RAPID COMMUNICATION

Phase Ⅱ study of protracted irinotecan infusion and a low-dose cisplatin for metastatic gastric cancer

Hiroshi Imamura, Masataka Ikeda, Hiroshi Furukawa, Toshimasa Tsujinaka, Kazumasa Fujitani, Kenji Kobayashi, Hiroyuki Narahara, Michio Kato, Haruhiko Imamoto, Arimichi Takabayashi, Hideaki Tsukuma

Hiroshi Imamura, Masataka Ikeda, Hiroshi Furukawa, Department of Surgery, Sakai Municipal Hospital, Osaka, Japan
Toshimasa Tsujinaka, Kazumasa Fujitani, Department of Surgery, Osaka National Hospital, Osaka, Japan
Kenji Kobayashi, Department of Surgery, Kinki Central Hospital, Hyogo, Japan
Hiroyuki Narahara, Hideaki Tsukuma, Department of Internal Medicine, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka, Japan
Michio Kato, Department of Surgery, Kinki University School of Medicine, Osaka, Japan
Haruhiko Imamoto, Department of Surgery, Kansai Rosai Hospital, Hyogo, Japan
Arimichi Takabayashi, Department of Surgery, Kitano Hospital & Research Institute, Osaka, Japan
Correspondence to: Hiroshi Imamura, Department of Surgery, Sakai Municipal Hospital, 1-1-1, Minamiyasui-cho, Sakai, Osaka 590-0064, Japan. imamura-h@city.sakai.osaka.jp
Telephone: +81-72-2211700 Fax: +81-72-2253303
Received: 2006-06-21   Accepted: 2006-07-18

Abstract

AIM: To test protracted irinotecan infusion plus a low-dose cisplatin in this Phase Ⅱ trial to decrease its toxicity.

METHODS: The eligibility criteria were: (1) histologically proven measurable gastric cancer; (2) performance status of 0 or 1; (3) no prior chemotherapy or completion of prior therapy at least 4 wk before enrollment; (4) adequate function of major organs; (5) no other active malignancy; and (6) written informed consent. The regimen consisted of irinotecan (60 mg/m^2) on d 1 and 15 by 24-h infusion and cisplatin (10 mg/m^2) on d 1, 2, 3, 15, 16, and 17. Treatment was repeated every 4 wk.

RESULTS: Thirty-one patients were registered between April 2000 and January 2001. The response rate for all 31 patients, 20 patients without prior chemotherapy, and 11 patients with prior chemotherapy was 52% (16/31), 60% (12/20), and 36% (4/11), respectively. The median survival time was 378 d. The median number of courses given to all patients was 2. Grade 4 neutropenia occurred in 11 (35%) patients, while grade 3 to 4 diarrhea or nausea occurred in 1 (3%) and 3 (10%) patients, respectively. Fatigue was minimal as grade 1 fatigue was found only in 3 (10%) patients. Other adverse events were mild and no treatment-related deaths occurred.

CONCLUSION: This regimen showed a high level of activity and acceptable toxicity in patients with metastatic gastric cancer.

INTRODUCTION

In Japan, for advanced gastric cancer, surgery is still the most effective treatment and good survival can be achieved if the tumor is resectable. On the contrary, unresectable advanced or recurrent gastric cancer still has a poor prognosis and chemotherapy is the most important treatment for survival prolongation. To date, combination chemotherapy with 5-fluorouracil (5-FU) and cisplatin has been used most widely. This two-drug regimen showed superior response rate in comparison with single-agent 5FU regimen, however, failed to demonstrate survival prolongation[1-3]. This regimen has response rates ranging from 10% to 35%, and the median survival time (MST) from 6 to 8 mo with around 10% in a 2-year survival[4]. Advent of new active agents is awaited.

Among new drugs, irinotecan, a derivative of camptothecin, has strong antitumor activity through inhibition of DNA topoisomerase I[5]. It has a single agent activity with a response rate of 23.3%[6]. As the response rate is not satisfactory, irinotecan was first investigated in combination with cisplatin. Phase I study was conducted for metastatic gastric cancer and treatment regimen of irinotecan (70 mr/m^2, d 1 and 15) and cisplatin (80 mg/m^2, d 1), every 4 wk, was recommended[7]. Boku's group tested this regimen for metastatic gastric cancer[8]. The overall response rate was 48% and the median survival time was 272 d. Although no treatment-related deaths occurred, adverse events were severe, including grade 4 neutropenia in

57% of the patients and grade 3 or 4 diarrhea in 20%. As for renal toxicity, they found a total of 34% (grade 1: 23%, grade 2: 11%) serum creatinine increase. This combination study was followed with modification of weekly schedule to reduce toxicity in western countries. Ajani *et al*[9] conducted phase Ⅱ study with irinotecan (65 mg/m^2) with cisplatin (30 mg/m^2), both administered intravenously 1 d per week for 4 consecutive weeks, followed by two weeks recovery period. Of the 36 patients registered, 21 achieved complete or partial response with response rate of 58%. They had one treatment-related death of neutropenic sepsis with multiple organ failure. Major toxic effects were diarrhea, neutropenia, and fatigue. The incidence of grade 3 or 4 neutropenia was 37%, however, grade 3 or 4 diarrhea was still found in 22% of patients. Surprisingly, grade 3 or 4 fatigue was 41%, a cause of delays or cancellation of drugs. To decrease adverse events, Fujitani *et al*[10] conducted a pharmacokinetic study of continuous infusion of irinotecan for 24 h combined with infusion of cisplatin over 90 min, and demonstrated only mild hematological and nonhematological adverse reactions, while protracted infusion of irinotecan increased the area under the concentration *vs* time curve (AUC) of SN-38.

Accordingly, we further investigated the safety and efficacy of this combined protracted infusion of irinotecan (to maintain a high AUC of SN-38) with a low-dose cisplatin to determine whether this regimen can improve response rate and reduce toxicity.

MATERIALS AND METHODS

Eligibility criteria
Patients were required to satisfy the following eligibility criteria; (1) histologically proven gastric cancer; (2) measurable metastatic lesions; (3) Eastern Clinical Oncology Group scale performance status of 0 or 1; (4) no prior chemotherapy or completion of therapy at least 4 wk before entry; (5) adequate function of the bone marrow WBC count $\geqslant 4 \times 10^9$ and $\leqslant 12 \times 10^9$, platelet count $\geqslant 100 \times 10^9$, and hemoglobin $\geqslant 95$ g/L), liver (serum bilirubin $\leqslant 25.6$ μmol/L and serum transaminases $\leqslant 1667$ nkat/L), and kidneys (serum creatinine $\leqslant 133$ μmol/L); (6) normal cardiac function; (7) no other severe medical conditions; (8) no other active malignancy; and (9) ability to give written informed consent. This study was approved by the institutional review boards of all participating hospitals.

Treatment schedule
On d 1, irinotecan (60 mg/m^2) was administered as a 24-h infusion; the drug was diluted in 500 mL of saline or 50 g/L glucose and was protected from the light. Cisplatin (10 mg/m^2) was administered as a 60-min intravenous infusion with adequate hydration on d 1, 2, and 3. The same doses of irinotecan and cisplatin were repeated on d 15 and 15-17, respectively, to complete one course. Treatment was repeated every 4 wk until the occurrence of disease progression, patient refusal, or unacceptable adverse reactions. On d 15, if the patient had leucopenia or thrombocytopenia of grade 2 or higher, diarrhea of grade 1 or higher, or fever (a temperature > 38℃) due to infection, administra-

tion of the second dose of irinotecan was delayed for one week. If recovery from the adverse reaction did not occur after one week, the second dose was skipped. If a grade 4 hematologic adverse event, grade 3 or 4 diarrhea, fever associated with infection, or omission of the second dose occurred, the dose of irinotecan for the second course was reduced to 50 mg/m^2. The antiemetic granisetron was given before cisplatin administration. Granulocyte colony-stimulating factor (G-CSF) was used when grade 4 leucopenia and/or neutropenia occurred. If the patient stopped treatment due to toxicity or tumor progression, other chemotherapy or surgery was offered.

Evaluation
The National Cancer Institute Common Toxicity Criteria (Version 2.0) were applied for the assessment of adverse events. The objective response of measurable lesions was evaluated by standard World Health Organization criteria. Both patient eligibility and the response to treatment were reviewed extramurally.

Statistical analysis
The expected efficacy rate of this regimen was hypothesized to be 50%, so the required number of patients was 25 when the 95% confidence interval was set at ± 20%. Because some patients might be excluded from analysis, the target number of patients for this study was set at 30. Analysis was performed on an intent-to-treat basis. The percentage of patients with complete remission (CR) plus partial remission (PR) among all treated patients was defined as the response rate. The 95% confidence interval (CI) of the response rate was calculated using the normal approximation and precision method. The Kaplan-Meier method was used to calculate the survival period.

RESULTS

Patients characteristics
Thirty-one patients were enrolled from April 2000 to January 2001. One patient was found to be ineligible because the performance status was 2. As analysis was performed on an intent-to-treat basis, this patient was also analyzed for efficacy and safety, so all 31 patients were assessed for efficacy and safety. Their clinical characteristics are shown in Table 1. The median age was 60.5 (range: 26-75 years) and 21 patients (68%) had performance status of 0. Sixteen patients (52%) had intestinal type adenocarcinoma and 14 patients had diffuse tumors. The measurable metastatic lesions were located in the lymph nodes in 20 patients (26 lesions), liver in 13 patients, peritoneum in 3 patients, ovary in 2 patients, and the skin, lung, and rectum in one patient each, respectively. Twenty patients (65%) had not received prior chemotherapy, while the other 11 patients had undergone chemotherapy with 5-FU, cisplatin plus 5-FU, or other drugs. All of the patients who had received prior therapy showed progressive disease before enrollment. The total number of treatment courses was 84 with a median number of 2 cycles per patient (range 1-5). A total of 149 of 168 planned CPT-11 administration was carried out. While a total of 112 of 122 (92%) planned CPT-11 was administered in the first and second cycle, a

Table 1 Patient profile

	n	Site of metastases	
Sex		Lymph nodes	26
Female	20		
Male	11	Perigastric	6
PS		Para-aortic	6
0	21	Virchow's	3
1	9	Neck	2
2	1	Mediastinum	1
Histology		Others	8
Intestinal	16	Liver	13
Diffuse	14	Peritoneal	3
Others	1	Skin	1
Prior chemotherapy		Lung	1
No	20	Ovary	2
Yes	11	Rectum	1

PS: Performance status.

Table 2 Response to therapy n (%)

	CR	PR	NC	PD	RR	95% CI
Overall	0	16 (52)	11 (35)	4 (13)	16 (52)	33-70
Prior chemotherapy						
Yes	0	4 (36)	4 (27)	3 (27)	4 (36)	11-69
No	0	12 (60)	7 (35)	1 (5)	12 (60)	36-81
Liver	2 (15)	5 (39)	5 (39)	1 (8)	7 (54)	
Lymph Nodes	2 (8)	12 (46)	12 (46)	0	14 (54)	
Peritoneal	0	1 (33)	1 (33)	1 (33)	1 (33)	
Ovary	0	0	1 (50)	1 (50)	0	
Lung	0	1 (100)	0	0	1 (100)	
Others	0	1 (50)	1 (50)	0	1 (50)	

CR: Complete remission; PR: Partial response; NC: No change; PD: Progressive disease; RR: Response rate.

Figure 1 Survival curves of all patients and patients without prior chemotherapy. —: Survival curve of all patients (median survival time, 378 d). …: Survival curve of patients without priorchemotherapy (median survival time, 509 d).

Table 3 Adverse reactions

	Grade (%)			
	1	2	3	4
Hematologic				
Leukopenia	1 (3)	14 (45)	8 (26)	3 (10)
Neutropenia	1 (3)	2 (6)	13 (42)	11 (35)
Thrombocytopenia	8 (25)	1 (3)	1 (3)	1 (3)
Anemia	5 (16)	13 (42)	7 (23)	2 (6)
Nonhematologic				
Fatigue	3 (10)	0	0	0
Nausea	12 (39)	8 (26)	3 (10)	0
Diarrhea	9 (29)	4 (13)	1 (3)	0
Abdo pain	2 (6)	2 (6)	1 (3)	0
Alopecia	11 (35)	10 (30)	1 (3)	0
AST	1 (3)	0	0	0
T. bilirubin	1 (3)	0	0	0
Cr	8 (26)	0	0	0

Abdo pain: Abdominal pain.

total of 37 of 46 (80%) planned CPT-11 administration in the third to fifth cycles. Dose reduction was not required in the first cycle, but it was needed in 8 patients in the second cycle and one patient in the third cycle. Causes of dose reduction were grade 4 neutropenia in 5 patients, grade 4 leukopenia in one patient, and second dose skip in 3 patients. Treatment was stopped due to tumor progression in 8 patients, refusal to continue in 9 patients, and insufficient recovery from adverse reactions in 3 patients. Median duration between the beginning and end of treatment was 75 d. The actual administered dose of CPT-11 in the all courses was 25.7 mg/m^2 per week and that of cisplatin was 13.0 mg/m^2 per week, which corresponded to 85.5% and 86.4% of the planned doses.

Response and survival

There were no complete remissions, but partial remission was achieved in 16 patients for a response rate of 52% (16/31 patients, 95% CI: 33% to 70%). The response rate was 60.0% for the 20 patients without prior chemotherapy (12/20 patients, 95% CI: 36% to 81%), while the rate for the 11 patients with prior chemotherapy was only 36% (4/11 patients, 95% CI: 11% to 69%). The response rate of patients with lymph node, liver, and peritoneal
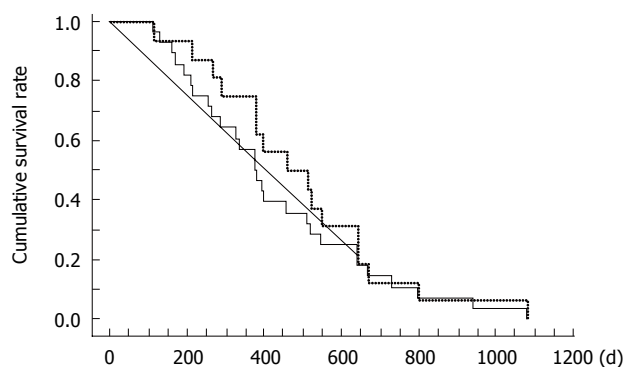
metastasis were 54% (14/26 patients), 54% (7/13 patients) and 33% (1/3 patients), respectively (Table 2). The median duration of response for all the patients was 218 d. The median survival time of all patients was 378 d, while the median survival time of the 20 patients without prior chemotherapy was 509 d. The 1-year and 2-year survival rates were 57% (95% CI: 37%-72%) and 9% (95% CI: 2%-23%), respectively (Figure 1).

Adverse reactions

Adverse reactions to this regimen are shown in Table 3. Grade 4 neutropenia, leukopenia, anemia, and thrombocytopenia were observed in 11 (35%), 3 (10%), 2 (6%), and 1 (3%) of the patients, respectively. The median nadir of the neutrophil count was seen on d 8 (range: d 2-19). G-CSF was administered to 15 patients (48%) during 28 courses. Non-hematologic adverse reactions (nausea, diarrhea, increased AST, and increased bilirubin) were all moderate, with grade 3 nausea (10%) and grade 3 diarrhea (3%) being the maximal reactions. Loperamide or other mild anti-diarrheal medicines were effective for diarrhea, while granisetron and other common anti-emetic medicines were effective for nausea without additional hydration. Renal

toxicity determined by the level of serum creatinine was also mild. We found 8 patients (26%) with only grade 1 abnormal creatinine level. Fatigue was found in only 3 patients and all grade 1. The non-hematologic reactions did not disrupt the treatment schedule and there were no treatment-related deaths.

DISCUSSION

The aim of this phase II study was to confirm the antitumor effects and safety of combined chemotherapy of protracted infusion of irinotecan and low-dose cisplatin[10]. Protracted infusion of irinotecan significantly increases the AUC of active metabolite, SN-38[10], suggesting it has the potential to maximize the effect of irinotecan. The response rate to irinotecan as a single agent for gastric cancer was reported to be 23.3%[6] and that for cisplatin was 20%[11]. The overall response rate of the 31 patients in the present series was 52% and that of 20 patients without any prior chemotherapy was 60%, with both rates being better than for single agent therapy. These data are consistent with a previous phase II study of cisplatin and irinotecan therapy[8,9], and confirms the activity of combined therapy of irinotecan and cisplatin.

Diarrhea is a serious toxicity of irinotecan therapy. The incidence of grade 3 or 4 diarrhea was reported to be 18.8% or 35.6% with irinotecan alone and 21.9% or 35.6% with bolus combined administration[12-15]. In the previous phase II studies of irinotecan and cisplatin, diarrhea was still one of the major cause that could affect treatment schedule and the incidence of grade 3 or 4 diarrhea was around 20%[8,9]. In the present study, grade 4 diarrhea did not occur and only one patient (3%) suffered from grade 3 diarrhea that did not necessitate a change of schedule.

The incidence of grade 3 or 4 neutropenia (77%) is still high in this study, and Boku *et al*[8] found the incidence of grade 3 or 4 neutropenia was 89%. Ajani *et al*[9] demonstrated that 37% grade 3 or 4 neutropenia by weekly administration. Sakaki *et al*[16] found a positive correlation between the AUC of irinotecan and the decrease of the white cell count, however, diarrhea has a stronger correlation with the AUC of SN-38 than with that of irinotecan. As this treatment regimen has greater AUC of SN-38 while AUC of irinotecan was same in comparison with 90-min infusion of irinotecan[10], we expected to find more hematological toxicities than diarrhea. To the contrary, we found significantly less common severe diarrhea, and high incidence of grade 3 or 4 neutropenia that was comparable to the previous Japanese trial[8]. The target dose of irinotecan for this study ($60 \text{ mg/m}^2 \times 2$) was lower than that used by Boku ($70 \text{ mg/m}^2 \times 2$)[8] or that used to treat lung cancer ($60 \text{ mg/m}^2 \times 3$)[17,18]. Actual dose of CPT-11 administered in the Boku's study was 28.5 mg/m^2 per week, and that in our study was 25.7 mg/m^2 per week, so our regimen seemed to reduce the incidence and grade of diarrhea while achieving a similar response rate with a lower dose of irinotecan.

Nausea and renal toxicity is a common problem with cisplatin therapy, so we administered a low dose of 10 mg/m^2 on six occasions to achieve a total dose of 60 mg/m^2. Grade 3 nausea occurred in 3 patients (10%) and there

was no grade 4 nausea. Low-dose, repeated administration has already been reported to decrease the incidence and grade of nausea due to cisplatin[19-22]. Some Japanese authors have reported that repeated cisplatin administration at a low dose reduces the incidence of nausea and allows outpatient treatment, and that this method achieves a high response rate and longer survival when combined with irinotecan without the need for 24-h infusion of the latter drug[9,23-25]. As for renal toxicity, Boku *et al* with high-dose cisplatin administration[8] found grade 1 or 2 serum creatinine increase in 23 and 11 % of patients, respectively. We found only grade 1 abnormality, and the incidence of 26%, demonstrating that renal toxicity with this regimen is minimal. As hydration is not required to prevent renal toxicity with low-dose therapy[20], continuous infusions are not necessary after finishing irinotecan administration on d 2, 3, 16, and 17.

In order to complete this regimen, hospitalization is required to receive 24-h irinotecan infusions and 6 divided dose of cisplatin. Therefore, this regimen is not applicable for out-patient basis; however, as the incidence of fatigue of this regimen was 10% (only grade 1), severe diarrhea was rare, and hydration was not necessary, it is possible to treat patients on an out-patient basis between infusions. Ajani et al demonstrated very high incidence (41%) of grade 3 or 4 fatigue with weekly irinotecan and cisplatin administration, and they discussed cisplatin might contribute to excessive fatigue, thus either the dose of cisplatin might be reduced, or cisplatin might be replaced by other agents. Our results with 10% grade 1 fatigue suggested that low dose cisplatin is a practical alternative for reducing the fatigue.

In conclusion, though hospitalization is required at this time, 24-h infusion of irinotecan combined with a low-dose, repeated administration of cisplatin achieved a high response rate and prolonged the survival of patients with metastatic gastric cancer. This regimen also reduces non-hematologic adverse reactions and thus shortens the time in hospital.

REFERENCES

1   **Cullinan SA**, Moertel CG, Wieand HS, O'Connell MJ, Poon MA, Krook JE, Mailliard JA, Tschetter LK. Controlled evaluation of three drug combination regimens versus fluorouracil alone for the therapy of advanced gastric cancer. North Central Cancer Treatment Group. *J Clin Oncol* 1994; **12**: 412-416

2   **Kim NK**, Park YS, Heo DS, Suh C, Kim SY, Park KC, Kang YK, Shin DB, Kim HT, Kim HJ. A phase III randomized study of 5-fluorouracil and cisplatin versus 5-fluorouracil, doxorubicin, and mitomycin C versus 5-fluorouracil alone in the treatment of advanced gastric cancer. *Cancer* 1993; **71**: 3813-3818

3   **Ohtsu A**, Shimada Y, Shirao K, Boku N, Hyodo I, Saito H, Yamamichi N, Miyata Y, Ikeda N, Yamamoto S, Fukuda H, Yoshida S. Randomized phase III trial of fluorouracil alone versus fluorouracil plus cisplatin versus uracil and tegafur plus mitomycin in patients with unresectable, advanced gastric cancer: The Japan Clinical Oncology Group Study (JCOG9205). *J Clin Oncol* 2003; **21**: 54-59

4   **Ohtsu A**. Current status and future prospects of chemotherapy for metastatic gastric cancer: a review. *Gastric Cancer* 2005; **8**: 95-102

5   **Kunimoto T**, Nitta K, Tanaka T, Uehara N, Baba H, Takeuchi M, Yokokura T, Sawada S, Miyasaka T, Mutai M. Antitumor activity of a new camptothecin derivative, SN-22, against

various murine tumors. *J Pharmacobiodyn* 1987; **10**: 148-151

6   **Futatsuki K**, Wakui A, Nakao I, Sakata Y, Kambe M, Shimada Y, Yoshino M, Taguchi T, Ogawa N. Late phase II study of irinotecan hydrochloride (CPT-11) in advanced gastric cancer. CPT-11 Gastrointestinal Cancer Study Group. *Gan To Kagaku Ryoho* 1994; **21**: 1033-1038

7   **Shirao K**, Shimada Y, Kondo H, Saito D, Yamao T, Ono H, Yokoyama T, Fukuda H, Oka M, Watanabe Y, Ohtsu A, Boku N, Fujii T, Oda Y, Muro K, Yoshida S. Phase I-II study of irinotecan hydrochloride combined with cisplatin in patients with advanced gastric cancer. *J Clin Oncol* 1997; **15**: 921-927

8   **Boku N**, Ohtsu A, Shimada Y, Shirao K, Seki S, Saito H, Sakata Y, Hyodo I. Phase II study of a combination of irinotecan and cisplatin against metastatic gastric cancer. *J Clin Oncol* 1999; **17**: 319-323

9   **Ajani JA**, Baker J, Pisters PW, Ho L, Mansfield PF, Feig BW, Charnsangavej C. CPT-11 plus cisplatin in patients with advanced, untreated gastric or gastroesophageal junction carcinoma: results of a phase II study. *Cancer* 2002; **94**: 641-646

10   **Fujitani K**, Tsujinaka T, Hirao M. Pharmacokinetic study of two infusion schedules of irinotecan combined with cisplatin in patients with advanced gastric cancer. *Oncology* 2003; **64**: 111-115

11   **Lacave AJ**, Izarzugaza I, Anton Aparicio LM, Valle Pereda M, Gracia Marco JM, Buesa JM. Phase II clinical trial of cis-dichlorodiammineplatinum in gastric cancer. *Am J Clin Oncol* 1983; **6**: 35-38

12   **Rothenberg ML**, Kuhn JG, Burris HA 3rd, Nelson J, Eckardt JR, Tristan-Morales M, Hilsenbeck SG, Weiss GR, Smith LS, Rodriguez GI. Phase I and pharmacokinetic trial of weekly CPT-11. *J Clin Oncol* 1993; **11**: 2194-2204

13   **de Forni M**, Bugat R, Chabot GG, Culine S, Extra JM, Gouyette A, Madelaine I, Marty ME, Mathieu-Boue A. Phase I and pharmacokinetic study of the camptothecin derivative irinotecan, administered on a weekly schedule in cancer patients. *Cancer Res* 1994; **54**: 4347-4354

14   **Rowinsky EK**, Grochow LB, Ettinger DS, Sartorius SE, Lubejko BG, Chen TL, Rock MK, Donehower RC. Phase I and pharmacological study of the novel topoisomerase I inhibitor 7-ethyl-10-[4-(1-piperidino)-1-piperidino]carbonyloxycamptothecin (CPT-11) administered as a ninety-minute infusion every 3 weeks. *Cancer Res* 1994; **54**: 427-436

15   **Abigerges D**, Chabot GG, Armand JP, Herait P, Gouyette A, Gandia D. Phase I and pharmacologic studies of the camptothecin analog irinotecan administered every 3 weeks in cancer patients. *J Clin Oncol* 1995; **13**: 210-221

16   **Sasaki Y**, Yoshida Y, Sudoh K, Hakusui H, Fujii H, Ohtsu T, Wakita H, Igarashi T, Itoh K. Pharmacological correlation between total drug concentration and lactones of CPT-11 and SN-38 in patients treated with CPT-11. *Jpn J Cancer Res* 1995; **86**: 111-116

17   **Negoro S**, Fukuoka M, Masuda N, Takada M, Kusunoki Y, Matsui K, Takifuji N, Kudoh S, Niitani H, Taguchi T. Phase I study of weekly intravenous infusions of CPT-11, a new derivative of camptothecin, in the treatment of advanced non-small-cell lung cancer. *J Natl Cancer Inst* 1991; **83**: 1164-1168

18   **Fukuda M**, Nishio K, Kanzawa F, Ogasawara H, Ishida T, Arioka H, Bojanowski K, Oka M, Saijo N. Synergism between cisplatin and topoisomerase I inhibitors, NB-506 and SN-38, in human small cell lung cancer cells. *Cancer Res* 1996; **56**: 789-793

19   **Kobayashi K**, Kudoh S, Takemoto T, Hino M, Hayashihara K, Nakahiro K, Ando M, Niitani H. In vitro investigation of a combination of two drugs, cisplatin and carboplatin, as a function of the area under the c/t curve. *J Cancer Res Clin Oncol* 1995; **121**: 715-720

20   **Kurihara N**, Kubota T, Hoshiya Y, Otani Y, Ando N, Kumai K, Kitajima M. Pharmacokinetics of cis-diamminedichloroplatinum (II) given as low-dose and high-dose infusions. *J Surg Oncol* 1996; **62**: 135-138

21   **Schellens JH**, Ma J, Planting AS, van der Burg ME, van Meerten E, de Boer-Dennert M, Schmitz PI, Stoter G, Verweij J. Relationship between the exposure to cisplatin, DNA-adduct formation in leucocytes and tumour response in patients with solid tumours. *Br J Cancer* 1996; **73**: 1569-1575

22   **Ikeda K**, Terashima M, Kawamura H, Takiyama I, Koeda K, Takagane A, Sato N, Ishida K, Iwaya T, Maesawa C, Yoshinari H, Saito K. Pharmacokinetics of cisplatin in combined cisplatin and 5-fluorouracil therapy: a comparative study of three different schedules of cisplatin administration. *Jpn J Clin Oncol* 1998; **28**: 168-175

23   **Sato A**, Kurihara M, Matsukawa M, Shimada K, Yamazaki T, Nakamachi M, Koda T. Preliminary study of fortnightly irinotecan hydrochloride plus cisplatin therapy in patients with advanced gastric and colorectal cancer. *Cancer Chemother Pharmacol* 2001; **47**: 380-384

24   **Ajani JA**, Baker J, Pisters PW, Ho L, Feig B, Mansfield PF. Irinotecan plus cisplatin in advanced gastric or gastroesophageal junction carcinoma. *Oncology* (Williston Park) 2001; **15**: 52-54

25   **Shimada S**, Yagi Y, Kuramoto M, Aoki N, Ogawa M. Second-line chemotherapy with combined irinotecan and low-dose cisplatin for patients with metastatic gastric carcinoma resistant to 5-fluorouracil. *Oncol Rep* 2003; **10**: 687-691

S- Editor Pan BR   **L- Editor** Ma JY   **E- Editor** Liu WF