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ORIGINAL ARTICLE

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Preventive effect of Kampo medicine (Hangeshashin-to) against irinotecan-induced diarrhea in advanced non-small-cell lung cancer

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Abstract *Purpose*: Kampo medicine Hangeshashin-to (TJ-14) which contains baicalin, a β-glucuronidase inhibitor, alleviates diarrhea induced by irinotecan (CPT-11). We conducted a randomized comparative trial to investigate whether support with TJ-14 would prevent and control CPT-11-induced diarrhea. *Methods*: Of 44 previously untreated patients with advanced non-small-cell lung cancer randomized, 41 (18 TJ-14 group, 23 control group) were available for evaluation. The chemotherapy regimen consisted of a combination of cisplatin and CPT-11. TJ-14 (7.5 g/day) was administered orally. *Results*: Of the 41 patients, 39 experienced diarrhea. Compared with the control group, the TJ-14 group showed a significant improvement in diarrhea grades ($P = 0.044$) as well as a reduced frequency of diarrhea grades 3 and 4 (one patient versus ten patients; $P = 0.018$). However, the two groups showed no differences in the frequency of diarrhea or the number of days the symptoms continued. This study was stopped at an interim evaluation. *Conclusion*: TJ-14 was effective in preventing and controlling CPT-11-induced diarrhea.

Keywords Non-small-cell lung cancer · Irinotecan · Diarrhea · Kampo medicine · Hangeshashin-to

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Introduction

Irinotecan hydrochloride (CPT-11), a semisynthetic derivative of camptothecin, is an anticancer drug which inhibits nucleic acid synthesis by topoisomerase I inhibition [7, 9]. CPT-11 possesses a wide antitumor spectrum, and has been proven to have antitumor effects against lung cancer [4, 8, 13, 14], colon cancer [17, 19] and malignant lymphoma [15]. At present, it is used in a large number of institutions in combination with other drugs [11, 16]. The leading side effects of CPT-11 include leukopenia and diarrhea. These side effects are the main reason for discontinuing administration, and the drug thus has dose-limiting toxicity [4, 13]. The reduction in leukocytes is usually improved by the administration of recombinant human granulocyte colony-stimulating factor (rG-CSF) [11, 16].

Studies of CPT-11 in monotherapy and combination therapy regimens have shown that diarrhea occurs in 63–79% of the patients [1, 4, 15, 16, 19]. There are two types of CPT-11-induced diarrhea: acute diarrhea that occurs during the early stages of drug administration, and delayed diarrhea that occurs during later stages. The former is thought to be caused by the anticholinesterase actions of CPT-11 [5]. It is mostly transient in nature, and can be treated effectively with anticholine drugs [17]. The latter, in contrast, can sometimes develop into severe diarrhea. Symptoms in some patients can become difficult to control, while other patients become unable to continue taking CPT-11 [17]. The following drugs are used in several institutions to treat diarrhea clinically: anticholine drugs [17], loperamide hydrochloride [1, 17], and Kampo medicine Hangeshashin-to (TJ-14) [18]. Animal experiments have shown that TJ-14 effectively prevents CPT-11-induced delayed diarrhea [20].

We conducted a randomized comparative trial to investigate whether support with TJ-14 would prevent and control CPT-11-induced-diarrhea in combination therapy with cisplatin and CPT-11 in advanced non-small-cell lung cancer (NSCLC).

Subjects and methods

Patient eligibility

Subjects entered into the study were NSCLC patients attending our hospital who underwent combination therapy with cisplatin and CPT-11. None of the patients had received prior therapy. Other eligibility criteria included an expected survival of at least 12 weeks, age ≤ 75 years, Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0–2, and adequate hematological function (WBC ≥4000/mm^3, platelet count ≥100,000/mm^3, hemoglobin ≥10 g/dl), renal function (serum creatinine ≤ 1.5 mg/dl, creatinine clearance ≥60 ml/min) and hepatic function (total serum bilirubin ≤ 1.5 mg/dl, glutamic oxaloacetic transaminase and glutamic pyruvic transaminase less than twice the upper limit of the normal range). This protocol was approved by the ethical committee of the Tochigi Cancer Center. Written informed consent was obtained from every patient stating that the patient was aware of the investigational nature of this treatment regimen. Patients with severe complications, diarrhea, massive pleural and cardiac effusion, and symptomatic brain metastasis were excluded from the study. Pretreatment evaluation included medical history, physical examination, complete blood count, serum biochemical analysis, chest roentgenogram, electrocardiogram, and urinalysis. All patients underwent a radionuclide bone scan, computerized tomography of the brain and thorax, and computerized tomography of the abdomen. All patients were admitted to the Tochigi Cancer Center Hospital during this trial. Complete blood count, biochemical tests, serum electrolytes, urinalysis, and chest roentgenograms were obtained weekly. Tests of measurable disease parameters such as computerized tomography were repeated every 4 weeks. Staging was according to the 4th edition of the UICC TNM classification.

TJ-14 administration

After informed consent had been obtained, patients were randomized using random numbers to receive either TJ-14 or not. Patients in the TJ-14 group were given a total of 7.5 g TJ-14 (Tsumura Company, Tokyo) three times a day before each meal in equal doses, beginning more than 3 days before the start of chemotherapy. The patients received TJ-14 for a minimum of 21 consecutive days after the start of chemotherapy. When the chemotherapy was administered for two or more courses, TJ-14 was administered following a similar schedule. However, the administration of TJ-14 after the second course was optional. Proper treatment was provided to patients with severe diarrhea, comprising loperamide hydrochloride for diarrhea grade 2 or higher under the common toxicity criteria (CTC) (version 2.0), and codeine phosphate and electrolyte parenteral fluid for grade 3 or 4 diarrhea.

Evaluation

The antidiarrheic responses to and adverse effects of TJ-14 were evaluated based on records kept by the patients and medical staff. Items recorded daily included the features and frequency of stool, presence and degree of abdominal pain during bowel movement, presence of night-time bowel movement, and presence of hemorrhagic diarrhea. Diarrhea was judged in accordance with the CTC criteria. Evaluation of diarrhea for both the TJ-14 group and the control group was made during the first course.

Study design

With regard to sample size calculations, the frequency of grade 3 diarrhea in the control group was estimated as 30%, and the frequency of diarrhea in the TJ-14 group as 10%. The number of subjects needed per group was estimated to be 50 under the conditions $\alpha = 0.05$, $\beta = 0.20$, by approximation to normality of the estimated difference in the frequency of the subjects who develop diarrhea. Therefore, the target number of subjects for each group was set at 60 in consideration of the presence of ineligible and nonassessable cases.

Interim evaluation was performed twice, i.e. when 20 and 40 subjects of each group became assessable. The efficacy and safety evaluations were performed on the basis of the results of these interim evaluations. With regard to the evaluation of efficacy and safety in the interim analysis, the study was to be terminated if a statistically significant between-group difference in the incidence of diarrhea of grade 3 or greater was observed. If no statistically significant difference was present, the study was to continue. In the final analysis, TJ-14 was to be evaluated as effective if a significant decrease in the incidence of diarrhea of grade 3 or greater was observed in the TJ-14 group.

To determine the significance of differences, the Wilcoxon rank-sum test, Student's t-test, and Fisher's χ^2 test were used in accordance with the nature of the variables.

Chemotherapy

The anticancer drug regimen consisted of combined CPT-11 plus infusional cisplatin with rG-CSF support. A dose of 160 mg/m^2 of CPT-11 (Daiichi Pharmaceutical Company, Japan) in 500 ml normal saline or 5% glucose was infused intravenously (i.v.) over 90 min on day 1, and 20 mg/m^2 of cisplatin was given daily for 5 days by continuous i.v. infusion. One-third of the daily dose was administered every 8 h dissolved in 800 ml physiological saline [11]. rG-CSF (Chugai Pharmaceutical Company, Japan) was administered subcutaneously at a dose of 2 μg/kg for, in principle, 16 days (days 6 to 21), beginning on the day after of completion of cisplatin administration, once every day, at the same time whenever possible. However, if the granulocyte count increased to more than 5000/mm^3 or the white blood count increased to more than 10,000/mm^3 after reaching a nadir, administration was discontinued. The course was repeated every 4 weeks. The antiemetic drugs used were metoclopramide (3 mg/kg per day, continuous infusion for 5 days), methylprednisolone (125 mg bolus infusion every 8 h, days 1–5), diphenhydramine (30 mg orally, days 1–7) and alprazolam (1.2 mg orally, days 1–7). The dose of CPT-11 was reduced to 120 mg/m^2 for the subsequent course if grade 3 or 4 diarrhea occurred.

Results

We performed an interim analysis. Of 44 patients randomized, 3 requested cancellation of oral administration of TJ-14 prior to the start of chemotherapy. Therefore, 41 patients were evaluable, 18 in the TJ-14 group and 23 in the control group. Table 1 shows the patient characteristics. Compared with the TJ-14 group, the control group had a slightly higher percentage of female, PS 2, stage III, and squamous cell carcinoma patients, although differences between the two groups were not significant. The TJ-14 group received an average 2.4 courses (1–4) of chemotherapy, and the control group, an average 2.5 courses (1–5). All except two patients in the TJ-14 group (i.e. 39 patients, 95%) had diarrhea. Diarrhea occurred on average 6.3 days after the start of chemotherapy in the TJ-14 group (range 1–11 days) and 5.9 days in the control group (range 1–11 days). The day on which diarrhea occurred most frequently was on average 9.2 days after the start of chemotherapy in the TJ-14 group (range 1–14 days) and 9 days (range 1–16 days) in the control group.

Table 1 Patient characteristics (values are number of patients, except age in years)

	TJ-14 group	Control group	*P* value
Total no. of patients	18	23	
Age (years)			0.834
Mean	61.2	60.4	
Range	37–75	44–74	
Sex			0.308
Male	15	16	
Female	3	7	
Performance status			0.800
0	2	3	
1	14	16	
2	2	4	
Stage			0.194
III	3	8	
IV	15	15	
Histological type			0.595
Adenocarcinoma	14	14	
Squamous cell carcinoma	4	8	
Adenosquamous	0	1	

Table 2 Evaluation of diarrhea

	TJ-14 group	Control group	*P* value
CTC grade (no. of patients)			0.044
0	2	0	
1	5	7	
2	10	6	
3	1	6	
4	0	4	
3 + 4	1	10	0.018
Frequency			
Mean	2.39	3.52	0.17
Total	204	515	0.32
Duration (days)			0.58
Mean	4.4	4.7	
Total	80	109	

Table 2 shows the evaluations of diarrhea in the TJ-14 group and the control group during the first course of chemotherapy. Compared with the control group, the TJ-14 group showed significantly improved grades of diarrhea ($P = 0.044$) and had a significantly lower incidence of diarrhea grades 3 and 4 ($P = 0.018$). However, no differences were seen between the two groups in terms of frequency of diarrhea or the number of days the symptoms continued.

After the second course and beyond, 6 out of 15 patients in the TJ-14 group did not receive TJ-14, while 2 out of 20 patients in the control group received TJ-14. With regard to changes in the grade of diarrhea during the course before and after TJ-14 administration, there was a change in only one patient in the TJ-14 group (from grade 1 to grade 2), while in the control group, one patient improved from grade 3 to grade 1. No serious side effects of TJ-14 were seen except for two patients who had grade 1 constipation. Thus, TJ-14 significantly reduced the time to onset of CPT-11-induced diarrhea. The study was stopped at an interim evaluation.

Discussion

Diarrhea of grade 3 or greater associated with anticancer drugs has been observed in 2% of patients receiving chemotherapy comprising cisplatin (bolus) and vindesine [3], while the corresponding figure in patients receiving a combination of cisplatin (continuous infusion) and vindesine was 17% [10]. The patients in these two studies cannot be compared without qualification because of differences in the patient background factors and dosage of cisplatin; nevertheless, the incidence of diarrhea of grade 3 or greater is likely to be higher in patients receiving continuous infusion than in those receiving bolus cisplatin. Additionally, the incidence of diarrhea of grade 3 or greater has been reported to be 16% with combination chemotherapy comprising cisplatin (bolus, 60 mg/m^2; day 1) and CPT-11 (60 mg/m^2; days 1, 8 and 15) [14]. Hence, because the present regimen involved the administration of CPT-11 at a dose of 160 mg/m^2 on day 1 in addition to cisplatin (continuous infusion, 20 mg/m^2; days 1–5), the overall incidence of diarrhea of grade 3 or greater was high (27%; TJ-14 group 6%, control group 43%).

A combination of cisplatin and CPT-11 was administered to treat advanced NSCLC, and random comparative tests were carried out to determine the usefulness of TJ-14 for the prevention and control of diarrhea induced by CPT-11. We performed an interim analysis in 44 patients randomized. TJ-14 significantly reduced the onset of CPT-11-induced diarrhea. In the TJ-14 group, the drug improved the grade of diarrhea ($P = 0.044$) and reduced the incidence of diarrhea grade 3 or 4 ($P = 0.018$). Thus our study was stopped at an interim evaluation.

It has been reported that medicines such as anticholine agents [17] and loperamide hydrochloride [1, 17] are effective in preventing CPT-11-induced diarrhea. A high dose of loperamide hydrochloride (2 mg loperamide hydrochloride once every 2 h) has been shown to be particularly effective against delayed diarrhea (diarrhea occurring 8 h and more after CPT-11 administration) that accompanies high doses of CPT-11 (between 400 and 600 mg/m^2 of CPT-11 administered once every 3 weeks) [1].

The mechanism of CPT-11-induced delayed diarrhea is as follows. CPT-11 is changed to 7-ethyl-10-hydroxycamptothecin (SN-38) in the liver, and SN-38 undergoes glucuronate conjugation changing into inactive SN-38 glucuronide. Later, it is excreted into the bile, and is then deconjugated by β-glucuronidase contained in the intestinal bacteria to become SN-38 once again [6]. This SN-38 directly damages the intestinal mucous membrane and induces delayed diarrhea [2]. Therefore, it is considered possible to prevent CPT-11-induced delayed diarrhea by using a glucuronide inhibitor of β-glucuronidase [12]. Kampo medicine (TJ-14) contains components of baic-

alin which serve as this glucuronide. Experiments with rats have shown that it effectively prevents CPT-11-induced delayed diarrhea [20], Sakata et al. [18] have reported that TJ-14 can effectively prevent diarrhea caused by CPT-11. As a side effect of TJ-14, constipation occurred in 10% of patients in the study by Sakata et al. [18] and in 11% of patients in our study, although they were all mild grade 1.

Concerning comparative tests using Kampo medicine as the control drug, we were unable to make a placebo formulation because of the Kampo drug's distinct shape and smell, and therefore could not carry out double-blind comparative tests. As our study did not use a double-blind test method, the results may have been affected, to a certain extent, by bias on the part of the patients and physicians.

In conclusion, TJ-14 was able to alleviate CPT-11-induced diarrhea in advanced NSCLC. The clinical usefulness of TJ-14 must be studied further, based on our results, by administering the drug to prevent the onset of CPT-11-induced diarrhea and conducting a large-scale cooperative trial with other institutions.

References

1. Abigerges D, Armand J-P, Chabot GG, Costa LD, Fadel E, Cote C, Herait D, Gandia D (1994) Irinotecan (CPT-11) high-dose escalation using intensive high-dose loperamide to control diarrhea. J Natl Cancer Inst 86:446
2. Asumi R, Suzuki W, Hakusui H (1991) Identification of the metabolites of irinotecan, a new derivative of camptothecin, in rat bile and its biliary excretion. Xenobiotica 21:1159
3. Fukuoka M, Masuda N, Furuse K, Negoro S, Takada M, Matsui K, Takifuji N, Kudoh S, Kawahara M, Ogawara M, Kodama N, Kubota K, Yamamoto M, Kusunoki Y (1991) A randomized trial in inoperable non-small-cell lung cancer: vindesine and cisplatin versus mitomycin, vindesine and cisplatin versus etoposide and cisplatin alternating with vindesine and mitomycin. J Clin Oncol 9:606
4. Fukuoka M, Niitani H, Suzuki A, Motomiya M, Hasegawa K, Nishiwaki Y, Kuriyama T, Ariyoshi Y, Negoro S, Masuda N, Nakajima S, Taguchi T (1992) A phase II study of CPT-11, a new derivative of untreated non-small-cell lung cancer. J Clin Oncol 10:16
5. Gandia D, Abigerges D, Armand J-P, Chabot G, Costa LD, Forni MD (1993) CPT-11 induced cholinergic effects in cancer patients (letter). J Clin Oncol 11:196
6. Kaneda N, Nagata H, Furuta T, Yokokura T (1990) Metabolism and pharmacokinetics of the camptothecin analogue CPT-11 in mouse. Cancer Res 50:1715
7. Kunimoto T, Nitta K, Tanaka T, Uehara N, Baba H, Takeuchi M, Yokokura T, Sawada S, Miyasaka T, Mutai M (1987) Antitumor activity of 7-ethyl-10-[4-(1-piperidino)-1-piperidino] carbonyloxy-camptothecin, a novel water soluble derivative of camptothecin, against murine tumors. Cancer Res 47:5944
8. Masuda N, Fukuoka M, Kusunoki Y, Mastui K, Takifuji N, Kudoh S, Negoro S, Nishioka M, Nakagawa K, Takada M (1992) CPT-11: a new derivative of camptothecin, for the treatment of refractory or relapsed small-cell lung cancer. J Clin Oncol 10:1225
9. Matsuzaki T, Yokokura T, Mutai M, Tsuruo T (1988) Inhibition of spontaneous and experimental metastasis by a new derivative of camptothecin, CPT-11, in mice. Cancer Chemother Pharmacol 21:308
10. Mori K, Saito Y, Tominaga K (1992) Phase II study of cisplatin continuous infusion plus vindesine in the treatment of non-small-cell lung cancer. Am J Clin Oncol 15:344
11. Mori K, Hirose T, Machida S, Yokoyama K, Tominaga K (1997) A phase I study of irinotecan and infusional cisplatin with recombinant human granulocyte colony-stimulating factor support in the treatment of advanced non-small cell lung cancer. Eur J Cancer 33:503
12. Narita M, Nagai E, Hagiwara H, Aburada M, Yokoi T, Kamataki T (1993) Inhibition of β-glucuronidase by natural glucuronides of Kampo medicines using glucuronide of SN-38 (7-ethyl-10-hydroxycamptothecin) as a substrate. Xenobiotica 23:5
13. Negoro S, Fukuoka N, Masuda N, Takada M, Kusunoki Y, Matsui K, Takifuji N, Kudoh S, Niitani H, Taguchi T (1991) Phase I study of weekly administration of CPT-11. J Natl Cancer Inst 83:1164
14. Noda K, Nishiwaki Y, Kawahara M, Negoro S, Sugiura T, Yokoyama A, Fukuoka M, Mori K, Watanabe K, Tamura T, Yamamoto S, Saijo N (2002) Irinotecan plus cisplatin compared with etoposide plus cisplatin for extensive small-cell lung cancer. N Engl J Med 346:85
15. Ohno R, Okada K, Masaoka T, Kuramoto A, Arima T, Yoshida Y, Ariyoshi H, Ichimaru M, Sakai Y, Oguro M, Ito Y, Morishima Y, Yokomaku S, Ota K (1990) An early phase II study of CPT-11: a new derivative of camptothecin, for the treatment of leukemia and lymphoma. J Clin Oncol 8:1907
16. Oshita F, Noda K, Nishiwaki Y, Fujita A, Kurita Y, Nakabayashi T, Tobise K, Abe S, Suzuki S, Hayashi I, Kawakami Y, Matsuda T, Tsuchiya S, Takahashi S, Tamura T, Saijo N (1997) Phase II study of irinotecan and etoposide in patients with metastatic non-small-cell lung cancer. J Clin Oncol 15:304
17. Rothenberg ML, Kuhn JG, Burris HA III, Nelson J, Eckardt JR, Tristan-Morales M, Hilsenbeck SG, Weiss GR, Smith LS, Rodriguez Gl, Rock MK, Von Hoff DD (1993) Phase I and pharmacokinetic trial of weekly CPT-11. J Clin Oncol 11:2194
18. Sakata Y, Suzuki H, Kamataki T (1994) Preventive effect of TJ-14, a Kampo (Chinese herb) medicine, on diarrhea induced by irinotecan hydrochloride (CPT-11) (in Japanese with English abstract). Jpn J Cancer Chemother 21:1241
19. Shimada Y, Yoshino M, Wakui A, Nakao I, Futatsuki K, Sakata Y, Kambe M, Taguchi T, Ogawa N (1993) Phase II study of CPT-11, a new camptothecin derivative, in metastatic colorectal cancer. J Clin Oncol 11:909
20. Takasuna K, Kasai Y, Kitano Y, Mori K, Kobayashi R, Hagiwara T, Kakihata K, Hirohashi M, Nomura M, Nagai E, Kamataki T (1995) Protective effects of Kampo medicine and baicaline against intestinal toxicity of a new anticancer camptothecin derivative, irinotecan hydrochloride (CPT-11), in rats. Jpn J Cancer Res 86:978