A Phase II Study of Irinotecan in Combination with Cisplatin as Second-line Chemotherapy in Patients with Metastatic or Locally Advanced Gastric Cancer

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Background: Gastric cancer remains one of the leading causes of cancer death worldwide. Currently, no standard secondary-line chemotherapy for locally advanced or metastatic gastric cancer is recommended. The aim of this study is to demonstrate and confirm the overall objective response rate to irinotecan plus cisplatin for previously treated patients with metastatic or locally advanced gastric cancer in Taiwan.

Methods: Patients in this study had been diagnosed with gastric adenocarcinoma with evidence of advanced disease and had failure of first line chemotherapy or documented disease progression while receiving adjuvant chemotherapy. Patients had good Eastern Cooperative Oncology Group performance status and adequate hematologic, renal and liver function. Patients received irinotecan 60 mg/m^2 followed by cisplatin 30 mg/m^2 on days 1 and 8, every 3 weeks. Treatment was administered until disease progression, intolerable toxicity or consent withdrawal. Evaluation was conducted every two cycles using the Response Evaluation Criteria in Solid Tumors. The toxicity was recorded by National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0, year 2003.

Results: From January 2007 to December 2008, 24 patients were enrolled. Their median age was 54 years (range 30 to 77 years). Fifteen patients (63%) were men. Five patients (21%) achieved partial response, while ten patients (42%) remained stable. The median progression-free survival was 109 days and median overall survival was 222 days. The major grade 3/4 toxicities were neutropenia (20.9%) and diarrhea (8.3%).

Conclusions: Second-line chemotherapy with irinotecan and cisplatin for advanced gastric cancer is effective and has acceptable toxicity.

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Gastric cancer remains one of the leading causes of cancer death worldwide.[1] In Taiwan, gastric cancer, which ranks fifth for cancer-related mortality among the major types of cancer malignancies, is

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responsible for approximately 2,400 deaths per year.[2] Randomized trials have proved that palliative chemotherapy has survival benefits over best supportive care for metastatic gastric cancer.[3] Palliative chemotherapy can prolong survival to 9-11 months, compared with 3-5 months in patients treated with best supportive care. Active chemotherapeutic agents in first line therapy for advanced gastric cancer include fluorouracil, cisplatin, and the anthracyclines.[3,4] New generation agents, including the taxanes group, ironotecan and oxaliplatin, have shown activity in treating gastric cancer.[4,5] The response rate of the above-mentioned single agent is around 10 to 25%. However, most tumors develop rapid drug resistance with disease progression within months. At this stage, no data from randomized-controlled trials suggest a benefit of second-line chemotherapy compared with supportive care alone.[6] Many drugs have been tested as second-line chemotherapy for advanced gastric cancer and have been shown to have activity. These include fluorouracil, docetaxel, S-1, cisplatin, irinotecan, mitomycin, methotrexate,vindesine, and bleomycin.[6]

Irinotecan (CPT-11), 7-ethyl-10-[4-(10piperidino)-1-piperidino] carboxy camptothecin, is a semisynthetic derivative of the compound camptothecin, which is derived from *Camptotheca acuminata*. Camptothecin and its analogues/derivatives appear to exert their antitumor activity by binding to topoisomerase I.[7] Irinotecan has been shown to have activity in gastrointestinal cancers and is used in a second-line setting for metastatic colon cancer, either alone or in combination with other agents (e.g. fluorouracil, bevacizumab, or cetuximab).[8,9] Based on data on the use of irinotecan for metastatic colon cancer, the efficacy and safety of irinotecan in second-line therapy for advanced gastric cancer has been studied since the early 1990's. Futatsuki et al. completed a phase II study of 60 evaluable patients treated with irinotecan 100 mg/m^2 weekly or 150 mg/m^2 biweekly.[10] The response rate (RR) in patients with prior chemotherapy was 16.1%. The grade III/IV toxicities were primarily leukopenia (41%), anemia (29%), diarrhea (22%), and anorexia (20%). In addition, Chun et al. studied 37 patients with failed cisplatin-based chemotherapy for metastatic gastric cancer who received irinotecan 125 mg/m^2 weekly for 4 weeks followed by a 2-week rest.[11] The RR was 20%, median progression free survival (PFS) was 2.6 months and median overall survival (OS) was 5.2 months.

Irinotecan has also been combined with cisplatin as a first -line treatment for advanced gastric cancer.[12,13] A phase I-II study of irinotecan combined with cisplatin in patients with advanced gastric cancer was conducted in Japan.[12] The major dose-limiting toxicity was neutropenia. Ten patients achieved a partial response (PR), and the overall response rate (ORR) was 41.7% among 24 patients (95% confidence interval, 21.9% to 61.4%). Another phase II study conducted by Ajani et al. for advanced, untreated gastric or gastroesophageal junction carcinoma showed that a combination of irinotecan 65 mg/m^2/weekly and cisplatin 30 mg/m^2/weekly for four consecutive weeks, with a break of two weeks achieved an ORR of 58% and a median survival of nine months.[13] The major toxicities were grade 3/4 diarrhea (22%), neutropenia (27%), fatigue (41%) and nausea (16%). Fifty-three out of 79 patients had cancellation or delay of weekly doses (66%) in the third or fourth week of the treatment cycle. That study found a combination of irinotecan and cisplatin is active against gastric or gastroesophageal adenocarcinoma and needs to be studied further. A modification in doses and schedules may be warranted to make the regimen more tolerable for patients. Herein, we modified irinotecan to 60 mg/m^2 and cisplatin 30 mg/m^2 on days 1 and 8, every 3 weeks for further second line chemotherapy for advanced gastric cancer patients. We aimed to demonstrate and confirm the clinical efficacy and tolerability of this modified schedule of irinotecan and cisplatin as a second-line therapy for previously treated patients with advanced gastric cancer.

METHODS

Eligibility

The primary end point of this study was to evaluate the ORR of irinotecan plus cisplatin for previously treated patients with metastatic or locally advanced gastric cancer. The secondary end point of this study was to evaluate the PFS, duration of response, OS, toxicity and tolerability. This was a prospective, open-labeled, non-randomized phase II study. Patients who had pathologically confirmed, measurable gastric adenocarcinoma which was defined as at least one lesion that can be measured in

at least 1 dimension as ≥ 20 mm with a conventional technique or ≥ 10 mm with spiral computed tomography (CT) and met the following criteria were enrolled: progression or recurrence after a chemotherapeutic regimen for metastatic disease or within six months of the last dose of adjuvant therapy; Eastern Cooperative Oncology Group performance status of 0, 1, or 2; age ≥ 20 years; absolute neutrophil count ≥ 1,500 cells/μL, platelet count ≥ 100,000 cells/μL; bilirubin < 2 x upper normal limit (UNL); aspartate aminotransferase < 2.5 x UNL and creatinine ≤ 1.5 x UNL. This study protocol was approved by the Institutional Review Board of Chang Gung Memorial Hospital and written informed consent was obtained from all participants.

Pretreatment evaluation

A complete medical history and physical examination, including vital signs, height, weight and assessment of performance status were obtained within two weeks before study registration. Radiographs used to establish measurable disease were completed within four weeks before registration. Blood count and the results of biochemisty tests were obtained within two weeks before registration. Prior to entry into this study, a hepatitis B surface antigen test and anti-hepatitis C antibody test were performed to clarify whether the patient was a hepatitis B or C carrier. If the result was positive, appropriate treatment was recommended.

Treatment

All patients received irinotecan (Irino@, TTY Biopharm Company, Taipei, Taiwan) 60 mg/m^2 as a 90-minute intravenous (i.v.) infusion followed by a cisplatin 30 mg/m^2 60-minutes i.v. infusion on days 1 and 8, every three weeks. Prior to chemotherapy, patients received an antiemetic, a 5-HT3 receptor antagonist, and steroids to prevent vomiting as well as atropine 0.25 mg subcutaneously to prevent irinotecan-related cholinergic effects. This treatment schedule was repeated every three weeks and treatment was administered until disease progression, intolerable toxicity, consent withdrawal or investigators' determination to end participation in the study. Dose reductions were made for objective or subjective toxicities. A maximum of one dose reduction was allowed per patient if there was more than grade III non-hematologic toxicity. In cases of grade III neutropenia, prophylactic granulocyte-colony stimulating factor was given during the following cycles of treatment. If patients did not recover from grade 3/4 toxicity within two weeks, they were withdrawn from the study. Delayed diarrhea, generally occurring more than 24 hours after administration of irinotecan, was treated promptly with loperamide. Administration of irinotecan was omitted on day 8 if diarrhea was still present.

Response and toxicity evaluation

Clinical assessment of the patient's disease (i.e., by physical examination), including blood counts, biochemistry results, and side effects, were performed before each treatment cycle. Indicator lesions were selected and measured periodically. All measurable lesions were measured by CT scan every six weeks. The response was evaluated by Response Evaluation Criteria in Solid Tumors (Version 1.0). All measurable lesions (up to a maximum of five lesions per organ and 10 lesions in total, representative of all involved organs) were selected on the basis of their size (those with the longest diameter). A sum of the longest diameters of all target lesions was calculated and reported as the baseline sum longest diameter. A complete response (CR) was defined as disappearance of all known disease. A PR was defined as a decrease of at least 30% in the sum of the products of the largest perpendicular diameters of all measurable lesions with none progressing and no new lesions appearing. Stable disease (SD) was defined as less than a 30% decrease and less than a 20% increase in the sum of the products of the largest perpendicular diameters of all measurable lesions. Progressive disease (PD) was defined as a greater than 20% increase in the size of the sum of the longest lesions or the appearance of a new lesion. Time to disease progression was defined as the interval between the date of enrollment (i.e., the date of registration) and the date of disease progression or the date that other antitumor therapy was started. OS was defined as the interval between the date of enrollment (i.e., the date of registration) and the date of death. The last date of contact was used for patients who could not be followed up. All efficacy analyses were based on the intent-to-treat and evaluable population. All patients who received at least one dose of any study drug underwent safety analyses. Toxicities were graded using the National

Cancer Institute Common Terminology Criteria for Adverse Events version 3.0. 2003.[14]

Statistical consideration

The sample size was calculated by Simon's optimal two-stage design. Based on previous data from Korea,[11] a response rate of approximately 20% is assumed for irinotecan- based chemotherapy in second-line therapy for metastatic gastric cancer patients. Using this approach, we tested a null hypothesis that the true-response probability would be less than an insignificant level (p_1) of 0.25 against the alternative hypothesis that the true response probability was at least as great as a target level (p_0) of 0.05. Response probabilities less than 5% would be considered inactive while response probabilities greater than 25% would be considered effective. Considering a design with $p_0 = 0.05$ and $p_1 = 0.25$, for which the α and β margin of error are both 0.1, these constraints could be met with a two-stage Simon's design of nine evaluable patients in the first stage and 15 evaluable patients in the second stage. The total evaluable patients for stage I and II was 24. If the dropout rate was assumed to be 15%, this would mean 29 patients in total were needed. If no responder was observed among the initial nine evaluable patients, then the clinical trial was to be terminated. If one or more responders were observed in the initial stage, the trial would proceed to stage II and an additional 15 patients would be recruited for stage II. If there were three or more responders in the total 24 evaluable patients, the regimen would be considered efficacious. Otherwise, the regimen would be considered inefficacious. Time to disease progression and OS were estimated using the Kaplan-Meier method. Incidence and type of adverse experiences were tabulated and summarized using descriptive statistics.

RESULTS

Patient characteristics

From January 2007 to December 2008, 24 patients with gastric adenocarcinoma with evidence of metastatic disease or locally advanced disease were enrolled. There were fifteen men and nine women with a median age of 54 years (range 30-77 years). Two patients had locally advanced disease, while 22 patients had metastatic disease. Two patients relapsed during adjuvant chemotherapy and 22 patients had failure from first line chemotherapy for metastatic gastric cancer. Baseline characteristics of the patients are listed in Table 1.

Efficacy

Responses could be assessed in 24 patients. However, one patient who showed a PR after two cycles of treatment was withdrawn from the study

Table 1. Patient Characteristics (n = 24)

Performance status (ECOG)	
0	5 (21%)
1	15 (62%)
2	4 (17%)
Gender: F/M	9 (37%) /15 (63%)
Age years median (range)	54 (30-77)
Prior chemotherapy	
Failure within 6 months of last dose adjuvant chemotherapy	2
Failure form 1st line chemotherapy for metastatic gastric cancer.	22
Surgery (gastrectomy)	
Yes	11
No	13
Pevious chemotherapy regimen	
Failure within 6 months of last dose adjuvant chemotherapy	
UFT	1
Weekly fluorouracil/LV	1
Failure from 1st line chemotherapy for metastatic gastric cancer	
Weekly fluorouracil/LV	3
Fluorouracil/Cisplatin/Mitomycin-C	4
Pemetrexed/Cisplatin	2
Oxaliplatin/UFT/LV	5
S-1	2
Fluorouracil/Cisplatin	1
Oxaliplatin/Docetaxel	5

Abbreviations: ECOG: Eastern Cooperative Oncology Group; UFT: tegafur-uracil; LV: leucovorin.

because of severe adverse events without confirming the response. Five patients achieved PR, ten patients had SD, and eight patients' disease PD. after treatment. Intent-to-treat analysis showed that the objective RR was 21% (5/24) (95% confidence interval [CI], 7.1%-42.2%). A mean 4.6 cycles of chemotherapy were given (95% confidence interval [CI] 3.4-5.96). The median PFS was 109 days (95% CI 91-149 days) (Figure A). The median OS was 222 days (95% CI 164-374 days) (Figure B). The one-year survival rate was 41.8%. Reasons for withdraw from this study included disease progression (n = 14), intolerable adverse events (n = 2), withdrawal of informed consent (n = 1), and investigator's discretion (n = 7). Among the latter 7 patients, 4 patients completed at least 6 cycles of chemotherapy and had minimal residual disease, 1 patient could not tolerate this regimen, but did not meet adverse event withdraw criteria. 1 patient had a port-A infection, and 1 patient had clinically suspected PD which could not be confirmed by image study.

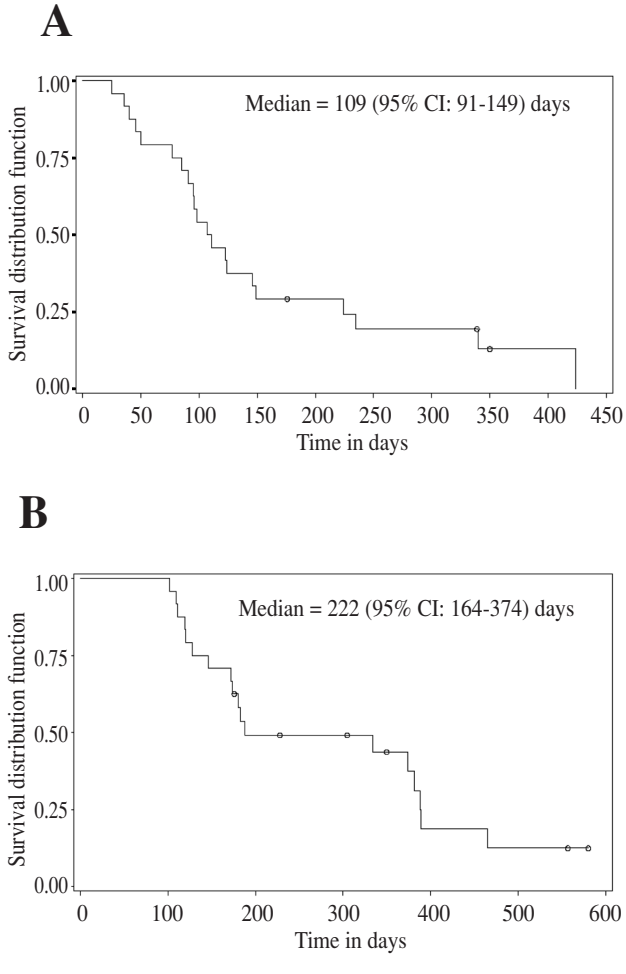

Figure (A) Kaplan-Meier plot for progression free survival of all patients. (B) Kaplan-Meier plot for overall survival of all patients.

Adverse events

Toxicity could be assessed in 24 patients. Only one patient had neutropenic fever. Grade III and IV neutropenia was observed in four (16.7%) and one (4.2%) patient(s), respectively. One patient had grade III thrombocytopenia. The major grade III/IV non-hematologic toxicities included diarrhea (8.3%), anorexia (4.2%), nausea (4.2%), vomiting (8.3%) and fatigue (8.3%). Toxicities observed during the treatment are listed in Table 2.

DISCUSSION

In this study, the intent to treat RR was 21% and PFS was 3.6 months. The OS was 7.4 months. Therefore, a combination regimen of irinotecan 60 mg/m^2 and cisplatin 30 mg/m^2 weekly on days 1 and 8, every 3 weeks as second-line chemotherapy for advanced gastric cancer was feasible. In addition, only 4.2% of patients had grade IV neutropenia and 8.3% had grade III/IV diarrhea. The side effects of our modified irinotecan-cisplatin combination regimen were more acceptable and manageable than those in a previous phase II study by Ajani et al.[13]

There have been several studies of the irinotecan-cisplatin combination regimen as second line therapy for advanced gastric cancer. Boku et al. studied 44 patients who received palliative chemotherapy with irinotecan 70 mg/m^2 and cisplatin 80 mg/m^2 every two weeks for advanced gastric cancer.[15] Fifteen of those 44 patients who had received first-line palliative chemotherapy for advanced gastric cancer, had an RR of 27%. But, the dose of irinotecan – cisplatin, which was higher than in our regimen, resulted in grade 4 neutropenia in 57% of patients and grade 3/4 diarrhea in 20%. Koizumi et al. studied 40 patients who received irinotecan 60 mg/m^2 and cisplatin 30 mg/m^2 biweekly for advanced gastric cancer,[16] which was quite similar to our regimen. The RR in the 25 patients who had received prior chemotherapy was 20.0%. Grade 3/4 neutropenia occurred in 40% of patients and grade 3

Table 2. Incidence of Adverse Events (n = 24)

Toxicity	NCI Common toxicity criteria grade				G3 & G4
	Grade 1	Grade 2	Grade 3	Grade 4	
Hematologic					
Anemia	3 (12.5%)	10 (41.7%)	9 (37.5%)	0	9 (37.5%)
Leucopenia	9 (37.5%)	10 (41.7%)	2 (8.3%)	0	2 (8.3%)
Neutropenia	1 (4.2%)	11 (45.8%)	4 (16.7%)	1 (4.2%)	5 (20.9%)
Thrombocytopenia	11 (45.8%)	2 (8.3%)	1 (4.2%)	0 (4.2%)	1
Non-hematologic					
Anorexia	9 (37.5%)	7 (29.2%)	1 (4.2%)	0	1 (4.2%)
Diarrhea	12 (50.0%)	6 (25.0%)	2 (8.3%)	0	2 (8.3%)
Nausea	6 (25.0%)	9 (37.5%)	1 (4.2%)	0	1 (4.2%)
Vomiting	4 (16.7%)	8 (33.3%)	2 (8.3%)	0	2 (8.3%)
Pain	9 (37.5%)	6 (25.0%)	1 (4.2%)	0	1 (4.2%)
Fatigue	9 (37.5%)	9 (37.5%)	1 (4.2%)	1 (4.2%)	2 (8.3%)

diarrhea in only 2.5%. The efficacy and toxicity were quite similar to those in our study.

Imamura et al. studied 31 patients who received irinotecan 60 mg/m^2 on day 1 and 15 by 24 hr infusion and low dose cisplatin 10 mg/m^2 on days 1, 2, 3, 15, 16 and 17 every four weeks.[17] The RRs for all 31 patients, the 20 patients without prior chemotherapy and the 11 patients with prior chemotherapy were 52%, 60% and 36%, respectively. Grade 3/4 diarrhea and nausea occurred in 3% and 10% of patients, respectively. Grade 4 neutropenia occurred in 35% of patients. The efficacy and toxicity is that study were similar to our results, despite the different schedule for irinotecan and cisplatin. Recently, Takahari et al. studied 87 patients with advanced gastric cancer after failureof S-1 therapy who received twice weekly irinotecan (70 mg/m^2) plus cisplatin (80 mg/m^2) as second-line chemotherapy.[18] Two patients had CR and 18 had PR. The ORR was 28.6% (95% CI, 18.4%-40.6%). The median time to progression and median survival time were 4.3 months and 9.4 months, respectively. Grade 3/4 neutropenia, anemia and thrombocytopenia were observed in 40%, 28% and 8% of patients, respectively. Grade 3/4 non-hematologic toxicities including anorexia, diarrhea, fatigue and nausea were observed in 17%, 6%, 5% and 2% of patients, respectively. The survival and RR were better than in our study, which could be attributed to the higher dose of cisplatin, but toxicity was also observed more frequently than in our study.

In our study, most patients had failure after fluorouracil or cisplatin. Assersohn et al. reported 38 patients who received irinotecan 180 mg/m^2 with fluorouracil 400 mg/m^2 i.v bolus and leucovorin 125 mg/m^2 followed by a fluorouracil 1200 mg/m^2 infusion over 48 hours every two weeks for primary refractory or relapsed advanced esophageal and gastric carcinoma.[19] The overall RR was 29%. The median failure-free survival was 3.7 months and median OS was 6.4 months. The authors concluded that fluorouracil/irinotecan is a valuable regimen for second-line treatment in fluorouracil/platinum-resistant esophageal and gastric cancer. In addition, Chun et al. studied 37 patients who received irinotecan for failed cisplatin-based chemotherapy for metastatic gastric cancer.[11] The RR was 20%, median PFS was 2.6 months and median OS was 5.2 months.

Based on the literature and our results (Table 3), irinotecan-based therapy as second line chemotherapy in patients with advanced gastric cancer is feasible even after failure of fluorouracil or cisplatin. The results of this study provide evidence for further clinical practice using this regimen in the second-line treatment of advanced gastric cancer in Taiwan. However, this combination regimen requires further phase III study to evaluate its clinical utility.

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Table 3. Studies of Irinotecan-based Second-line Chemotherapy for Gastric Cancer

	N	Regimen	Response rate (%)	PFS† (months)	OS‡ (months)	Grade 3/4 hematologic toxicity (%)				Grade 3/4 non-hematologic toxicity (%)					
						WBC	Neutrophil	Anemia	Platelet	Nausea	Vomiting	Diarrhea	Mucositis	Liver	Renal
Boku[15]	15	Irinotecan 70 mg/m² d1, d8, cisplatin 80 mg/m² d1 every 3 weeks	27	NA§	NA	57	88.6	56.8	11.4	18.2	0	20.5	–	7	0
Koizumi[16]	25	Irinotecan 60 mg/m² cisplatin 30 mg/m² every 2 weeks	20	NA	9.1	27.5	40	30	5.0	0	0	2.5	–	5	–
Takahari[18]	87	Irinotecan 70 mg/m², cisplatin 80 mg/m² every 2 weeks	28.6	4.3	9.4	–	40	28	8	2	–	6	–	–	–
Imamura[17]	11	Irinotecan 60 mg/m² d1, d15, cisplatin 10 mg/m² d1, 2, 3, 15, 16, 17 every 4 weeks	36	NA	NA	36	77	29	6	10	–	3	–	–	–
Assersohn[19]	37	Irinotecan 180 mg/m², leucoverin 125 mg/m² IV, 5-FU*400 mg/m² IV, 5-FU 1200 mg/m² IVF for 2 days every 2 weeks	29	3.7	6.2	–	26.4	13.2	0	–	13.2	7.9	2.6	–	–
Chun[11]	38	Irinotecan 125 mg/m²/weekly for 4 weeks, rest 2 weeks	20	2.6	5.4	45.9	67.6	56.8	8.1	–	18.9	18.9	5.4	10.8	–
CGMH	24	Irinotecan 60 mg/m², d1, d8 cisplatin 30 mg/m² d1, d8 every 3 weeks	21	3.6	7.4	8.3	20.9	37.5	4.2	4.2	8.3	8.3	0	8.3	0

*: 5-FU: flurouracil; †: Progression free survival; ‡: Overall survival; §: No analyses.

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合併 Irinotecan 及 Cisplatin 用於第二線晚期胃癌病患第二期臨床試驗

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背 景： 胃癌爲常見癌症死因之一。然而對於晚期胃癌的第二線治療並無準則可依循。此研究的目的，即是要評估以 irinotecan (益立諾) 及 cisplatin (鉑金) 合併用藥對於晚期胃癌的第二線治療反應率。

方 法： 納入此臨床試驗的病人需確定爲晚期胃腺癌，也需曾接受過一線化學治療，且病人之血球、肝、腎功能需達到標準。病人納入試驗後，會於每療程的第一天及第八天接受 irinotecan 60 mg/m^2 及 cisplatin 30 mg/m^2 的治療。每三週爲一個療程。若病人疾病惡化，副作用太大，或病人不願意再接受治療即退出此臨床試驗。

結 果： 從 2007 年一月至 2008 年十二月，總共有二十四位病人納入。五位病患達到部份緩解，十位病患疾病穩定。中位疾病惡化期 109 天，中位存活期 222 天。第三級及第四級血液毒性發生率爲 20.9%，第三級及第四級腸胃道毒性發生率爲 8.3%。

結 論： 根據本研究結果，以益立諾及鉑金合併用藥對於晚期胃癌的第二線治療反應率不錯，且副作用也可接受。

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關鍵詞： 胃癌，化學治療，益立諾，鉑金

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