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Phase I Study of Single-Dose Oxaliplatin in Japanese Patients with Malignant Tumors

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Background: Oxaliplatin, a platinum compound, has been commonly used around the world for treating advanced colorectal cancer. The generally recommended dose and schedule of oxaliplatin monotherapy is 130 mg/m^2 every 3 weeks. This trial was conducted to evaluate the safety and pharmacokinetics of oxaliplatin monotherapy in Japanese patients with solid tumors.
Methods: Oxaliplatin was administered as a 2-h intravenous infusion every 3 weeks at a dose of 90 and 130 mg/m^2. Blood was collected to determine the total platinum and the ultrafiltrate platinum concentrations in plasma in all cycles.
Results: Nine patients were enrolled; three were given oxaliplatin monotherapy at 90 mg/m^2 and six received 130 mg/m^2. All tumors were colorectal cancer. The major adverse reactions included myelosuppressive, neurological and gastrointestinal toxicities, although most were grades 1 and 2 at both dose levels. Peripheral sensory neuropathy of without movement disturbance (grade 1 or 2) was observed in all patients at both dose levels. The 130 mg/m^2 dose level was not found to be the maximum tolerated dose, but was judged to be the recommended dose. No objective responses were seen and five cases of no change were observed. A bi-exponential open model best described the disappearance of platinum in the plasma, and a tri-exponential open model best described the disappearance of ultrafilterable platinum in the plasma at both dose levels. No racial difference was suggested in the pharmacokinetics of oxaliplatin.
Conclusions: The oxaliplatin monotherapy dose schedule of 130 mg/m^2 every 3 weeks, recommended worldwide, is acceptable for Japanese patients.

Key words: oxaliplatin – phase I study – safety – pharmacokinetics

INTRODUCTION

Oxaliplatin (trans-*l*-diaminocyclohexane oxalatoplatinum) is a platinum coordination complex. In preclinical studies, oxaliplatin has shown significant activity against a broad spectrum of tumors: murine leukemia, lymphoma, melanoma, lung and colon carcinoma, and fibrosarcoma, and human ovarian cancer, non-small cell lung cancer, neuroblastoma, non-seminomatous germ cells, erythroleukemia, and breast and colon cancer (1–9).

The pharmacokinetic properties, tolerability and maximum tolerated dose of oxaliplatin have been studied primarily in Western countries (10–11). Additional phase II and phase III studies of oxaliplatin in Western countries demonstrated significant activity for metastatic colorectal cancer, both as a single agent (12) and in combination with 5-fluorouracil and leucovorin (13–18). The FOLFOX regimen of oxaliplatin and infused fluorouracil plus leucovorin should be considered as the standard therapy for patients with advanced colorectal cancer.

In early clinical trials, a phase I study of single-dose oxaliplatin was conducted in Japan (19). However, the criteria for the evaluation of clinical toxicity and the measurement techniques for the pharmacokinetic analysis of oxaliplatin in that study were different from those used in recent trials. Therefore, we conducted another phase I study of oxaliplatin in Japan using the more recent criteria for evaluation of toxicity and new measurement techniques for pharmacokinetic analysis (Inductively Coupled Plasma Mass Spectrometry; ICP-MS), thereby allowing valid comparisons with data from Western

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countries. This study was conducted to clarify the safety and pharmacokinetic profile of single-dose oxaliplatin for Japanese patients.

PATIENTS AND METHODS

Patient Selection

Patients were entered into the study only if they met the following eligibility criteria: histological or cytological confirmation of a malignant tumor, a malignant tumor that was refractory to standard therapy or for which there was no effective therapy, a solid tumor, age between 20 and 74 years, performance status ≤2 on the Eastern Cooperative Oncology Group scale, adequate bone marrow function (absolute white blood cell count 3000–12 000/μl, hemoglobin levels ≥9.0 g/dl and platelet count ≥100 000/μl), adequate liver function (serum total bilirubin level ≤1.5 mg/dl and serum transaminase and alkaline phosphatase levels less than 2.5 times the upper standard limits), adequate renal function (serum creatinine level less than the upper standard limit), normal electrocardiogram, life expectancy of at least 9 weeks and provision of written informed consent. Furthermore, at least 4 weeks must have elapsed since the completion of any previous therapy and patients must have recovered from the toxic effects of any previous therapy. Exclusion criteria include the following: pregnancy, lactation, hepatitis B or C virus infection, human immunodeficiency virus infection, a history of hypersensitivity reactions to any drugs, neurological symptoms, brain metastasis, severe pleural effusion and ascites and any serious medical condition.

Treatment Schedule, Starting Dose And Dose-Escalation Schedule

Oxaliplatin was provided by Yakult Honsha Company (Tokyo, Japan) in a 100-mg vial. Oxaliplatin was administered in 250 ml of 5% glucose solution as a 2-h intravenous infusion. Needles or infusion sets containing aluminum components were not used for the preparation or administration of oxaliplatin due to the risk of degradation of the agent. Granisetron was routinely administered by 30 min intravenous infusion as an antiemetic treatment before the administration of oxaliplatin. No other prophylactic premedication was administered. This treatment was repeated every 3 weeks until disease progression or severe toxicity was observed or until 6 cycles were completed.

The starting dose (level 1) of oxaliplatin was 90 mg/m^2, corresponding to 70% of the previously reported standard dose (130 mg/m^2) for oxaliplatin monotherapy. The dose of oxaliplatin at level 2 was 130 mg/m^2. No more dose escalation was planned, as the objective of this study was to estimate the safety of the standard dose of oxaliplatin. Initially, three patients were treated at each dose level. Three additional patients were entered at a given dose if dose-limiting toxicity (DLT) was observed in 0–2 of the initial three patients. The maximum tolerated dose (MTD) was defined as the dose level at which three of 3–6 patients experienced DLT during the first cycle. If the level 2 dose was not found to be the MTD, the dose at level 2 was defined as the recommended dose. The definition of DLT was as follows: (i) grade 4 hematological toxicities or (ii) grade 3 or 4 non-hematological toxicities except for nausea. No intrapatient dose-escalation was allowed.

In patients receiving the initial cycle of treatment, a subsequent cycle was started after recovery from the toxic effects of the previous cycle. Before the next cycle was started, the leukocyte count had to be 3000–12 000/μl, the platelet count ≥100 000/μl, and the liver and renal function had to satisfy the eligibility criteria. Patients requiring more than 6 weeks to recover from the toxicity of a cycle were withdrawn from the study.

Evaluation

Patients were evaluated by appropriate investigation, including physical examination, chest X-ray, and computed tomography of the abdomen and chest, before entry into the study to determine the extent of disease. A complete blood cell count, liver function tests, renal function tests and urinalysis were performed for all patients before the study entry, on days 8 and 15 of the initial treatment cycle and before each subsequent treatment cycle. Appropriate investigations were repeated as necessary to evaluate the sites of marker lesions before every other course.

The toxicities were evaluated using the National Cancer Institute common toxicity criteria (20) regarding toxicities other than peripheral sensory neuropathy and by following the Oxaliplatin-specific scale. The definition of the Oxaliplatin-specific scale, which developed as a specific scoring scale for oxaliplatin-inducing peripheral sensory neuropathy, was as follows: grade 1—transient dysesthesia and/or paresthesia lasting less than 7 days; grade 2—transient dysesthesia and/or paresthesia lasting more than 7 days or longer; and grade 3—proprioceptor impairment inducing functional discomfort in everyday life (difficulty fastening buttons, writing, etc). Antitumor activity was evaluated in accordance with the World Health Organization scale (21).

Pharmacokinetics

Blood was collected to determine the total platinum concentration in plasma, the ultrafiltrate platinum concentration in plasma and the platinum concentration in blood cells. Blood specimens were obtained immediately before infusion, just before the end of infusion and at 0.25, 0.5, 0.75, 1, 3, 6, 9, 24, 48, 168, 336 and 504 h after the infusion during the initial cycle of the treatment. Furthermore, blood samples were taken before infusion, just before the end of infusion and at 504 h after the infusion for the second and subsequent cycles. Blood samples were collected into polyester tubes (VP-H070; Terumo Co., Tokyo, Japan) containing sodium heparin and immediately centrifuged (1000 *g*, 10 min, 4°C). From the

upper layer, an aliquot of plasma was preserved for total platinum determination. The remainder of the supernatant was processed for ultrafiltrate platinum separation (1000 *g*, 60 min, 4°C using Amicon Centrifree™ ultrafiltration filters, cut-off: 30 kD; Millipore Co., Bedford, MA, USA). The red blood cells in the lower layer were washed twice with equal volumes of 4°C saline. All samples (each about 1 ml) were frozen until analysis. Fractionated urine was collected in glass containers before infusion and from the start of infusion to 24 h after administration of the drug. The total volume of each fraction was recorded and a 100-ml aliquot was obtained and frozen at −20°C until analysis.

All of the samples were analyzed by ICP-MS (Inductively Coupled Plasma Mass Spectrometry). Samples were diluted 1/20 (for plasma and red blood cells) and 1/10 (for free platinum) in an aqueous solution containing 1% nitric acid and 100 μg/l of europium used as an internal standard.

The plasma concentration–time data following administration was analyzed by a noncompartmental method using the computer program WinNonlin (Ver.3.1, Pharsight Co., Mountain View, CA, USA). The peak plasma concentration, C_{max}, and the time to reach the peak concentration, T_{max}, were recorded directly from the experimental observations. The area under the plasma concentration–time curve (AUC) from time 0 to T, $AUC_{(0\text{-}T)}$, where T is the time of the last measurable concentration, was calculated by the trapezoidal method.

Ethics

This trial was approved by the institutional review board of the clinical oncology program at all hospitals participating in this study and conducted in accordance with the Japanese Good Clinical Practice guidelines.

This study was supported by Yakult Honsha Co., Ltd.

RESULTS

Patient Characteristics

From June 1999 to January 2000, nine patients were enrolled in this study. Their characteristics are listed in Table 1. The four men and five women had a median age of 51 years (range, 31–61 years). Four patients had a performance status of 0, while the other five had a performance status of 1. All tumors were colorectal cancer; four were specifically colon cancer and the other five were specifically rectal cancer. All patients had previously undergone surgical resection for primary tumors, and three had also received radiation therapy and all had received prior chemotherapy. The mean number of previous chemotherapy regimens was 2.8 (range: 2–3).

Three patients were entered at dose level 1 and 6 patients at dose level 2. A total of nine cycles at dose level 1 was given (median cycles per patient: 3: range: 2–4) and a total of nine cycles at dose level 2 was given (median cycles per patient: 1.5; range: 1–2).

Table 1. Patient characteristics

		No. of patients
Total no. of patients		9
Sex	Male	4
	Female	5
Age	Median (range)	51 (31–61)
ECOG* performance status	0	4
	1	5
Primary cancer	Colon	4
	Rectum	5
Prior treatment	Surgery	9
	Radiation	3
	Chemotherapy	9

*Eastern Cooperative Oncology Group.

Toxicity

Toxicity was assessed in all nine patients. At dose level 1, none of the patients exhibited toxicities of grades 2, 3 or 4 during the first cycle. At dose level 2, none of the patients exhibited grade 4 toxicity, while grade 3 toxicity was seen as a decline in serum sodium and grade 2 toxicity was evident as anemia, neurotoxicity, anorexia, nausea, vomiting, fatigue and ALT elevation during the first cycle. The level 2 dose was not found to be the MTD, but dose level 2 (130 mg/m^2) was judged to be the recommended dose.

Table 2 shows the highest grade of toxicities during all treatment courses according to patients. At dose level 1, grade 4 neutropenia and grade 2 leukopenia were observed in one of three patients, and another patient developed grade 2 fatigue. At dose level 2, grade 2 anemia (2/6), neurotoxicity (1/6), anorexia (2/6), nausea (3/6), vomiting (3/6), diarrhea (1/6), fatigue (3/6) and ALT elevation (1/6) were observed, and grade 3 decreases in serum sodium (1/6) and potassium (1/6) were observed.

In all nine patients and all 18 cycles of treatment, neurotoxicity developed. Neurotoxicity in all patients receiving nine cycles of the level 1 dose (90 mg/m^2) was grade 1. Neurotoxicity in patients receiving the level 2 dose (130 mg/m^2) was seen as grade 1 in seven cycles and grade 2 in two cycles. This neurotoxicity was evident as a transient peripheral neuropathy manifesting as paresthesia and dysesthesia in the extremities and perioral area, triggered or enhanced by exposure to cold. There was no evidence of grade 3 neurotoxicity such as fine movement disturbance (difficulty fastening buttons, writing, etc) or moderately sensitive ataxia. These symptoms lasted between a few hours and a few days (grade 1: <7 days, grade 2: ≥7 days) and were reversible. Cumulative neurologic toxicity was not definitively observed in this study.

Major adverse reactions included neurotoxicity, myelosuppression and gastrointestinal toxicities; most cases were grades 1 or 2. No serious renal toxicity or hepatotoxicity,

Table 2. Toxicity

Toxicity	90 mg/m^2 (n = 3)				130 mg/m^2 (n = 6)			
	G 1	G 2	G 3	G 4	G 1	G 2	G 3	G 4
Leukopenia	1	1	0	0	2	0	0	0
Neutropenia	1	0	0	1	0	0	0	0
Anemia	0	0	0	0	0	2	0	0
Thrombocytopenia	0	0	0	0	2	0	0	0
Neurotoxicity	3	0	0	–	5	1	0	–
Anorexia	3	0	0	0	3	2	0	0
Nausea	2	0	0	0	2	3	0	0
Vomiting	1	0	0	0	0	3	0	0
Diarrhea	1	0	0	0	2	1	0	0
Fatigue	0	1	0	0	0	3	0	0
Alopecia	1	0	–	–	0	0	–	–
ALT	0	0	0	0	0	1	0	0
Creatinine	0	0	0	0	2	0	0	0
Decline of serum sodium	0	0	0	0	1	0	1	0
Decline of serum potassium	0	0	0	0	0	0	1	0

G, grade; ALT, alanine aminotransferase.

which usually occurs with other platinum agents, was observed. No patients discontinued the oxaliplatin regimen due to toxicity. No dose reduction was required in any patient in any administration. No treatment related-deaths occurred during the study.

RESPONSE

Response was assessed in all nine patients. No objective responses were seen. No change occurred in two of the three patients at dose level 1 and in three of the six patients at dose level 2, while the remaining four patients showed signs of progressive disease.

PHARMACOKINETICS

Pharmacokinetic analysis was performed on blood and urine specimens from all nine patients. The pharmacokinetic parameters are summarized in Table 3. Each parameter showed relatively small inter-individual variability.

The mean plasma concentration–time profiles are shown in Fig. 1. A bi-exponential open model best described the disappearance of platinum in the plasma at both dose levels, and a tri-exponential open model best described the disappearance of ultrafilterable platinum in the plasma at both dose levels.

The peak plasma concentration (C_{max}) and the AUC for platinum and ultrafilterable platinum in the level 2 patients (130 mg/m^2) were larger than those in the level 1 patients (90 mg/m^2) (Table 3). In the second cycle, the trough values of the platinum and ultrafilterable platinum in the plasma were higher, although by less than 2-fold, than in the first cycle ($P < 0.05$) (Table 4). Furthermore in the second cycle, the trough value of the platinum concentration in the red blood cells was higher, although by less than 2-fold, than that in the first cycle ($P < 0.001$) (Table 4). These findings on the platinum accumulation in the plasma and the red blood cells were observed at both dose levels.

The mean urinary excretion of oxaliplatin for 24 h was 28.4 ± 7.6% of the level 1 administered dose (90 mg/m^2) and 33.9 ± 8.8% of the level 2 administered dose (130 mg/m^2).

DISCUSSION

Oxaliplatin is recognized as one of the key drugs for the treatment of colorectal cancer, and in particular the FOLFOX regimen of oxaliplatin and infusional fluorouracil plus leucovorin is the standard therapy for patients with metastatic colorectal cancer in Western countries (17,18). We conducted this phase I study in Japanese patients to confirm the safety and pharmacokinetics profile of oxaliplatin monotherapy administered as 130 mg/m^2 in a 2-h infusion every 3 weeks as recommended worldwide.

In our trial, the major adverse reactions included myelosuppressive, neurological and gastrointestinal toxicities, although most were grades 1 and 2 at both dose levels of 90 and 130 mg/m^2. The incidence and degree of toxicity did not differ much from those of other phase I studies in Western countries (10,11). Earlier phase I (10,11) and phase II (13–16) studies in Western countries indicated that peripheral neuropathy, the most severe result of toxicity from oxaliplatin therapy, can be maintained at or below grade 2 at the recommended dose of 130 mg/m^2, and the toxicity profile is particular in its reversibility, as well as in its rapid onset, location and intensity of sensory disturbance with the absence of a motor component. Our results regarding neurotoxicity were almost the same as those of the Western phase I and II studies (10,11,13–16). However, the cumulative neurological toxicity reported in Western phase II studies (13–16) was not clearly observed in our study. Extra et al. (11) reported that grade 3 neurotoxicity has been observed at cumulative doses greater than 540 mg/m^2. Because the patients were given at most 360 mg/m^2 (median dose: 270 mg/m^2) in this study, we did not expect to observe this cumulative phenomenon.

A bi-exponential open model best described the disappearance of platinum in the plasma at both dose levels of 90 and 130 mg/m^2, and a tri-exponential open model best described the disappearance of ultrafilterable platinum in the plasma at both dose levels. The same findings were observed in other studies (10,19). In their assessment of dose proportionality for total plasma platinum, Taguchi et al. (19) reported that the mean C_{max} and AUC_{0-24} for single 1-h infusion increased in a dose-related manner over the dose range of 20–180 mg/m^2. Our result was not inconsistent with the manner of dose proportionality.

Pharmacokinetic parameters showed relatively small inter-individual variability in our data. These parameters of platinum

in plasma and plasma ultrafiltrate taken from Western patients administered 2-h oxaliplatin infusion of 130 mg/m^2 were previously reported, and the values were measured by ICP-MS (Inductively Coupled Plasma Mass Spectrometry), which we used in our study. These values of the C_{max}, AUC, terminal $t_{1/2}$ and CL were very similar to our data in the patients given the 130 mg/m^2 dose (10).

The elimination of platinum occurs mainly in urine rather than in feces (10). In this study, mean urinary excretion of oxaliplatin for 24 h was 33.9% of the level 2 administered dose (130 mg/m^2). This value was almost identical to the value of 35.9% in Western patients given a dose of 135–150 mg/m^2 (11).

Graham et al. (10) reported that limited platinum accumulation was observed in plasma and blood cells, but not in plasma ultrafiltrate. Our data on the platinum accumulation in Japanese patients was the same as that in Western patients, except for the data on the plasma ultrafiltrate. However, the degree of accumulation was less than 2-fold in both studies.

In conclusion, the worldwide standard dose of 130 mg/m^2/q3w for oxaliplatin monotherapy is also acceptable for treating

Table 3. Pharmacokinetic parameters of oxaliplatin

	90 mg/m^2 (n = 3)	130 mg/m^2 (n = 6)	Graham et al. (13)
Plasma platinum			
C_{max} (ng/ml)	2263.3 ± 145.7	3220.0 ± 177.9	3200 ± 340
PK model	2-CBM*	2-CBM*	–
$t_{1/2}\alpha$(h)**	7.6 ± 4.8	7.8 ± 3.3	–
$t_{1/2}\beta$(h)**	308.2 ± 29.6	259.8 ± 26.9	239 ± 54.4
CL (l/h/m^2)	0.37 ± 0.03	0.52 ± 0.13	–
V_{ss} (l/m^2)	110.3 ± 13.7	127.2 ± 19.4	–
AUC (μg.h/m/l)	244.3 ± 19.7	258.3 ± 58.3	207 ± 60.9
Plasma ultrafilterable platinum			
C_{max} (ng/ml)	963.3 ± 101.3	1450.0 ± 166.5	1210 ± 100
PK model	3-CBM***	3-CBM***	3-CBM***
$t_{1/2}\alpha$(h)**	0.18 ± 0.01	0.17 ± 0.02	0.28 ± 0.06
$t_{1/2}\beta$(h)**	14.0 ± 1.0	14.5 ± 1.0	16.3 ± 2.90
$t_{1/2}\gamma$(h)**	246.7 ± 32.2	258.9 ± 61.4	273 ± 19.0
CL (l/h/m^2)	11.6 ± 1.4	11.7 ± 1.4	10.1 ± 3.07
V_{ss} (l/m^2)	1433.4 ± 196.3	1612.7 ± 360.5	582 ± 261
AUC (μg.h/m/l)	7.9 ± 0.9	11.3 ± 1.5	11.9 ± 4.60

Mean ± SD.
*Two-compartment Baysian model.
**Half-life.
***Three-compartment Baysian model.
CL, clearance; V_{ss}, volume of distribution at steady state; AUC, area under the plasma concentration–time curve

Table 4. The trough values of oxaliplatin

	90 mg/m^2 (n = 3)	130 mg/m^2 (n = 3)
Plasma platinum (ng/ml)		
1st cycle	131.7 ± 21.5	158.0 ± 14.2
2nd cycle	184.7 ± 19.9	235.3 ± 47.6
Plasma ultrafilterable platinum (ng/ml)		
1st cycle	1.5 ± 0.2	2.3 ± 0.2
2nd cycle	2.1 ± 0.2	3.2 ± 0.3
Blood cell platinum (ng/ml)		
1st cycle	483.7 ± 94.2	606.3 ± 73.3
2nd cycle	742 ± 46.2	951.0 ± 83.6

Mean ± SD.

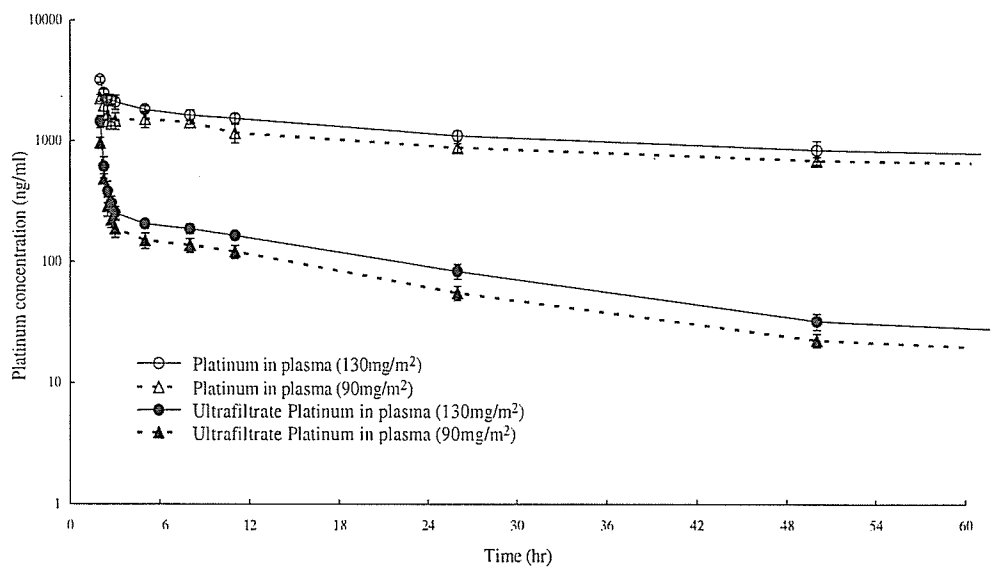

Figure 1. Mean plasma concentration–time curve for oxaliplatin.

Japanese patients, with only mild myelosuppression, neurotoxicity and gastrointestinal toxicities. No racial difference was suggested in the pharmacokinetics of oxaliplatin. A phase II study of oxaliplatin monotherapy and a phase I/II study of the combination of oxaliplatin with fluorouracil plus leucovorin have finished in Japanese patients with metastatic colorectal cancer. Further large clinical trials on oxaliplatin are warranted to evaluate the toxicity profiles and the clinical antitumor activity in Japanese patients.

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S-1の基礎と臨床
胃癌

胃癌に対するCPT-11+S-1併用（IRIS）療法
—S-1 2週投薬法—

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Irinotecan Plus Oral S-1 in Patients with Advanced Gastric Cancer—Biweekly IRIS Regimen: Yoshito Komatsu[*1,3], Satoshi Yuki[*1,3], Takuto Miyagishima[*2,3] and Masahiro Asaka[*1,3] ([*1]*Third Dept. of Internal Medicine, Hokkaido University School of Medicine*, [*2]*Dept. of Internal Medicine, Kushiro Rosai Hospital*, [*3]*Hokkaido Gastrointestinal Cancer Study Group (HGCSG)*)

Summary

We reported the results of phase I study with CPT-11 and S-1 (IRIS) in advanced gastric cancer (AGC) patients at ASCO 2002. Now I present an outline of this phase I/II trial. A combined treatment of IRIS (CPT-11+S-1) was given to the AGC patients who had not received prior chemotherapy. S-1 was orally administered twice a day for 14 days, and CPT-11 was administered as a 90-minute intravenous infusion on days 1 and 15. This schedule was repeated every 4 weeks. Fifteen patients were registered in this phase I study and 9 patients were added in this phase II study. Non-hematological toxicities were almost classified as grade 2 or lower, except for grade 3 nausea and grade 3 dermatitis of level 2.

These adverse events were manageable by administering anti-emetic drugs and a drug rest. As for hematological toxicities, grade 4 neutropenia occurred with one patient at level 1 and level 2 in phase I. And grade 4 neutropenia occurred with four patients at level 2 in phase II. However, they recovered after the drug rest, and we could continue the administration based on the standard dose modifications. These side effects were tolerable, and the overall response rate was 54.2%. MST of this regimen is 581 days. The IRIS treatment is effective and tolerable for outpatient treatments. Key words: Advanced gastric cancer, CPT-11, S-1, IRIS, HGCSG, Corresponding author: Yoshito Komatsu, Third Department of Internal Medicine, Hokkaido University School of Medicine, 7 West, 15 North, Kita-ku, Sapporo 060-8638, Japan

要旨 はじめに: われわれはHokkaido Gastrointestinal Cancer Study Group (HGCSG) において，手術不能または術後再発胃癌に対し，外来でも投与可能で有効な併用療法の開発のために2001年初めよりCPT-11+S-1併用(IRIS)療法(S-1 2週・CPT-11のbiweekly投与法)の臨床第I/II相試験を計画し実施した。対象・方法: この併用療法の適切な投与量を決定するための臨床第I相試験ではCPT-11は100 mg/m²から25 mg/m²ずつ150 mg/m²まで増量する3段階のレベルを設定し，day 1, 15に90分で点滴静注するものとした。S-1はカプセル剤であるため，体表面積ごとの通常投与法(80, 100, 120 mg/2×)で固定し，day 1, 14までの2週間の内服とした。結果: 臨床第I相試験の結果よりCPT-11の推奨投与量はレベル2の125 mg/m²に決定した。この推奨投与量にて早期臨床第II相試験へ移行し，さらに9例を追加して効果と安全性を確認した。臨床第I/II相試験としての奏効率は54.2%，全24例のMSTは581日と良好な結果であった。考察: IRIS療法(2週間法)は，進行胃癌に対する第一選択療法として外来でも安全に投与可能であり，将来の標準的化学療法の候補の一つとなり得るものと思われる。

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はじめに

手術不能または術後再発胃癌患者に対する化学療法は多岐を極め，様々な研究がなされてきたにもかかわらず，いまだ標準的治療といえる治療は報告されていない。胃癌患者に対する化学療法の有効性はいくつかの研究によってその生存期間の延長への寄与が証明されてはいるが十分なものではなく，必ずしも胃癌患者の quality of life (QOL) へ貢献できているとはいい難い。したがって胃癌に対する化学療法の進歩には有効な新薬の開発や併用療法の開発が必須であった。そんななかで，本邦では新しいフッ化ピリミジン系経口抗癌剤 S-1 が登場した。臨床成績も臨床第II相試験結果が報告[1]され奏効率は49%と単剤の抗癌剤としては驚くべき効果であった。また irinotecan (CPT-11) も日本で開発された薬剤であり大腸癌に有効な薬剤であることが報告されていた。また胃癌に対しても単剤で20%[2]，併用療法では CDDP との組み合わせで約50%の奏効率が報告[3]され，胃癌に対しても有用な薬剤として知られていた。当時，欧米を中心に大腸癌の初回治療例に対する CPT-11＋5-FU＋Leucovorin (IFL) の有用性が確認され[4]，本邦においても進行大腸癌に対して CPT-11＋5-FU 併用療法の臨床試験が終了しており[5]，CPT-11 と 5-FU 併用での有効性は確認されていた。したがって S-1 と CPT-11 の併用療法は消化器癌に対して非常に有効であることが予想された。また S-1 が経口剤であるという点からも，外来での効果的な化学療法が可能となることも予想された。そこでわれわれは手術不能または術後再発胃癌に対し，外来でも投与可能でかつ有効な併用療法の開発のために2001年初めより CPT-11＋S-1 (IRIS) 併用療法の臨床試験を計画し開始した。

I. 対象・方法

対象は組織学的に胃癌が証明された転移を伴う手術不能または術後再発胃癌患者で，年齢は20～75歳，PS が良好で，前治療歴のない書面による同意の得られた患者を対象とした。当時この併用療法の報告は皆無であり，われわれが最初の実施グループであったため，この併用療法の適切な投与量を決定するために臨床第 I/II相試験を計画した。本来新規薬剤である S-1 を増量するべきであったが，S-1 はカプセル剤であり体表面積から算出した量の投与は困難であるため，現在の投与法である体表面積ごとで固定した。また先発薬剤である CPT-11 は，単剤における 100 mg/m²の毎週投与，150 mg/m²の2週間ごとの安全性が証明されているため[6,7]，100 mg/m²から 25 mg/m²ずつ 150 mg/m²まで増量する3段階のレベルを設定し，2週間おきに90分で点滴静注するものとした。当初 S-1 の投与期間について熟考したが，副作用の強いとされる CPT-11 との併用療法であることや，外来化学療法であることを考慮し，単剤であれば強い副作用が生じない2週間の内服とした (Fig. 1)。

II. 結　果

2001年2月から2002年12月の間に，当科を中心に組織された Hokkaido Gastrointestinal Cancer Study Group (HGCSG) の参加施設において24例が登録された。全投与サイクル数は91サイクル，平均は5.9サイクルであった。また2コース以上の完遂率は92%であった。臨床第 I 相試験ではレベル1(6例)，レベル2(6例)，レベル3 (3例) がエントリーした。非血液毒性に関しては grade 2 の下痢がレベル2で1例発現した。血液毒性では grade 4 の好中球減少がレベル1で1例，レベル2で2例に出現した。レベル1で CR 1例を含む3例，レベル2で3例，レベル3で2例が PR となり全体では奏効率53% (8/15) であった[8]。結果としてレベル3でも DLT に到達しなかったが，効果安全委員会での相談によりそれ以上のレベルアップはしないこととなった。したがって本併用療法の推奨投与量は規定により CPT-11 が150

Body surface area (BSA: m²)	Initial dosage of S-1 (mg/day, as the tegafur dose)	Level	CPT-11 (mg/m²)
<1.25	40×2	1	100
1.25-<1.50	50×2	2	125
1.50≦	60×2	3	150

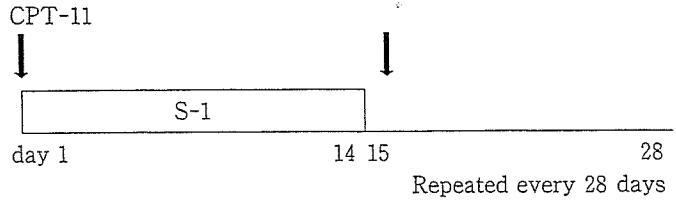

Fig. 1 Treatment schedule of S-1＋CPT-11

Table 1 Toxicities

Level	1				2				3			
CPT-11	100 mg/m²				125 mg/m²				150 mg/m²			
No	6				15				3			
grade	1	2	3	4	1	2	3	4	1	2	3	4
Neutrocyte	1	2	2	1	3	1	3	6	1	1	1	0
Platelets	0	0	0	0	3	1	0	0	1	0	0	0
Hemoglobin	1	2	1	0	5	4	1	0	1	0	0	0
Diarrhea	1	0	0	0	5	2	1	0	2	0	0	0
Nausea/vomiting	1	1	1	0	4	1	4	0	1	0	0	0
Dermatitis	0	0	0	0	1	0	1	0	1	0	0	0
Alopecia	0	0	0	0	0	1	0	0	0	0	0	0

Table 2 Response

	No	CR	PR	NC	PD	RR (%)
Overall	24	1	12	10	1	54.2

mg/m²となるところであったが，日本におけるCPT-11単剤での隔週投与の推奨投与量が150 mg/m²であり，レベル1でも非常に重篤な骨髄抑制が1例出現したことを十分に考慮し，その後の臨床第II相試験に参加する施設の医師の意見を取り入れ，効果安全委員会との相談の上，レベル2の125 mg/m²に決定した。この推奨投与量にて早期臨床第II相試験へ移行し，さらに9例を追加して効果と安全性を確認した。全部でgrade 4の好中球減少患者が4例となったが，いずれも減量休薬基準に従って治療を継続することができた(Table 1)。臨床第I/II相試験としての奏効率は54.2% (13/24) と良好な結果であった(Table 2)。本治療で注目すべきは臨床第I/II相試験とはいえ，全24例のMSTは581日 (Fig. 2) と非常に素晴らしい結果であった[9]。

III. 考 察

このIRIS療法の組み合わせが優れていることの理論的背景としては以下の報告がある。S-1はDPD阻害剤CDHPを含有しており，DPD高発現症例に有効であることが報告されている[10]。しかし高TS発現症例には，5-FU系製剤は効果が低いことも以前から報告されており，S-1単剤ではあまり効果が期待できない可能性がある。しかし，高TS発現症例はI型DNA topoisomerase (topo-I) の発現量も高く相関性があることが報告されているため[11]，TS高発現症例に対してtopo-I阻害剤であるCPT-11を使用するとTSが下がることも報告されており，その有効性が期待されている。したがってCPT-11とS-1は，両薬剤の弱点を補い合うことが期待されるため，併用療法として最適な組み合わせであると

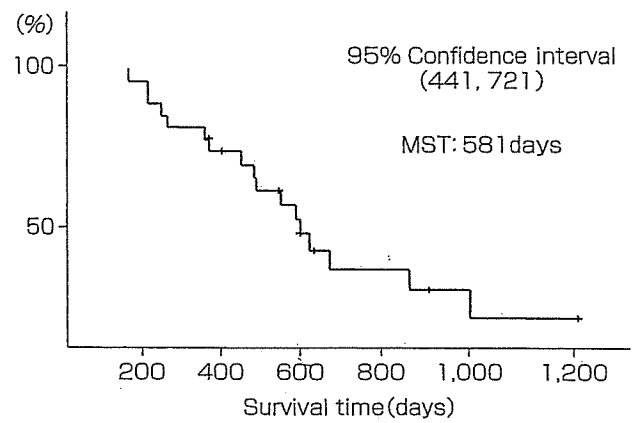

Fig. 2 Overall survival

考えている。S-1の投与日数が違うレジメンも報告されているが，単剤のdose intensityを越えてしまうようなものは，CPT-11との併用でさらに毒性が増強する可能性があり，一般に広く普及するには危険であると思われる。また投与間隔もわれわれのものはbiweeklyであり2週ごとの来院で治療が可能であるが，この間隔は日本の保険制度や日常の通院回数からいっても，1週ごとあるいは3週ごとといったものよりも受け入れやすい間隔であるものと考えられる。また他の併用療法も多数報告されているが，S-1+CDDPそしてCPT-11+CDDPの併用療法などは高い奏効率が報告されてはいるが，CDDPの投与に伴いハイドレーションが必要であり毎コースごとに入院を必要とする。しかし，われわれの併用療法は入院を必要としないため，すべて通院で治療を継続できるという意味でQOLの改善にも寄与できると考えられる。また奏効率自体は54%であるが，本療法のもう一つの注目点としては腫瘍制御率 (CR+PR+SD) が95.8%と非常に有効であることが予想される。以上より，副作用が耐用可能であり外来治療が可能でQOLの改善に寄与し高い奏効率を示し，そして臨床第I/II相試験ではあるがMST 581日という素晴らしい生存（サバイバルベネフィット）を得たことから，このわれわれの

CPT-11＋S-1併用療法（2週間法）は，進行胃癌に対する第一選択療法として，将来の標準的化学療法の候補の一つとなり得るものと思われる。2005年JCOG消化器内科グループにて実施されていた5-FU単独療法とS-1単独療法，CPT-11＋CDDP併用療法の臨床第III相比較試験（JCOG 9912）への最終登録も終了し現在フォローアップ期間となっているが，2006年末あるいは2007年早々にはその結果が報告され，本邦における進行胃癌治療に対する新標準的治療が決定する。それ以外にもS-1を標準的治療と想定した企業主導の大きな臨床第III相試験（S-1＋CPT-11，S-1＋CDDPなど）もすでに登録が終了していることから，2007年には本邦の胃癌の新標準的治療法が決定しそうであり，その報告が待たれる。

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Original article

Phase I-II study of biweekly paclitaxel administration with fixed-dose-rate cisplatin in advanced gastric cancer

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Abstract

Background. **Both paclitaxel (TXL) and cisplatin (CDDP) show efficacy against gastric cancer. The aim of this phase I-II study was to determine the maximum tolerated dose (MTD) and to evaluate the toxicity and efficacy of combination chemotherapy with these two agents.**

Methods. **Nineteen patients entered the phase I part of the study, and 21 patients entered the phase II part. TXL infusions were administered on days 1 and 15, with a fixed 30 mg/m² dose of CDDP.**

Results. **In the phase I part of the study, we determined dose level 5, which represented a TXL dose of 180 mg/m², with CDDP 30 mg/m², to be the MTD. The recommended dose (RD) was level 4, with a TXL dose of 160 mg/m² with CDDP, 30 mg/m². In the phase II part of the study, the response rate was 25.0%; five patients had a partial response, seven had stable disease, 6 had progressive disease, and 2 were not evaluable. Grade 3 or 4 neutropenia was the most common adverse event and occurred in 65% of the patients. During treatment, 25% of the patients received granulocyte colony-stimulating factor, but febrile neutropenia was not shown in any of the patients. Major nonhematological toxicities were nausea/vomiting, anorexia, fatigue, alopecia, and sensory neuropathy. Adverse reactions of grade 3 or 4 were shown by two patients, one with anorexia (5%) and the other with sensory neuropathy (5%).**

Conclusion. **The RD was determined to be TXL 140 mg/m², with CDDP 30 mg/m².**

Key words Paclitaxel · Cisplatin · Gastric cancer

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Introduction

Although various chemotherapy regimens have been reported for use in patients with gastric cancer, the median prognosis for survival in patients with chemotherapy for advanced gastric cancer remains less than 9–12 months [1]. Given these conditions, we sought to develop a new active combination therapy regimen to prolong median survival, while also seeking a regimen that would be suitable for outpatient clinical use, in order to decrease time of hospitalization.

Paclitaxel (TXL) is thought to be an effective drug for gastric cancer, with reported response rates ranging from 20% to 28% in single-agent phase II studies [2–4]. In two of these studies, median survival times were 234 and 340 days, respectively, although more than 50% of the patients had previously received chemotherapy [3,4]. Thus, it appears that TXL may prolong survival in gastric cancer patients.

Cisplatin (CDDP) is an active chemotherapeutic agent against gastric cancer. Treatment regimens including CDDP have shown high response rates [5–7]. CDDP has demonstrated synergism with variety of cytotoxic drugs, and synergism between TXL and CDDP has been established and reported [8,9].

Therapy combining CDDP and TXL has been reported in various regimens [10–14]. Most of these regimens consisted of administering 60 to 80 mg/m² of CDDP. However, patients receiving more than 50 mg/m² of CDDP may suffer nausea and vomiting [15], and they would then need hydration to prevent CDDP renal toxicity. Thus, more than 50 mg/m² of CDDP is not suitable for outpatient clinical use.

We sought to confirm the efficacy and toxicity of combination therapy with TXL and a fixed-dose administration of 30 mg/m² CDDP.

A biweekly regimen has been proposed to increase the dose intensity of TXL and to improve the ease of adoption for outpatient use. For this reason, we planned to evaluate biweekly TXL with a 30 mg/m² fixed-dose CDDP regimen.

Table 1. Dose levels (phase I)

Level	Paclitaxel (mg/m²)	Cisplatin (mg/m²)	No. of patients
1	100	30	3
2	120	30	4
3	140	30	3
4	160	30	6
5	180	30	3

Patients and methods

Patients

The objectives of this study were to determine the maximum tolerated dose (MTD) and to evaluate the toxicity and the preliminary activity of the above combination.

The criteria for eligibility included the following: (1) prior chemotherapy regimen completed 4 weeks before entry; (2) adequate bone marrow function (white blood cell [WBC] count ≥ 4000/mm³, platelet count ≥ 100 000/mm³, hemoglobin ≥ 9.0 g/dl), adequate liver function (serum bilirubin level ≤ 1.5 mg/dl and serum transaminase level ≤ twice the upper limit of the normal range; if hepatic metastasis had been documented, then serum transaminase level ≤ three times normal range) and adequate renal function (serum creatinine level ≤ 1.5 mg/dl, 24-h creatinine clearance ≥ 60 ml/min), normal electrocardiogram (ECG); (3) Eastern Clinical Oncology Group (ECOG) performance status (PS) of 2 or less; (4) age between 20 and 79 years; (5) absence of any other serious medical conditions; (6) absence of any other active malignancy; (7) life expectancy greater than 2 months.

Written informed consent was obtained from all patients prior to study entry. This study was approved by the Ethics Committees at the participating sites.

Treatment regimens

TXL infusions were administered on days 1 and 15, with a fixed 30 mg/m² dose of CDDP. To prevent hypersensitivity reactions, all patients were premedicated with 20 mg of dexamethasone intravenously, 50 mg of diphenhydramine orally, and 50 mg of ranitidine intravenously 1 h before TXL infusion. The starting dose of TXL was 100 mg/m², and it was intravenously infused within 1 to 3 h before 1- to 3-h infusion of CDDP. The TXL dose then consisted of increments of 20 mg/m² until severe or life-threatening toxicities were observed. Patients were administered this regimen once every 2 weeks unless disease progress or intolerable toxicity was observed. If WBC counts fell below 3000/mm³ or platelet counts fell below 75 000/mm³; or if grade 3 or 4 nonhematological toxicity occurred; or if body temperature rose over 38 °C or PS was over 3 immediately before administration, treatment was postponed.

For the first cycle of this therapy, the dose-limiting toxicity (DLT) was defined as National Cancer Institute Common Toxicity Criteria (NCI-CTC) grade 3 or 4 neutropenia with infection or fever; or thrombocytopenia of 25 000/mm³ or less; or NCI-CTC grade 3 or 4 nonhematological toxicity, except for anorexia, nausea/vomiting, and alopecia. Treatment delay DLT was defined as treatment delay of 1 to 2 weeks for reasons of toxicity. The treatment dose at each level is summarized in Table 1.

At least three patients were treated at each dose level. If none of the first three patients experienced DLT, escalation to the next TXL level was permitted. If one of three patients experienced a DLT, three other patients were enrolled at this level. Among the resulting six patients, if one or two experienced DLT, escalation was permitted; if more than two patients experienced DLT, that level was deemed the MTD. If two or three of three patients experienced DLT, that level was also considered the MTD. After confirmation of the MTD, the recommended dose (RD) for a phase II study was defined as one level below the MTD.

In the phase II part of the study, patients were not eligible if they had received chemotherapy that involved more than one regimen or contained platinum derivatives and/or taxane derivatives, or if they had suffered more than grade 2 peripheral neuropathy in prior chemotherapy. If the following adverse events had been observed during the previous treatment, the dose for the following treatment would be reduced by one level: hematological toxicity of at least grade 4; nonhematological toxicity of at least grade 3; peripheral neuropathy of at least grade 2. For other inclusion and exclusion criteria, treatment schedules were the same as for the phase I part of the study.

Response evaluation and toxicity

Patients were evaluated before entry into this study, to determine the extent of disease, by physical examination, chest X-ray, computed tomographic (CT) scan of

Table 2. Patient characteristics

	Phase I ($n = 19$)	Phase II ($n = 20$)
Median age, years (range)	62 (50–78)	60 (45–76)
Male/Female	17/2	16/4
EOCG PS		
0	6	11
1	13	8
2	0	1
Histological type		
Intestinal type	11	7
Diffuse type	8	13
Primary surgical resection	8	12
Prior chemotherapy (including adjuvant)		
Yes	14	16
No	5	4
Prior chemotherapy regimen		
S-1	13	11
S-1 + CDDP	1	1
S1 + CPT-11	0	1
MTX + 5FU	0	1
MMC (i.a.)	0	1
UFT	0	1

chest and abdomen, and endoscopic examination of the upper gastrointestinal tract. Complete blood cell counts, liver function test, renal function test, and urinalysis were assessed at least once every 2 weeks during treatment. CT scans were repeated as necessary to evaluate measurable lesions.

NCI-CTC version 2 was applied to evaluate adverse drug reactions during the first and second cycles of treatment. The response criteria of the Japanese Research Society for Gastric Cancer [16] and the Response Evaluation Criteria in Solid Tumors Group criteria [17] were used to evaluate objective tumor response. In brief, the response criteria of the Japanese Research Society for Gastric Cancer define complete response (CR) as the complete disappearance of all measurable and evaluable lesions for a minimum of 4 weeks. A partial response (PR) is defined as a 50% or greater reduction in the sum of the products of the longest diameters of measurable lesions for a minimum of 4 weeks. Stable disease (SD) is defined as failure to observe a PR or CR and progressive disease for at least 4 weeks. Progressive disease (PD) is defined as a 25% or greater increase in the sum of the products of the longest perpendicular diameters of measurable lesions, or the appearance of new lesions. The response to primary tumors was assessed by the same Japanese criteria, based on roentgenographic and endoscopic findings.

Statistical considerations

The phase II part of this study was designed to test the null hypothesis that the true response probability is less than the not clinically significant level of 20%. The response rate was expected to be 40%. The probability of accepting the treatment with response probability (20%) is $P = 0.05$. The probability of rejecting the treatment with response probability (40%) is $P = 0.10$. Therefore, the sample size was 50 patients with $P = 0.05$; $P = 0.1$. After the enrollment of 20 patients, we planned to evaluate the toxicity, with the main point of the evaluation being suitability for an outpatient setting.

In the phase II part of the study, survival was calculated, from the date of treatment initiation, by the Kaplan-Meier method.

Results

Patient characteristics

In the phase I part of the study, 19 patients entered this trial between September 2001 and May 2003. Patient characteristics are summarized in Table 2. All 19 patients were evaluated for toxicity, and 13 patients exhibited measurable lesions evaluable for response. The median age of the patients was 62 years (range, 50 to 78 years). Ten patients had gastric cancer as a primary lesion, while 8 patients had undergone surgical resection for primary gastric cancer. Six patients had an

ECOG PS of 0, and 13 patients had an ECOG PS of 1. Histologically, 11 patients had intestinal-type adenocarcinoma, and 8 patients had the diffuse type. All patients had metastatic lesions. The metastatic sites were the lung in 1 patient, the liver in 6, the lymph nodes in 7, and the peritoneum in 8. Fourteen patients had received prior chemotherapy; 13 patients had received S-1 alone, and 1 had received S-1 plus CDDP. All prior chemotherapy was completed 4 or more weeks before entry: 5 patients were prior chemotherapy-naïve.

In the phase II part of the study, 21 patients entered between July 2003 and May 2004. One patient refused to receive the treatment regimen after the first administration, and this patient was excluded from analysis. Characteristics of the phase II patients are summarized in Table 2. In an interim analysis of safety, our group decided to cease continuing this part of the study because of the high proportion of dose reductions and treatments delays within the first cycle.

The median age of the patients was 60 years (range, 45 to 76 years). Eight patients had gastric cancer as a primary lesion, and 12 patients had undergone surgical resection for primary gastric cancer. Eleven patients had an ECOG PS of 0, 8 had an ECOG PS of 1, and 1 had an ECOG PS of 2. Histologically, 7 patients had intestinal-type adenocarcinoma, and 13 had the diffuse type. All patients had metastatic lesions. The metastatic sites were the lymph node in 15 patients; liver in 15; peritoneum in 4; and bone, ovary, and esophagus in 1 patient each. Sixteen patients had received chemotherapy; 11 had received T-S1 alone, 1 had received S-1 plus irinotecan (CPT-11), 1 had received T-S1 plus CDDP, 1 had received methotrexate plus 5-fluorouracil (5FU), 1 had received uracil/tegafur (UFT), and 1 had received mitomycin C as intraarterial chemotherapy for liver metastasis. All prior chemotherapy was completed 4 or more weeks before entry: 4 patients were chemotherapy-naive (3 had had adjuvant chemotherapy only).

Determination of MTD in the phase I part of the study

In the phase I part of the study, all patients were evaluable for adverse reactions, and 18 patients completed one or more cycles of treatment. At levels 1 and 2, one patient exhibited grade 4 neutropenia during the first cycle. At level 4, one of the first three patients exhibited grade 4 febrile neutropenia, while three other patients were enrolled to this level. At level 5, one patient exhibited grade 3 motor neuropathy, while one exhibited grade 3 myalgia with grade 3 dyspnea. We therefore determined dose level 5, which represented a TXL dose of 180 mg/m^2, with CDDP 30 mg/m^2, to be the MTD, and the RD to be level 4, with a TXL dose of 160 mg/m^2 plus CDDP 30 mg/m^2. The most common adverse reactions in the phase I part of the study are summarized in Table 3.

Safety

All 20 patients enrolled in the phase II part of the study were assessable for safety, and received a total of 48.5 cycles. The median number of cycles was 2. In these 20 patients, treatment delay, dose reduction, or both, occurred in 6, 2, and 3 patients, respectively, within 1 cycle (a total of 11 patients could not be administered the RD) and all of the dose reductions and treatment delays were due to a decrease in the WBC count or delay in recovery of neutropenia.

For the phase II part of the study, the overall numbers of hematological and nonhematological toxicities are listed in Table 3. Grade 3 or 4 neutropenia was the most common adverse event and occurred in 65% of the patients. During treatment, 25% of the patients received granulocyte colony-stimulating factor (G-CSF), but no patients had febrile neutropenia. Major nonhematological toxicities were nausea/vomiting, anorexia, fatigue, alopecia, and sensory neuropathy. Two patients showed adverse reactions of grade 3 or 4. One patient had anorexia (5%) and other had sensory neuropathy (5%). None of the patients had an increase of serum creatinine of more than grade 3 within two cycles.

Efficacy

In the phase I part of the study, 4 of the 19 patients showed no measurable lesions, while 2 patients discontinued the protocol due to DLT, all 6 being determined as not evaluable (NE). The remaining 13 patients were evaluable for efficacy. This group included 6 patients with a PR, 4 with SD, and 3 with PD, yielding a response rate of 46.1% in the evaluable patients (6 of 13 patients). The response rates in the evaluable patients with intestinal-type adenocarcinoma and diffuse-type adenocarcinoma were 50% (4/8) and 40% (2/5), respectively. The response rate of the evaluable patients with prior chemotherapy was 55.5% (5/9). The response rate of the evaluable patients without prior chemotherapy was 25% (1/4). (Table 4).

In the phase II part of the study, a total of 20 patients were evaluated to determine the response rate at the RD. The overall response rate was 25.0%; 5 patients had PR as the best response, 7 had SD, 6 had PD, and 2 were defined as not evaluable (NE). Subgroup analysis by pathological type for the 20 patients showed that the response rates were 28.6% (2/7) for those with intestinal-type adenocarcinoma who were evaluable and 23.1% (3/13) for evaluable patients with the diffuse type. Subgroup analysis by prior chemotherapy for the 20 patients showed that the response rate was 25.0%

Table 3. Adverse reactions

Toxic effects	Grade (no. of patients)				Grades 3 and 4 (%)
	1	2	3	4	
Phase I					
Hematological					
Leucopenia	3	6	4	0	21.1
Neutropenia	4	1	4	5	47.4
Anemia	6	8	0	0	0
Thrombocytopenia	1	0	0	0	0
Nonhematological					
Fever (noninfection)	2	1	0	0	0
Nausea/Vomiting	4	1	0	0	0
Constipation	0	2	0	0	0
Anorexia	4	2	0	0	0
Fatigue	1	2	0	0	0
Rash	1	0	0	0	0
Alopecia	2	1	—	—	0
Dyspnea	0	0	1	0	5.3
Neuropathy — motor	1	0	1	0	5.3
Neuropathy — sensory	2	0	0	0	0
Myalgia	2	0	1	0	5.3
Arthralgia	2	0	0	0	0
Earache	1	0	0	0	0
Heartburn	1	0	0	0	0
Phase II					
Hematological					
Leucopenia	4	5	5	1	30.0
Neutropenia	1	1	6	7	65.0
Anemia	3	7	3	0	15.0
Thrombocytopenia	0	0	1	0	5.0
Nonhematological					
Fever (noninfection)	2	0	0	0	0
Nausea/Vomiting	4	4	0	0	0
Diarrhea	3	0	0	0	0
Constipation	0	1	0	0	0
Stomatitis	2	0	0	0	0
Anorexia	3	2	1	0	5.0
Fatigue	4	3	0	0	0
Rash	1	1	0	0	0
Alopecia	8	3	—	—	0
Neuropathy — motor	3	0	0	0	0
Neuropathy — sensory	5	1	1	0	5.0
Myalgia	4	0	0	0	0
Arthralgia	4	0	0	0	0
Hypotension	1	0	0	0	0
Creatinine	1	1	0	0	0

(4/16) for the evaluable patients with prior chemotherapy and 25.0% (1/4) for those without prior chemotherapy (Table 4).

The median survival time was 272 days and the 1-year survival rate was 30% (Fig. 1).

Determination of MTD in the phase II part of the study

As mentioned above, 11 of the 20 patients (55% of the study subjects) could not be administered the RD on a biweekly schedule, so we decided on a new RD, as one level under the previous RD, which represented a TXL dose of 140 mg/m^2 with CDDP 30 mg/m^2. At this new RD, we are now performing a new phase II study to check the efficacy and feasibility of the regimen.

Discussion

This study determined the MTD and RD, and also evaluated the preliminary toxicity and activity of TXL with fixed doses of CDDP for advanced gastric cancer. TXL is a promising drug for use in combination with

Table 4. Overall response to treatment

Patients	*n*	CR	PR	SD	PD	NE	RR (%)[a]
Phase I							
Overall	19	0	6	4	3	6	46.1
Level							
1	3	0	2	1	0	0	66.6
2	4	0	2	2	0	0	50.0
3	3	0	1	0	1	1	50.0
4	6	0	1	1	2	2	25.0
5	3	0	0	0	0	3	0.0
Histological type							
Intestinal	11	0	4	2	2	3	50.0
Diffuse	7	0	2	2	1	2	40.0
Prior chemotherapy							
No	4	0	1	2	1	0	25.0
Yes	15	0	5	2	2	6	55.5
Phase II							
Overall	20	0	5	7	6	2	25.0
Histological type							
Intestinal	7	0	2	2	3	0	28.6
Diffuse	13	0	3	5	3	2	23.1
Prior chemotherapy							
No	4	0	1	1	2	0	25.0
Yes	16	0	4	7	4	2	25.0

[a] Response rate (RR) was estimated in evaluable patients only

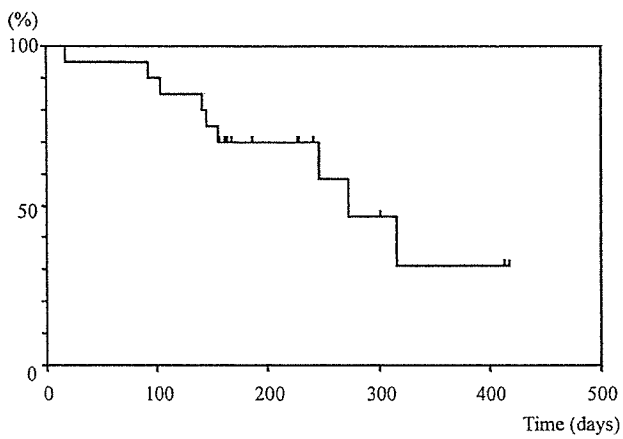

Fig. 1. Overall survival in the phase II part of the study

CDDP, and there are several phase I reports of combination chemotherapy involving TXL and CDDP. These two drugs have different mechanisms of action and fewer overlapping toxicities than other combinations, without neurotoxicity. When TXL was administered in combination with CDDP, treatment was sometimes delayed by the resulting neurotoxicity. When TXL administered every 3 weeks was compared to weekly TXL, the toxicity profile was better tolerated (particularly with respect to myelosuppression and peripheral neuropathy) at the weekly schedule, while efficacy remained almost unchanged [18]. This result shows that divided administrations of TXL may reduce myelosuppression and neuropathy. Before increasing dose-intensity, we conducted a phase I-II study of a biweekly regimen, because a biweekly schedule is suitable for outpatient clinical use.

Although high doses of CDDP are often used in combination regimens for gastric cancer, the efficacy of high doses is still open for debate. We set the CDDP dose at 30 mg/m^2 (because high doses of CDDP add to toxicity and require intense intravenous hydration to protect against renal toxicity) to develop a well-tolerated regimen ideal for the outpatient setting.

Compared with the results of a phase II study of a TXL-containing regimen for gastric cancer, our regimen was less toxic than the triweekly administration of TXL in that study [2–4], with especially notable reduced risks of grade 3 or 4 neutropenia and neuropathy. Kornek et al. [19] reported a phase II study of a biweekly schedule of combination therapy with 160 mg/m^2 TXL and 60 mg/m^2 CDDP in gastric cancer patients, with the regimen being based on a phase I study reported by van der Gaast et al. [14]. In the report of Kornek et al. [19], the regimen offered promising therapeutic activity, with a response rate of 44% among patients who had not undergone previous chemotherapy. However, 73% of their patients received G-CSF, 49% suffered peripheral neuropathy, and 11% developed documented infections though G-CSF support. An important issue in patients with gastric cancer is toxicity. The elderly or poor-performance-status patient population cannot tolerate aggressive regimens such as those with high doses of CDDP. Because treatment regimens with G-CSF support are still under consideration [20],

we should confirm the safety and the absence of need for G-CSF support treatment.

In the present study, we developed a treatment regimen without fluoropyrimidine for advanced gastric cancer. As most of the regimens that are expected to be first-line therapy contain fluoropyrimidines to prolong survival, treatments for fluoropyrimidine-resistant gastric cancer are necessary as second-line therapy. TXL is a good candidate for this situation because of its lack of cross-resistance to fluoropyrimidine. In the phase II part of the present study, about 75% of the patients had received a fluoropyrimidine-based regimen as first-line therapy. We found a response rate of 25.0% in the phase II part of the study, although more than 50% of the patients could not receive the RD on the biweekly schedule.

In our determination of the new RD, we discussed a dose reduction of the RD in the interim analysis, in which treatment delay and dose reduction had occurred in a total of 11 patients within one cycle on the enrollment of 20 patients in the phase II part of the study. Based on the phase I part of the study, we discussed that we should reduce the dose of TXL and start a new phase II study at the TXL dose of 140 mg/m^2. The outcome will depend on the point of whether efficacy can be observed at dose level one or dose level two (level 1 showed two PRs and one SD, while level 2 showed two PRs and two SDs) and whether these treatments could be continued until disease progression (data not shown) in the phase I part. Our initial concept was to develop a new treatment option which has good feasibility within the outpatient setting.

To determine the optimal RD is sometimes very difficult in a phase I study. The IFL regimen (irinotecan, 5FU, and leucovorin combination regimen) is a good example of such a difficulty. A phase I study of the IFL regimen was first reported by Saltz et al. [21], and after a phase III study [22], this regimen showed a high mortality rate within 60 days, and a new RD was decided upon as a modified IFL regimen. In the light of this example, we decided to decrease the TXL dose to one level below that in the phase I part of the present study.

Finally, we decided to reduce the dose of TXL from 160 mg/m^2 to 140 mg/m^2. We are now conducting a phase II study at the new RD to evaluate the efficacy and long-term feasibility of the regimen, particularly with respect to peripheral neuropathy, a characteristic side effect of TXL administration.

In conclusion, with regard to the TXL-plus-CDDP combination in our study: (1) the recommended dose was determined to be TXL 140 mg/m^2 with CDDP 30 mg/m^2; and (2) we found that this regimen showed modest efficacy and a safe toxicity profile so that it could be offered as a candidate component of standard regimens for treating gastric cancer. We are now performing another phase II study, with the Korea-Japan Collaborative Study Group, to confirm the efficacy and feasibility of TXL 140 mg/m^2 with CDDP 30 mg/m^2.

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ORIGINAL ARTICLE

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Phase II study of single-agent gemcitabine in patients with advanced biliary tract cancer

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Abstract *Purpose*: This phase II study was conducted to evaluate the efficacy and toxicity of single-agent gemcitabine in patients with advanced or metastatic biliary tract cancer. *Patients and methods*: Gemcitabine 1,000 mg/m^2 was administered as an intravenous 30-min infusion on days 1, 8, and 15 for every 28 days. *Results*: Forty chemonaive patients with a median age of 61 (range 33–73) were enrolled, and all 40 patients were involved in efficacy and safety analyses. Seven (17.5%) achieved partial response; 15 (37.5%) had stable disease; 17 (42.5%) had progressive disease; and 1 (2.5%) was not evaluated. The median survival time was 7.6 months, and the 1-year survival rate was 25.0%. Grade 3/4 neutropenia occurred in 12 patients (30.0%), leukopenia in five patients (12.5%), and anemia in four patients (10.0%). The most common grade 3/4 nonhematologic toxicities were elevated ALT (15.0%) and elevated γ-GTP (12.5%). One patient had grade 4 hemolytic uremic syndrome and recovered after discontinuation of gemcitabine. *Conclusions*: In single-agent therapy, gemcitabine demonstrated moderate efficacy with manageable toxicity in patients with advanced or metastatic biliary tract cancer. Further evaluations are warranted, including the exact impact of gemcitabine on the management of advanced or metastatic biliary tract cancer.

Keywords Biliary tract cancer · Chemotherapy · Clinical trial · Gallbladder cancer · Gemcitabine

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Introduction

The incidence of biliary tract cancer has increased markedly in Japan over the past several decades. In 2002, biliary tract cancer was the sixth leading cause of cancer death in Japan with approximately 16,000 deaths and a mortality rate of 12.5 per 100,000. A continued sharp increase in age-adjusted mortality is predicted over the next 10 years [22, 25, 30].

Of all the treatment modalities for biliary tract cancer, only resection offers the opportunity for cure. However, because of metastases or invasion of the tumor directly into the adjacent liver or the hepatic artery, only a small minority of biliary tract cancer patients are candidates for resection with curative intent. The prognosis for these patients is dismal, and the impact of existing chemotherapy is virtually negligible. Therefore, there is a clear need for new, effective, chemotherapeutic regimens in the management of biliary tract cancer.

Gemcitabine is a novel nucleoside analogue, which requires to be phosphorylated to its active metabolite, gemcitabine triphosphate. Gemcitabine triphosphate competes with deoxycytidine triphosphate for incorporation into DNA, inhibiting DNA synthesis [16]. Gemcitabine has shown broad activity in a variety of tumors and is currently approved for use in non-small-cell lung

cancer and pancreatic cancer in Japan. Based on the results obtained in early phase studies in other locales and the established safety profile of the agent [3, 7, 8, 12, 24, 34, 35, 40], our group has conducted a multicenter, phase II trial of single-agent gemcitabine to investigate the response rate, toxicity, and time-to-event variables (progression-free survival, duration of tumor response, and survival time) in patients with advanced or metastatic biliary tract cancer.

Patients and methods

Eligibility criteria

Enrolled patients had histologically or cytologically confirmed adenocarcinoma of biliary tract, extrahepatic bile duct, gallbladder, or ampulla of Vater. Each patient was required to meet the following eligibility criteria: unresectable biliary tract cancer with at least one bidimensionally measurable tumor; no history of prior chemotherapy; no history of prior antitumor treatment for biliary tract cancer except resection and intraoperative or postoperative adjuvant radiotherapy; an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; 20–74 years of age; estimated life expectancy ≥2 months; adequate renal function (creatinine ≤ upper limit of normal [ULN]); adequate liver function (bilirubin ≤ 2 times ULN and aspartate/alanine transaminases [AST/ALT] ≤ 2.5 times ULN); adequate bone marrow reserve (white blood cells ≤ 4,000/mm^3, neutrophils ≥2,000/mm^3, platelets ≥100,000/mm^3, and hemoglobin ≥10 g/dl); and written informed consent. Patients with pre-existing obstructive jaundice were also eligible after their bilirubin levels met the criteria by biliary stent insertion or percutaneous biliary drainage.

Patients were excluded from the study if they had pulmonary fibrosis, interstitial pneumonia, New York Heart Association class III or IV congestive heart failure, myocardial infarction within the preceding 6 months, diabetes mellitus with severe complications, marked pleural or pericardial effusion, marked peripheral edema, or active infection. Additional exclusion criteria included pregnant or lactating females, patients of reproductive potential who did not use effective contraception, severe drug hypersensitivity, central nervous system metastases, active concomitant malignancy, other serious medical conditions, or patients receiving any investigational drug within 30 days before enrollment.

The study was conducted in accordance with the ethical principles stated in the most recent version of the Declaration of Helsinki or the applicable guidelines on good clinical practice, whichever represented the greater protection of the individual. In addition, the study design was approved by the appropriate ethical review boards.

Study treatment

Gemcitabine (supplied by Eli Lilly, Japan) 1,000 mg/m^2 was administered as an intravenous 30-min infusion on days 1, 8, and 15 for every 28 days. The treatment was continued until evidence of disease progression or unacceptable toxicity.

For white blood cells < 2,000/mm^3, neutrophils < 1,000/mm^3, platelets < 70,000/mm^3, bilirubin > 3 times ULN, or AST/ALT > 5 times ULN, gemcitabine was omitted on that day and postponed to the next scheduled treatment day.

In subsequent cycles, gemcitabine was reduced to 800 mg/m^2 if neutrophils < 500/mm^3 for 4 days, white blood cells < 1,000/mm^3 for 4 days, platelets < 25,000/mm^3, bilirubin > 3 times ULN, or AST/ALT > 5 times ULN. Gemcitabine was also reduced to 800 mg/m^2 if a platelet transfusion was performed due to thrombocytopenia or if gemcitabine was omitted twice in succession due to toxicity. No dose adjustment was allowed during the same cycle. The treatment was discontinued if a second dose reduction was needed, if bilirubin > 5.0 times ULN, AST/ALT > 20 times ULN, or tumor progression was observed. The use of granulocyte colony-stimulating factor (G-CSF) was permitted for any grade 4 leukopenia or neutropenia or grade 3 neutropenia with high fever (38.0°C). Prophylactic administration of antiemetics was allowed.

Baseline and treatment assessments

Pretreatment evaluation included complete history and physical examination. In addition, complete blood count, biochemistry tests, urinalysis, and chest X-ray were performed. Performance status and laboratory tests, except for urinalysis, were assessed weekly. Urinalysis was performed during days 15–28 in each cycle. Tumor size was measured by CT scan or MRI during days 22–28 in each cycle. Carcinoembryonic antigen (CEA) and carbohydrate antigen 19–9 (CA19–9) were quantified every 4 weeks. All 40 patients who received at least one dose of gemcitabine were involved in the efficacy analyses.Objective tumor response was assessed every 4 weeks using WHO criteria [41]. The duration of response was calculated from the first day of treatment until documentation of disease progression. Survival was measured from the first day of treatment.

Toxicity was assessed using the National Cancer Institute Common Toxicity Criteria version 2.0 [27]. A monitoring committee independently evaluated the efficacy and safety of the study.

Statistical analysis

Considering the results of previous trials using gemcitabine for advanced or metastatic biliary tract cancer, we expected an overall response rate of 15–20% in this