, one postulate regarding our success with OA and CD would involve the reduced uptake of these metabolites, lessening the impact on the intestinal mucosa. As such, we could expect less CPT-11-induced diarrhea.

In terms of additional side effects seen with CPT-11 use, leukopenia, both granulocytopenia and lymphocytopenia, was significantly decreased in patients treated by OA and CD (Table III), with significantly fewer group B patients suffering grade 3 or greater leukopenia. CPT-11-induced hematologic effects on leukocyte production might therefore also be reduced with this therapy. Although there was no significant difference with respect to grade 2 or greater anemia or thrombocytopenia, nor a statistical difference in mean nadir hemoglobin or platelet counts between groups, the incidence of grade 3 or greater anemia and thrombocytopenia was significantly greater in group A (no OA and CD). Despite a statistically significant difference in the ADI of CPT-11 between groups A and B (Table V), we did not observe a significant difference in response rates. However, clinical response was not the primary endpoint of this study; therefore any association between response rates and OA and CD use could not be accurately attributed to the noted increase in ADI.

We are planning another phase II study to address this issue. However, it is worth noting that the patient response rates in this study do indicate that OA and CD did not compromise the clinical efficacy of CPT-11/CDDP combination therapy. This would suggest that, although a reduced amount of CPT-11 and SN-38 may be circulated enterohepatically, the increased ADI conferred by OA and CD results in maintenance of the same degree of clinical efficacy. There have yet to be any reports concerning an altered bioavailability of CPT-11 and SN-38 circulated enterohepatically as a consequence of this therapy. Our clinical data suggest changes in the pharmacokinetics of CPT-11 and SN-38 secondary to decreased reabsorption of these molecules by the intestinal epithelium as a consequence of the OA and CD treatment.

In summary, OA and CD treatment, as practiced by the oral administration of sodium bicarbonate, magnesium oxide, basic water and UDCA for 4 days after the administration of CPT-11, appears to reduce the incidence of side effects such as delayed diarrhea, emesis and leukopenia. In addition, this treatment may prove useful in preventing the occurrence of severe delayed diarrhea induced by CPT-11.

ACKNOWLEDGEMENTS

We thank Dr. Yasushi Matsuzaki for thoughtful discussion and Hirohiko Maeda (Yakult Honsha Co. Ltd., Tokyo) for assistance in preparing our study. We also express our deepest gratitude to all the coordinating nurses (Satoe Kikuchi, Rika Fujita and others) and all those who provided care and support for the patients participating in this study.

REFERENCES

1. Kawato Y, Aonuma M, Hirota Y, Kuga H, Sato K. Intracellular roles of SN-38, a metabolite of the camptothecin derivative CPT-11, in the antitumor effect of CPT-11. Cancer Res 1991;51:4187–91.
2. Cunningham D, Pyrhoenen S, James RD, Punt CJA, Hickish TS, Heikkila R, et al. Randomized trial of irinotecan plus supportive care versus supportive care alone after fluorouracil failure for patients with metastatic colorectal cancer. Lancet 1998;352:1413–8.
3. Rougier P, Cutsem EV, Bajetta E, et al. Randomized trial of irinotecan versus fluorouracil by continuous infusion after fluorouracil failure in patients with metastatic colorectal cancer. Lancet 1998;352:1407–2.
4. Salt LB, Locker PK, Pirotta N, Elfring GL, Miller LL. Weekly irinotecan (CPT-11), leucovorin (LV), and fluorouracil (FU) is superior to daily x 5 LV/FU in patients with previously untreated metastatic colorectal cancer. Proc Am Soc Clin Oncol 1999;18:233a.

5. Fukuoka M, Niitani H, Suzuki A, et al. A phase II study of CPT-11, a new derivative of camptothecin, for previously untreated non-small-cell lung cancer. J Clin Oncol 1992;10:16–20.
6. Ohno R, Okada K, Masaoka T, et al. An early phase II study of CPT11: a new derivative of camptothecin for the treatment of leukemia and lymphoma. J Clin Oncol 1990;8:1907–12.
7. Masuda N, Fukuoka M, Kusunoki Y, Matsui K, Takifuji N, Kudoh S, Negoro S, Nishioka M, et al. CPT-11, a new derivative of camptothecin for the treatment of refractory or relapsed small-cell lung cancer. J Clin Oncol 1992;10:1225–9.
8. Takeuchi S, Takamizawa H, Takeda Y, Ohkawa T, Tamaya T, Noda K, Sugawa T, Sekiba K, et al. An early phase II study of CPT-11 for gynecologic cancers Jpn J Cancer Chemother 1991;18:579–84.
9. Maenpaa J, Kaar K, Kivinen S, Pohto M, Jekunen A. Docetaxel and CPT-11 for recurrent ovarian cancer—a phase II study. Proc Am Soc Clin Oncol 1999;18:1403.
10. Kobayashi K, Shinbara A, Kamimura M, Takeda Y, Kudo K, Kabe J, Hibino S, et al. Irinotecan (CPT-11) in combination with weekly administration of cisplatin (CDDP) for non-small-cell lung cancer. Cancer Chemother Pharmacol 1998;42:53–8.
11. Karato A, Sasaki Y, Shinkai T, et al. Phase I study of CPT-11 and etoposide in patients with refractory solid tumors. J Clin Oncol 1993; 11:2030–5.
12. Bleiberg H, Cvitkovic E. Characterisation and clinical management of CPT-11 (irinotecan)-induced adverse events: the European perspective. Eur J Cancer 1996;32A(supple3):S18–S23.
13. Merrouche Y, Extra JM, Abigerges D, Bugat R, Catimel G, Suc E, Marty M, et al. High dose-intensity of irinotecan administered every 3 weeks in advanced cancer patients: A feasibility study. J Clin Oncol 1997;15:1080–6.
14. Rivory LP, Bowles MR, Robert J, Pond SM. Conversion of irinotecan (CPT-11) to its active metabolite, 7-ethyl-10-hydroxycamptothecin (SN-38), by human liver carboxylesterase. Biochemical Pharmacol 1996;52:1103–1.
15. Atsumi R, Suzuki W, Hakusui H. Identification of the metabolites of irinotecan. a new derivative of camptothecin, in rat bile and its biliary excretion. Xenobiotica 1991;21:1159–69.
16. Haaz MC, Rivory LP, Rishe C, Robert J. Metabolism of irinotecan (CPT-11) by human hepatic microsomes: participation of cytochrome P-450 3A (CYP3A) and drug interactions. Proc Am Assoc Cancer Res 1997;38:17.
17. Fassberg J, Stella VJ. A kinetic and mechanistic study of the hydrolysis of camptothecin and some analogues. J Pharm Sci 1992;81: 676–84.
18. Akimoto K, Kawai A, Ohya K. Kinetic studies of the hydrolysis and lactonization of camptothecin and its derivatives, CPT-11 and SN-38, in aqueous solution. Chem Pharm Bull 1994;42:2135–8.
19. Chu XY, Kato Y, Sugiyama Y. Multiplicity of biliary excretion mechanisms for irinotecan, CPT-11, and its metabolites in rats. Cancer Res 1997;57:1934–8.
20. Lokiec F, Canal P, Gay C, Chatelut E, Armand JP, Roche H, Bugat R, Goncalves E, Mathieu-Boue A. Pharmacokinetics of irinotecan and its metabolites in human blood, bile, and urine. Cancer Chemother Pharmacol 1995;36:79–82.
21. Kobayashi K, Bouscarel B, Matuzaki Y, Ceryak S, Kudoh S, Fromm H. pH-dependent uptake of irinotecan and its active metabolite, SN-38, by intestinal cells. Int J Cancer 1999;83:491–6.
22. Charman WN, Porter CJ, Mithani S, Dressman JB. Physiochemical and physiological mechanisms for the effects of food on drug absorption: the role of lipids and pH. J Pharm Sci 1997;86:269–82.
23. Bugaut M. Occurrence, absorption and metabolism of short chain fatty acids in the digestive tract of mammals. Comp Biochem Physiol 1987;86B:439–2.
24. Atsumi R, Okazaki O, Hakusui H. Pharmacokinetics of SN-38 [(+)-(4S)-4,11-diethyl-4,9-dihydroxy-^{1}H-pyrano [3′,4′:6,7]-indolizino [1,2-b]quinoline-3,14(4H,12H)-dione], an metabolite of irinotecan, after a single intravenous dosing of ^{14}C-SN-38 to rats. Biol Pharm Bull 1995;18:1114–9.
25. Araki E, Ishikawa M, Iigo M, Koide T, Itabashi M, Hoshi A. Relationship between development of diarrhea and the concentration of SN-38, an active metabolite of CPT-11, in the intestine and the blood plasma of athymic mice following intraperitoneal administration of CPT-11. Jpn J Cancer Res 1993;84:697–02.
26. Takasuna K, Hagiwara T, Hirohashi M, Kato M, Noura M, Nagai E, Yokoi T, Kamataki T. Involvement of beta-glucuronidase in intestinal microflora in the intestinal toxicity of the antitumor camptothecin derivative irinotecan hydrochloride. Cancer Res 1996;56:3752–7.
27. Ikuno N, Soda H, Watanabe M, Oka M. Irinotecan (CPT-11) and characteristic mucosal change in the mouse ileum and cecum. J Natl Cancer Inst 1995;87:1876–83.
28. Gupta E, Mick R, Ramirez J, Wang X, Lestingi TM, Vokes EE, Ratain MJ. Pharmacokinetic and pharmacodynamic evaluation of the topoisomerase inhibitor irinotecan in cancer patients. J Clin Oncol 1997;15:1502–0
29. Gandia D, Abigerges D, Armand JP, Chabot G, Costa LD, Forni MD, Mathieu-Boue A, Herait P. CPT-11-induced cholinergic effects in cancer patients. J Clin Oncol 1993;11:196–7.
30. Strazzabosco M, Sakisaka S, Hayakawa T, Boyer JL. Effect of UDCA on intracellular and biliary pH in isolated rate hepatocyte couplets and perfused livers. Am J Physiol 1991;109:G58–G69.
31. Shimokura GH, McGill JM, Schlenker T, Fitz JG. Ursodeoxycholate increases cytosolic calcium concentration and activates Cl^- currents in a biliary cell line. Gastroenterology 1995;109:965–72.
32. Dumont M, Erlinger S, Uchman S. Hypercholeresis induced by ursodeoxycholic acid and 7-ketolithocholic acid in the rat: possible role of bicarbonate transport. Gastroenterology 1980;79:82–9.
33. Tsujii T, Kubo R, Takaya A. Treatment of intrahepatic cholestasis. Kan-Tan-Sui 1986;11:911–9 (in Japanese).