ANTICANCER RESEARCH *25*: 1257-1262 (2005)

Phase I/II Study of Bi-weekly Irinotecan plus Cisplatin in the Treatment of Advanced Gastric Cancer

W. KOIZUMI[1], M. KURIHARA[2], A. SATOH[3], H. TAKIUCHI[4], S. TANABE[1], K. SHIMADA[3], R. IWASAKI[5] and K. SAIGENJI[1]

[1]Department of Gastroenterology/Medical Oncology, Kitasato University East Hospital, 2-1-1 Asamizodai, Sagamihara, Kanagawa 228-8520;
[2]The Tokyo Cooperative Oncology Study Group, 2-4-8 Shibadaimon, Minato-ku, Tokyo 105-0012;
[3]Department of Internal Medicine, Northern Yokohama Hospital,35-1 Chuo, Chigasaki, Tsukiji-ku, Yokohama, Kanagawa 224-8503;
[4]Second Department of Internal Medicine, Osaka Medical College, 2-7 Daigakucho, Takatsuki-city, Osaka 569-8686; and
[5]Iwasaki Internal Medicine Clinic, 30-16 Nisikusabukathyou, Shizuoka-city, Shizuoka 420-0866, Japan

Abstract. *Objectives: To conduct a phase I/II study of irinotecan with cisplatin to establish a recommended dose, and assess the safety, efficacy and feasibility of this regimen in unresectable advanced or recurrent gastric cancer. Patients and Methods: In the phase I portion of the study, patients received a fixed dose of cisplatin (30 mg/m^2) with escalating doses of irinotecan, ranging from 30 mg/m^2 to 70 mg/m^2, on days 1 and 15. In the phase II portion of the study, 40 patients were evaluated for response and safety at the recommended dose. Results: Eighteen patients were enrolled in the phase I study. Dose-limiting toxicity (diarrhea and neutropenia) appeared at the irinotecan dose of 70 mg/m^2. Therefore, the recommended irinotecan dose was 60 mg/m^2. In the phase II study, 40 patients received cisplatin (30 mg/m^2) plus irinotecan (60 mg/m^2). Twenty-five out of 40 patients had received prior chemotherapy. The median number of cycles was 3.5. The response rate was 32.5% (13/40) overall, and 53.3% (8/15) in patients without prior chemotherapy. The median time to tumor progression (TTP) was 162 days. The median survival time was 288 days. Four patients (10%) developed grade 4 neutropenia and 3 patients (7.5%) developed grade 4 anemia. The only observed non-hematological toxicity at grade 3 or higher was diarrhea, seen in 2.5% (1/40) of the patients. Conclusion: Bi-weekly administration of irinotecan and cisplatin is safe and active for the management of unresectable advanced or recurrent gastric cancer.*

Correspndence to: W. Koizumi, Department of Gastroenterology/ Medical Oncology, Kitasato University East Hospital, 2-1-1 Asamizodai, Sagamihara, Kanagawa 228-8520, Japan. Tel: +81-42-748-9111, Fax: +81-42-748-5120, e-mail: koizumi@med.kitasato-u.ac.jp

Key Words: Irinotecan, cisplatin, advanced gastric cancer, phase I/II trial.

In 2001, 49,958 patients died from gastric cancer in Japan, making gastric cancer the second deadliest cancer, surpassed only by lung cancer. Deaths from gastric cancer account for 16.6% of all cancer deaths. In a comparison of age-adjusted mortality rate from gastric cancer in 28 countries, Japan led all other nations for both men and women, indicating that the number of gastric cancer patients is greater in Japan than in any other country (1).

Chemotherapy is recognized as an effective treatment method for advanced gastric cancer (2, 3). However although phase III comparative studies have been carried out, the standard-of-care chemotherapy regimen has not yet been established (4). Thus, new, more effective therapies are desired.

Irinotecan (7-ethyl-10-[4-(1-piperidino)-1-piperidino] carbonyloxycamptothecin) is a semi-synthetic compound derived from a plant alkaloid camptothecin, extracted from *Camptotheca acuminata* (5, 6).

Unlike conventional anticancer drugs, irinotecan inhibits DNA topoisomerase I (7, 8). In Japan, a late phase II multicenter study of irinotecan demonstrated efficacy in patients with advanced gastric cancers.The response rate was 23.3% (14/60). The recommended dose for irinotecan monotherapy in Japan was 100 mg/m^2 weekly or 150 mg/m^2 bi-weekly.

Currently, ongoing studies combine irinotecan with other agents to improve antitumor effects (9). The combination of irinotecan and cisplatin has been shown to enhance cytotoxicity against target cells *in vitro* (10-13). Clinical

Table I. *Dose -escalation schedule* and number of patients in phase I study.*

Dose level	Dose (mg/m^2) irinotecan	cisplatin	No. of patients
1	30	30	3
2	40	30	3
3	50	30	3
4	60	30	3
5	70	30	6

*irinotecan and cisplatin on days 1 and 15.

studies of combination therapy using irinotecan and cisplatin have shown better efficacy than monotherapy in patients with gastric cancer(14, 15). Preclinical studies have also shown that the additive effects *in vitro* are highest when cells are simultaneously treated with irinotecan and cisplatin, with the cytotoxic activity depending on the area under the drug concentration-time curve and maintained when cells are intermittently exposed to treatment (10, 16). We conducted a multi-center phase I/II clinical study to identify a recommended dose of bi-weekly concomitant treatment of irinotecan and cisplatin and to determine the safety and efficacy of this combination in patients with advanced or recurrent gastric cancer.

Patients and Methods

Eligibility criteria. Patients with unresectable advanced or recurrent gastric cancer were enrolled. The patients were required to satisfy the following eligibility criteria: histologically confirmed diagnosis of gastric cancer; age of 20 to 75 years; Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0, 1, or 2; ≤1 chemotherapy regimen completed 4 weeks before entry; leukocyte count of 4,000-12,000/mm^3 and platelet count of ≥100,000/mm^3; total bilirubin level of ≤2.0 mg/dL and aspartate aminotransferase and alanine aminotransferase levels not more than three times the upper limit of normal; creatinine level of ≤1.5 mg/dL, blood urea nitrogen level of ≤25 mg/dL, and creatinine clearance of ≥50 mL/min; and an estimated survival of at least 3 months. Before enrollment, all subjects provided a written informed consent to participate in the study. Patients with any of the following conditions were excluded: severe co-existing medical illness (intestinal paresis or ileus, interstitial pneumonia, pulmonary fibrosis, poorly controlled diabetes mellitus), active multiple cancers, severe psychiatric disturbances, or a history of hypersensitivity to either irinotecan or cisplatin. This study was conducted after being approved by the ethics committee of each participating institution.

Treatment schedule. In the phase I portion of the study, irinotecan was initially given at a dose of 30 mg/m^2 over 90 min by intravenous infusion on days 1 and 15. The irinotecan dose was then escalated in 10 mg/m^2 increments to confirm the safety of the treatment (Table I). Cisplatin, at a fixed dose of 30 mg/m^2, was given after irinotecan by intravenous infusion over 90 min with adequate hydration (a total of 1-2 L) on days 1 and 15. This treatment was repeated every 4 weeks until disease progression, refusal by the patient, or unacceptable adverse reactions.

Prior to chemotherapy, patients received antiemetics of 5-HT$_3$ receptor antagonist and steroids. Episodes of diarrhea were treated with loperamide hydrochloride as required.

The following dose adjustments were permitted: irinotecan was reduced to 50 mg/m^2 for grade 3 hematological toxicity or grade 2 non-hematological toxicity (excluding hair loss, nausea and vomiting); cisplatin was reduced to 20 mg/m^2 for renal toxicity.

Maximum-tolerated dose and recommended dose. In the phase I portion of the study, dose-limiting toxicity during the first cycle of therapy was defined as any of the following: grade 4 hematological toxicity, grade 3 non-hematological toxicity (excluding hair loss, nausea and vomiting), or withholding of treatment for 3 weeks or longer due to delayed resolution of adverse events. Three patients were assigned to each dose level. If any patient experienced dose-limiting toxicity, 3 more patients were assigned to receive the same dose. If 3 or more of the 6 patients experienced dose-limiting toxicity, the dose level was defined as the maximum-tolerated dose. The recommended dose of irinotecan for the phase II study was defined as 10 mg/m^2 lower than the maximum-tolerated dose.

Table II. *Clinical characteristics of patients in phase I and phase II studies.*

Characteristic	Phase I (n=18) No.	%	Phase II (n=40) No.	%
Age, years				
Median	63		62	
Range	(26 - 74)		(40-75)	
Sex				
Male	13	72.2	30	75.0
Female	5	27.8	10	25.0
Performance status (ECOG)				
0, 1	16	88.9	38	95.0
2	2	11.1	2	5.0
Histology				
Intestinal type	8	44.4	19	47.5
Diffuse type	10	55.5	21	52.5
Site of metastasis				
Liver	4	22.2	19	47.5
Lymph nodes	7	38.9	24	60.0
Lung	1	2.5	1	2.5
Other	2	11.1	1	2.5
Prior chemotherapy				
No			15	37.5
Yes			25	62.5
Oral fluorouracil/cisplatin			16	64.0
Oral fluorouracil alone			3	12.0
MTX/5FU/cisplatin			5	20.0
Taxanes			1	4.0

ECOG, Eastern Cooperative Oncology Group.

Table III. *Toxicity (phase I study).*

First course

Toxicity	Dose level	No. of patients	Grade				Incidence of Grade 3 & 4 (%)
			1	2	3	4	
Leukopenia	1	3	1	2	0	0	0
	2	3	3	0	0	0	0
	3	3	1	1	0	0	0
	4	3	1	1	0	0	0
	5	6	2	2	1[*1]	1[*2]	33.3
Neutropenia	1	3	0	1	1	0	33.3
	2	3	1	1	0	0	0
	3	3	0	0	1	0	33.3
	4	3	0	0	0	0	0
	5	6	0	1	2	1[*2]	50.0
Thrombocytopenia	1	3	0	0	0	0	0
	2	3	0	0	0	0	0
	3	3	0	0	0	0	0
	4	3	0	0	0	0	0
	5	6	1	0	0	0	0
Decreased hemoglobin	1	3	0	2	0	0	0
	2	3	0	1	1	0	33.3
	3	3	2	1	0	0	0
	4	3	1	0	1	0	33.3
	5	6	3	1	1	0	16.7
Diarrhea	1	3	0	0	0	0	0
	2	3	0	0	0	0	0
	3	3	1	0	0	0	0
	4	3	0	0	0	0	0
	5	6	0	1[*3]	1[*2]	0	16.7
Nausea / vomiting	1	3	0	1	0	0	0
	2	3	0	0	0	0	0
	3	3	2	1	0	0	0
	4	3	1	0	0	0	0
	5	6	1	0	0	0	0

[*1] Delayed for 28 days for leukopenia.
[*2] One patient had Grade 3 diarrhea and Grade 4 leukopenia and neutropenia.
[*3] Delayed for 28 days for diarrhea.

Evaluation. The tumor response was evaluated based on changes in the size of measurable lesions and assessment of evaluable lesions. Measurable lesions and evaluable lesions were defined and efficacy evaluated in accordance with the Japanese Criteria for Evaluating the Efficacy of Chemotherapy and Radiation Therapy in the Treatment of Gastric Cancer (17). In brief, complete remission was defined as the disappearance of all evidence of the tumor for at least 4 weeks. Partial remission was defined as 50% or greater reduction in the sum of the products of the perpendicular diameters of all measurable lesions for at least 4 weeks without any evidence of new lesions or the progression of any existing lesions. Stable disease was defined as less than 50% reduction or less than 25% increase in the sum of the products of the perpendicular diameters of all lesions for at least 4 weeks, without any evidence of new lesions or the progression of any existing lesions. Progressive disease was defined as a ≥25% increase of one or more lesions or the appearance of new lesions. Tumor measurements were performed every 4 weeks using computed tomography, plain chest X-ray films, upper gastrointestinal endoscopy and ultrasonography. Primary tumors were classified into the following 3 categories based on X-ray and endoscopic findings: measurable, not measurable but evaluable, and diffuse infiltration.

World Health Organization criteria were applied to evaluate adverse events. The eligibility and suitability for assessment of the subjects and response to treatment were reviewed by an independent review committee.

Results

Phase I Study

Patient characteristics. A total of 18 patients (13 men, 5 women) were enrolled in the phase I study between November 1997 and September 1999. The clinical characteristics of the patients

Table IV. *Response (phase II study).*

		CR		PR		NC		PD		NE		RR	
	No.	No.	%	No.	%	No.	%	No.	%	No.	%	%	95% CI
Overall	40	0	0.0	13	32.5	14	35.0	11	27.5	2	5.0	32.5	18.6-49.1
Prior chemotherapy													
Yes	25	0	0.0	5	20.0	10	40.0	9	36.0	1	4.0	20.0	6.8-40.7
Oral fluorouracil/cisplatin	16	0	0.0	4	25.0	6	37.5	6	37.5	0	0.0	25.0	
Oral fluorouracil alone	3	0	0.0	1	33.3	2	66.6	0	0.0	0	0.0	33.3	
MTX/5FU/cisplatin	5	0	0.0	0	0.0	2	40.0	3	60.0	0	0.0	0.0	
Taxanes	1	0	0.0	0	0.0	1	100.0	0	0.0	0	0.0	0.0	
No	15	0	0.0	7	53.3	4	26.7	2	13.3	1	6.7	53.3	21.3-73.4
Primary	30	0	0.0	10	33.3	14	46.7	4	13.3	0	0.0	33.3	17.3-52.8
Liver	20	0	0.0	7	35.0	9	45.0	4	20.0	0	0.0	35.0	15.4-59.2
Lymph nodes	23	1	4.3	7	30.4	13	56.5	2	8.7	0	0.0	34.8	16.4-57.3
Lung	1	0	0.0	1	100.0	0	0.0	0	0.0	0	0.0	100.0	

CR, complete response; PR, partial response; NC, no change; PD, progressive disease; NE, not evaluable; RR, response ratio.

are shown in Table II. The median age was 63 years (range, 26-74). The performance status was 0 or 1 in 16 patients and 2 in 2 patients. Histologically, 8 patients had intestinal type adenocarcinoma and 10 had diffuse type adenocarcinoma. Safety was evaluable in all 18 patients. Three patients were initially assigned to receive dose level 1. Cohorts of 3 patients each were likewise assigned to dose levels 2, 3, 4 and 5. Dose-limiting toxicity occurred at dose level 5, and 3 patients were added to this dose cohort. Table I summarizes the number of patients in each dose cohort.

Dose-limiting toxicity and recommended dose for phase II study. Three out of 6 patients at dose level 5 (irinotecan 70 mg/m^2 + cisplatin 30 mg/m^2 on days 1 and 15) experienced dose-limiting toxicity. One patient developed grade 4 leukopenia/neutropenia and grade 3 diarrhea. Two patients exhibited delayed resolution of adverse events, persisting beyond day 28, of whom one patient had leukopenia that persisted for longer than 28 days (Table III). The other patient had persistent diarrhea that required postponement of treatment. Thus, 70 mg/m^2 was established as the maximum-tolerated irinotecan dose, and a combination of irinotecan 60 mg/m^2 and cisplatin 30 mg/m^2, given on days 1 and 15 in a 28-day cycle, was recommended for use in the phase II study.

Phase II Study

Patient characteristics. Forty patients were enrolled in the phase II study between October 1999 and December 2000. The clinical characteristics of the patients are shown in Table II. All patients met the entry criteria and were included in the analysis. The subjects consisted of 30 men (75.0%) and 10 women (25.0%). Fifteen patients (37.5%) had not received prior chemotherapy, while 25 patients (62.5%) had . The median age of the patients was 62 years (range, 40-75). Histologically, 19 patients had intestinal type adenocarcinoma and 21 had diffuse type adenocarcinoma. Performance status was 0 or 1 in 38 patients (95.0%).

Tumor response and survival. Among the 40 patients with evaluable lesions, 13 (32.5%) exhibited a partial response. The response rate in the patients who had not received prior chemotherapy was 53.3% (8/15), compared to 20.0% (5/25) in those who had received prior chemotherapy (p=0.041, Fisher's exact test). The response rate according to site was 33.3% (10/30) at primary sites, 35.0% (7/20) for liver metastases, 34.8% (8/23) for abdominal lymph node metastases, including 1 complete response, and 100% (1/1) for lung metastases (Table IV). The response rate according to histological type was 21.1% (4/19) in the intestinal type and 42.9% (9/21) in the diffuse type. The median time to progression was 162 days (range, 14-395 days). By Kaplan-Meier analysis, the median survival was 288 days in the 40 subjects (Figure 1), 302 days in the patients who had received no prior chemotherapy, and 274 days in the patients who had received prior chemotherapy. The median number of treatment cycles given was 3.5 (range, 1-7.5; 143 courses, 275 administrations in total).

Patients were taken off the study because of the emergence of a new lesion (11 cases), worsening of the primary disease (19 cases), ineffectiveness (2 cases), deterioration in the patient's general condition (2 cases), request by the patient (5 cases), an adverse reaction (1 case), or a severe complication (2 cases).

Safety. Hematological toxicities of grade 3 or higher observed were leukopenia in 27.5% of the patients, neutropenia in 40.0%, thrombocytopenia in 5.0%, and

decreased hemoglobin level in 30.0% (Table V).The non-hematological toxicities of grade 3 or higher were elevated aspartate aminotransferase (in 5.0% of the patients), elevated alanine aminotransferase (5.0%), elevated total bilirubin (2.5%), elevated alkaline phosphatase (2.5%) and diarrhea (2.5%). There were no treatment-related deaths.

Dose intensity. The actual administered dose in the first two courses was 27.1 mg/m^2/week for irinotecan and 13.6 mg/m^2/week for cisplatin, which correspond to 90.3% and 90.6% of the planned doses.

The drug administration was postponed or skipped in 4 patients on day 15 in the first cycle, and 2 patients postponed the second drug administration in the first cycle. Ten patients delayed the start of the next cycle.

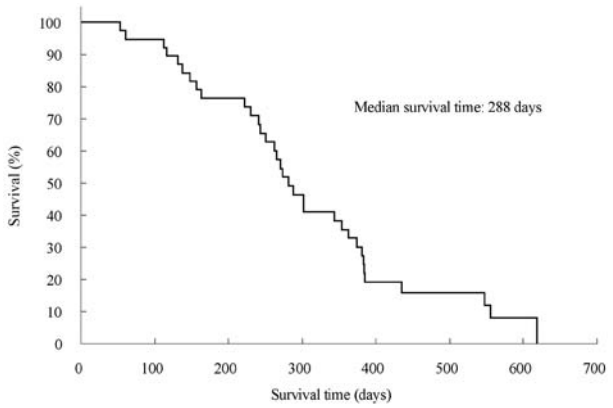

Figure 1. *Survival Curve Derived by Kaplan-Meier Analysis.*

Discussion

The phase I study established the maximum-tolerated dose of irinotecan to be 70 mg/m^2 when given with 30 mg/m^2 of cisplatin. Thus, the recommended dose for the phase II study was 60 mg/m^2 of irinotecan and 30 mg/m^2 of cisplatin given intravenously on days 1 and 15 in a 4-week, repeated cycle. This dosage was effective and caused no dose-limiting toxicity, such as severe diarrhea, leukopenia, or neutropenia.

In the phase II study, the tumor response rate with acceptable toxicity was 32.5% (13/40, 95% CI, 18.6%-49.1%) overall and 53.3% (8/15, 95% CI, 27.9%-78.7%) in patients who had not received prior chemotherapy. The median survival was 288 days overall, and 302 days in patients who had not received prior chemotherapy.

These findings show that the recommended dose of irinotecan is 60 mg/m^2. Regarding the recommended dose of irinotecan in colorectal cancer, Cerea *et al.* suggested that the dose reduction of CPT-11 does not influence its efficacy, because they found no significant difference in the disease control (PR + SD) between patients treated with a weekly dose of 125 mg/m^2 and those who received a half-dose (18).

The combination of irinotecan and cisplatin has previously been studied in various tumor types. Kobayashi *et al.* conducted a phase I clinical study of a weekly regimen of irinotecan and cisplatin in patients with non-small cell lung cancer (irinotecan 60 mg/m^2 + cisplatin 27-40 mg/m^2, days 1, 8, 15, one week rest) and reported a high efficacy (19), although the dose-limiting toxicity of irinotecan, such as diarrhea and leukopenia, occurred frequently 7 days after administration. Ajani *et al.* conducted a phase II clinical study of a weekly regimen of irinotecan and cisplatin in advanced, untreated gastric cancer or cancer of the gastroesophageal junction (irinotecan 65 mg/m^2 + cisplatin 30 mg/m^2, weekly x 4, two weeks rest) and reported a high efficacy, although modifying the dose and schedule is necessary, because 66% of the patients experienced adverse effects, requiring a delay or cancellation of drug administration (20). These findings indicate that administering irinotecan and cisplatin weekly on schedule is difficult due to toxicity.

Table V. *Toxicity (phase II study).*

Toxicity (n = 40)	Grade 1	2	3	4	Incidence of Grade 3 & 4 (%)
Leukopenia	6	16	11	0	27.5
Neutropenia	3	11	12	4	40.0
Thrombocytopenia	6	4	2	0	5.0
Decreased hemoglobin	7	17	9	3	30.0
AST	3	4	2	0	5.0
ALT	5	1	2	0	5.0
T-Bilirubin	0	0	1	0	2.5
Al-p	2	3	1	0	2.5
Diarrhea	5	5	1	0	2.5
Nausea/vomiting	14	8	0	0	0.0

AST, L-Aspartate aminotransferase; ALT, L-Alanine aminotransferase; Al-p, Alkaline phosphatase.

Boku *et al.* (14) conducted a phase II clinical study of irinotecan and cisplatin in metastatic gastric cancer (irinotecan 70 mg/m^2 on days 1 and 15 + cisplatin 80 mg/m^2 on day 1 in a four-week cycle) and reported a high efficacy with overall response rate of 48% (21/44), and 27% in previously-treated patients (4/15). However, leukopenia (59.1%), neutropenia (88.6%) and grade 3 or worse diarrhea (20.5%) were observed. They reported that the second dose of irinotecan was postponed in 82 (56%) cycles and was not given in 34 (23%) cycles out of 146 cycles overall. It was indicated that combining cisplatin once every four weeks with irinotecan bi-weekly did not reduce the

number of cycles delayed or skipped. In contrast, the adverse events of grade 3 and higher in our study were leukopenia (27.5%), neutropenia (40%) and diarrhea (2.5%). Among all the cycles administered, the second dose in the cycle was postponed in 19 cycles (13%) and skipped in 11 cycles (7.7%), so that the two agents could be administered essentially according to schedule.

Regarding the actual dose in the two doses of the initial cycle, Boku *et al.* (14) reported that the actual dose administered for irinotecan was 28.5 mg/m^2/week and cisplatin was 18 mg/m^2/week, so that the actual dose/planned dose was 81.4% for irinotecan and 89.9% for cisplatin. Although this schedule differs from our schedule, we nearly replicated the equivalent dose intensity. The response rate as second-line treatment of 20% and the median survival of 274 days indicate good efficacy. The study of second-line treatment of gastric or gastroesophageal junction carcinoma by Ajani *et al.* (15) reported a response rate of 31% and median survival of 5 months. We observed a response rate of 25% (4/16), even in patients previously treated with cisplatin plus oral 5FU. We conclude that our regimen may also be effective as a second-line treatment.

Phase III studies are necessary to establish the clinical utility of irinotecan/cisplatin.

Acknowledgements

We would like to thank Dr. Noriyuki Masuda (Kitasato University, Japan) for his review and constructive comments on the manuscript.

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Received September 7.2004
Revised February 7, 2005
Accepted February 18, 2005