A Pilot Study of Cisplatin, Irinotecan, Leucovorin and 5-fluorouracil (PILF) Combination Chemotherapy for Advanced Gastric Cancer

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Purpose: Irinotecan, in combination with leucovorin/5-fluorouracil (FU) or with cisplatin, is known to be active for treating advanced gastric cancer (AGC). This pilot study evaluated a novel three-drug combination of irinotecan, leucovorin/FU and cisplatin as a first-line treatment of AGC. The primary endpoint was to assess the feasibility in anticipation of conducting a larger phase II study.

Materials and Methods: Chemotherapy-naïve AGC patients received irinotecan 150 mg/m² on day 1, and leucovorin 200 mg/m² and a 22-h infusion of FU 1000 mg/m² on days 1 and 2. Cisplatin 30 mg/m² was administered on day 2. Treatment was repeated every 2 weeks until disease progression or unacceptable toxicity.

Results: Of the 17 eligible patients, two patients had an ECOG performance status of 2 and their median age was 48 years (range: 31 to 69). A total of 117 chemotherapy cycles were delivered (median: 6, range: 1 to

12). The causes of treatment discontinuation were disease progression in 9 patients (53%), refusal (35%) and toxicity (12%). Although grade 3 or 4 neutropenia (41% of patients) was the major toxicity that required dose adjustments, only one episode of febrile neutropenia occurred. Grade 3 or 4 nausea and vomiting, diarrhea and fatigue were observed in 35%, 35% and 29% of patients, respectively. None of the patients died of toxicity during treatment. Of the 16 patients who were evaluable for response, 7 (44%) experienced a partial response.

Conclusion: This novel multi-drug combination was tolerated well in patients with AGC. Based on the encouraging efficacy and tolerability, a randomized phase II study is ongoing in this disease setting. (*Cancer Res Treat. 2006;38:121-125*)

Key Words: Stomach neoplasm, Irinotecan, 5-fluorouracil, Cisplatin

INTRODUCTION

Gastric cancer is the most frequently occurring malignancy in Korea, and it is one of the main causes of cancer death (1). The benefit of systemic chemotherapy for advanced gastric cancer (AGC) in the palliative setting has long been known. Several randomized trials have demonstrated that 5-fluorouracil (FU)-based chemotherapy is superior to the best supportive care in terms of survival and preservation of the quality of life (2,3). While the treatment options for AGC have expanded in recent years to include newer agents such as taxanes (paclitaxel and

docetaxel), irinotecan and oxaliplatin, FU remains the backbone of most of the current chemotherapy protocols (4,5).

In general, multi-drug combinations have provided significantly higher response rates, but no better overall survival (6). However, combination regimens that are mostly FU-based have been widely used in most countries because FU monotherapy has only limited activity. To date, only two triplet combinations, namely ECF (epirubicin, cisplatin and FU) and DCF (docetaxel, cisplatin and FU), have demonstrated survival benefit for the patients with AGC (7,8). However, the obtained median survival times were limited to within 10 months.

Irinotecan is a water-soluble camptothecin derivative, and it has demonstrated antitumor activity against gastric cancer as a monotherapy (9), and in combination with leucovorin/FU (ILF) (10), or cisplatin (IP) (11). A previous randomized study of an ILF regimen versus IP for patients with AGC showed that ILF produced an overall response rate of 42% and a median survival of 10.7 months, which were significantly better than the results with the IP regimen (12). However, since cisplatin is still considered to be one of the key drugs for the treatment of gastric cancer, a combination of these three active drugs

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(cisplatin, irinotecan and leucovorin/FU) seems to be a promising strategy for treating advanced AGC. This three-drug combination has been reported to have a promising therapeutic efficacy of 74% to 85% objective response rates (13,14), but this has been achieved at the cost of considerable toxicity (i.e., severe neutropenia in 90% of patients).

Based on these considerations, we adapted a modified regimen of biweekly administered cisplatin, irinotecan and leucovorin/FU (PILF). We conducted a pilot study with this PILF combination on patients with AGC to determine its tolerability and to obtain the feasibility data in anticipation of performing a larger, formal phase II study.

MATERIALS AND METHODS

For this single-center, pilot study, the eligibility criteria included histologically confirmed, recurrent or metastatic gastric adenocarcinoma, patients who were aged 75 years or less, an Eastern Cooperative Oncology Group (ECOG) performance status of 0~2 and normal marrow (a neutrophil count $>1,500/\text{mm}^3$ and a platelet count $>100,000/\text{mm}^3$), hepatic (AST/ALT ≤ 2.5 ULN and bilirubin ≤ 1.5 mg/dl) and renal function (creatinine clearance ≥ 60 ml/min or serum creatinine $\leq$ ULN). No prior chemotherapy or only adjuvant chemotherapy that had been completed >6 months before patient enrollment and no radiotherapy was given within 4 weeks before the study were allowed. Patients were excluded from the study if they had any severe comorbid illness, a known history of anaphylaxis of any origin or a history of severe adverse events to the drugs used in this study. The study protocol was reviewed and approved by the Gil Medical Center institutional review board. We obtained informed consents after the nature of the study was fully discussed before the initiation of treatment, including an explanation of the risk and the possibility of discomfort, as well as the potential benefits.

Treatment consisted of irinotecan 150 mg/m^2 on day 1, leucovorin 200 mg/m^2 and a 22 h infusion of FU $1,000 \text{ mg/m}^2$ on days 1 and 2. Cisplatin 30 mg/m^2 was administered on day 2, along with appropriate iv saline hydration of one liter over 2 hours prior to and again after cisplatin infusion. Treatment was repeated every 2 weeks until disease progression, unacceptable toxicity or patient's refusal. The use of hematopoietic growth factors was not allowed during treatment, except for patients with febrile neutropenia or grade 4 myelosuppression, at the investigators' discretion. No primary prophylaxis with atropine was given unless a patient experienced grade ≥ 2 diarrhea. Supportive care, including administration of blood transfusions, antiemetics and analgesics was provided according to our department policy. If this combination chemotherapy failed, then second-line chemotherapy was recommended to all patients if their performance status was still preserved.

The dosage of the subsequent cycles was adjusted according to the toxic effects that developed during the preceding cycle. Chemotherapy was delayed for a week if the neutrophil count was $<1,500/\text{mm}^3$ or the platelet count was $<100,000/\text{mm}^3$ on day 1. If the nadir neutrophil count was $<500/\text{mm}^3$ or the nadir platelet was $<50,000/\text{mm}^3$, then the doses of irinotecan and FU were reduced to 80% of the initial doses. If grade ≥ 2 non-

hematologic toxicity occurred, then chemotherapy was withheld until the patients recovered to grade ≤ 1 . In the case of diarrhea, patients were treated with loperamide (starting dose: 4 mg, followed by 2 mg every 2 h as long as diarrhea continued to a maximum dose of 16 mg/day). When the diarrhea persisted for more than 24 h or it occurred in combination with neutropenia, fever or dehydration, the patients were hospitalized and treated with antibiotics. The dose of cisplatin could be reduced for a reversible decrease of creatinine clearance. If chemotherapy was delayed >2 weeks, then the patient was treated off the protocol. Throughout the study, the dose of leucovorin was unchanged.

Baseline evaluation included a complete medical history and physical examinations, blood counts, serum chemistry, chest x-ray and abdominopelvic computed tomography (CT) scans. Follow-up history, physical examinations and toxicity assessments were performed before each 2-week cycle of treatment. The toxicity grading was based on the National Cancer Institute criteria (NCI-CTCAE version 3). The first evaluation with imaging was done after the completion of 4 cycles of PILF chemotherapy. The response was evaluated according to the WHO criteria and the response was assessed by abdominopelvic CT or by the same tests that were used to initially stage the tumor. If a patient had no measurable lesions, then the response was only classified as complete response, stable disease or progressive disease. Progression in non-measurable lesions that led to deterioration of the patient's status was classified as progressive disease, regardless of the status of the measurable lesions.

The estimated number of patients for this pilot feasibility study with using the PILF combination was felt to be approximately 14 patients. That is, the evaluation of toxicity was the primary endpoint and myelosuppression, specifically grade 3 or 4 neutropenia, is considered to be the dose limiting toxicity. The sample size was determined based on this focused toxicity endpoint (15). A prior study has demonstrated a 66% rate of grade 3 or 4 neutropenia with IP, and 27% rate with ILF (12). With using dosage modification, we anticipated that the overall rate of grade 3 or 4 neutropenia would be approximately 30%. All analyses were performed on the intent-to-treat population, and this was defined as all registered patients who signed an informed consent.

RESULTS

Among a total of 17 patients who were registered between October 2004 and May 2005, one patient was not evaluable for response due to early discontinuation of treatment. The characteristics of the patients are listed in Table 1. The median age was 48 years (range: 31 to 69 years) and two-thirds of patients had symptomatic (ECOG performance status ≥ 1) AGC. Six patients had been previously treated with adjuvant FU-based chemotherapy and two patients had been previously treated with cisplatin during their adjuvant chemotherapy regimen. The most common sites of metastatic disease were the intra-abdominal lymph nodes, peritoneum and liver.

The patients received a total of 117 PILF cycles (median: 6, range: 1 to 12). Two patients discontinued treatment due to

Table 1. Patient characteristics

No. of patients	17
Age in years	
Median (range)	48 (31 to 69)
Male gender	11
Prior antitumor treatment	
Curative resection of tumor	7
Palliative surgery	5
Adjuvant chemotherapy	6
ECOG performance status*	
0	6
1	9
2	2
Site(s) of metastatic disease [†]	
Abdominal lymph node	14
Peritoneum	10
Liver	8
Lung and/or malignant pleural effusion	1
Ovary	1
Bone	1

*ECOG denotes Eastern Cooperative Oncology Group. [†] Because the patients could have metastases at multiple sites, the total numbers of metastases are greater than the number of patients.

Table 2. Maximum grade toxic effects per patient

	Grade 1 or 2	Grade 3 or 4
Anemia	4	3
Neutropenia	5	7
Thrombocytopenia	4	1
Febrile neutropenia		1
Hepatic	1	0
Renal	1	0
Fatigue	3	5
Peripheral neuropathy	2	2
Emesis	5	6
Stomatitis	7	2
Diarrhea	4	6
Skin	1	0

toxicity, 6 declined further treatment and 9 had progression of disease while receiving PILF chemotherapy. Chemotherapy was delayed in 17 out of the 117 cycles (15%). As dose intensities of cisplatin 15 mg/m²/week, irinotecan 75 mg/m²/week and FU 1,000 mg/m²/week were planned, the relative dose intensities of each drug were 96% (95% confidence interval [CI]: 86 to 105%), 91% (95% CI: 78 to 104%) and 91% (95% CI: 78 to 105%), respectively. The hematologic and non-hematologic toxicities are summarized in Table 2. The most frequently encountered severe toxicities were neutropenia and gastrointestinal toxicity, which were managed with rest, a dose reduction or treatment discontinuation. Although grade 3 or 4 neutropenia was the major toxicity that required dose adjust-

Fig. 1. Progression-free survival and overall survival.

ments (41% of the patients), only one episode of febrile neutropenia occurred. None of the patient died of toxicity during the PILF chemotherapy.

We offered salvage chemotherapy to 13 patients after failure. The second-line treatment after PILF was mostly S-1-based (16): 12 patients received mitomycin-C *plus* S-1 and one received docetaxel. Palliative surgery was required for 3 patients.

No patient achieved a complete clinical response. Of the 16 patients who were evaluable for responses, 7 partial responses (44%) were observed (95% CI: 18 to 65%). Taking into account the additional 7 patients who had stable diseases, 88% of the overall patients achieved adequate disease control. With a median follow-up duration of 15.7 months (95% CI: 13.7 to 17.8 months), the median progression-free survival was 6.2 months (95% CI: 5.8 to 6.6 months). The median overall survival was 13.8 months (95% CI: 8.9 to 18.7 months, Fig. 1), and the one-year survival rate was 59%.

DISCUSSION

In this small feasibility study, PILF combination chemotherapy demonstrated very good tolerability and activity for patients with AGC. To define an appropriate combination regimen for further improvement, we selected irinotecan, leucovorin/FU and cisplatin on the basis of their proven clinical activity for gastric cancer, and also because of their apparent synergistic activity and that they are not cross-resistant.

The best choice of chemotherapy regimen for patients with AGC is still a matter of controversy and this requires further investigation (6). The efficacy of treatment with the PILF combination is promising with an overall response rate of 41% and a median progression-free survival of 6.2 months. Although the data presented here is from a relatively small feasibility study, the results suggest that the addition of cisplatin could improve efficacy over the ILF regimen without compromising safety. Moreover, the median overall survival of 13.8 months achieved with PILF chemotherapy is quite encouraging.

One may argue that the doses of each drug in the regimen were suboptimal. Although biweekly irinotecan is usually

administered as a 180 mg/m² dose, several phase II studies have demonstrated that antitumor activity with acceptable toxic effects could be achieved when irinotecan 150 mg/m² and leucovorin/FU were administered to AGC patients as a second-line treatment (17,18). Cisplatin at a dose intensity of 15 mg/m²/week was chosen in accordance with a prior study (14).

The main concern before designing this three-drug combination was the anticipated risk of severe acute toxicity. Because cisplatin-containing regimens are significantly more toxic than those regimens without cisplatin, which is due to the excessive non-hematologic toxicity of cisplatin, this small feasibility study was conducted as a pilot study. As expected, grade 3 or 4 neutropenia was the predominant toxicity, as well as gastrointestinal side effects. In contrast, the incidence of febrile neutropenia was much lower than expected with only one episode in 117 delivered cycles. Of note, the overall toxicity profiles were acceptable and they compared well with the experiences of other studies that used irinotecan-based regimens. Although difficult to differentiate from the symptoms of the underlying disease, these non-hematologic toxicities would be considered reasonable and not unexpected in this patient population that was treated with systemic chemotherapy. In retrospect, it would have been safer if a lower dose of leucovorin was used because leucovorin probably increases the incidence of non-hematologic toxicities with FU (19). FU modulated by leucovorin was associated with increased gastrointestinal toxicity, but it did not improve survival. Moreover, the use of high-dose leucovorin combined with FU failed to improve survival for patients with metastatic colorectal cancer (20). As this was a small pilot study, the efficacy data was exploratory; nevertheless, it was sufficiently encouraging to justify further evaluation as part of a formal phase II study. The irinotecan-based combination has a good safety profile and, in our opinion, it compares favorably with the anthracycline- or taxane-based regimen (7,8). Therefore, we adapted a modified version of this regimen as one arm of a randomized phase II study for evaluating ILF with or without cisplatin for treating AGC (*ClinicalTrials.gov*, NCT00320294). The dose of leucovorin was reduced to 20 mg/m²/day in order to reduce the incidence of gastrointestinal toxicity.

CONCLUSIONS

Four-drug combination of PILF is tolerable and has encouraging efficacy outcomes for AGC.

REFERENCES

- Bae JM, Won YJ, Jung KW, Park JG. Annual report of the Korean central cancer registry program 2000. *Cancer Res Treat.* 2002;34:77-83.
- Pyrhonen S, Kuitunen T, Nyandoto P, Kouri M. Randomised comparison of fluorouracil, epirubicin and methotrexate (FEMTX) plus supportive care with supportive care alone in patients with non-resectable gastric cancer. *Br J Cancer.* 1995;71:587-91.
- Glimelius B, Ekstrom K, Hoffman K, Graf W, Sjoden PO, Haglund U, et al. Randomized comparison between chemotherapy plus best supportive care with best supportive care in advanced gastric cancer. *Ann Oncol.* 1997;8:163-8.
- Cullinan SA, Moertel CG, Wieand HS, O'Connell MJ, Poon MA, Krook JE, et al. 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;12:412-6.
- Ohtsu A, Shimada Y, Shirao K, Boku N, Hyodo I, Saito H, et al. 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 (JCOG 9205). *J Clin Oncol.* 2003;21:54-9.
- Ohtsu A, Yoshida S, Saijo N. Disparities in gastric cancer chemotherapy between the East and West. *J Clin Oncol.* 2006;24:2188-96.
- Webb A, Cunningham D, Scarffe JH, Harper P, Norman A, Joffe JK, et al. Randomized trial comparing epirubicin, cisplatin, and fluorouracil versus fluorouracil, doxorubicin, and methotrexate in advanced esophagogastric cancer. *J Clin Oncol.* 1997;15:261-7.
- Moiseyenko VM, Ajani JA, Tjulandin S, Van Cutsem E, Fodor M, Majlis A, et al. Final results of a randomized controlled phase III trial (TAX 325) comparing docetaxel (T) combined with cisplatin (C) and 5-fluorouracil (F) to CF in patients with metastatic gastric adenocarcinoma (MGC). *Proc Am Soc Clin Oncol.* 2005;23:308s (abstr 4002).
- Kohne CH, Catane R, Klein B, Ducreux M, Thuss-Patience P, Niederle N, et al. Irinotecan is active in chemonaive patients with metastatic gastric cancer: a phase II multicentric trial. *Br J Cancer.* 2003;89:997-1001.
- Bouche O, Raoul JL, Bonnetain F, Giovannini M, Etienne PL, Lledo G, et al. Randomized multicenter phase II trial of a biweekly regimen of fluorouracil and leucovorin (LV5FU2), LV5FU2 plus cisplatin, or LV5FU2 plus irinotecan in patients with previously untreated metastatic gastric cancer: a Federation Francophone de Cancerologie Digestive Group Study--FFCD 9803. *J Clin Oncol.* 2004;22:4319-28.
- Ajani JA, Baker J, Pisters PW, Ho L, Mansfield PF, Feig BW, et al. CPT-11 plus cisplatin in patients with advanced, untreated gastric or gastroesophageal junction carcinoma: results of a phase II study. *Cancer.* 2002;94:641-6.
- Pozzo C, Barone C, Szanto J, Padi E, Peschel C, Bukki J, et al. Irinotecan in combination with 5-fluorouracil and folinic acid or with cisplatin in patients with advanced gastric or esophageal-gastric junction adenocarcinoma: results of a randomized phase II study. *Ann Oncol.* 2004;15:1773-81.
- Schleucher N, Tewes M, Wilke HJ, Eberhardt W, Buechele T, Hense J, et al. Phase I/II study with weekly infusional high-dose 5-fluorouracil/leucovorin/irinotecan in combination with biweekly cisplatin as first-line chemotherapy for metastatic gastric carcinoma. *Proc Am Soc Clin Oncol.* 2003;22:343 (abstr 1378).
- Niederman TM, Stone E. Fluorouracil, leucovorin, irinotecan, and cisplatin (FLIP) in chemotherapy naive metastatic gastric carcinoma: final results of a pilot phase II trial. *Proc Gastrointestinal Cancers Symposium 2006*:abstr 79.
- Fleming TR. One-sample multiple testing procedure for phase II clinical trials. *Biometrics.* 1982;38:143-51.
- Shin DB, Lee SI, Park SH, Bang SM, Cho EK, Lee JH. Second-line chemotherapy with mitomycin C and S-1 in patients with advanced gastric cancer. *Proc Am Soc Clin Oncol.* 2006;24:abstr 14083.
- Bleiberg H. CPT-11 in gastrointestinal cancer. *Eur J Cancer.* 1999;35:371-9.
- Kim ST, Kang WK, Kang JH, Park KW, Lee J, Lee SH, et al.

- al. Salvage chemotherapy with irinotecan, 5-fluorouracil and leucovorin for taxane- and cisplatin-refractory, metastatic gastric cancer. *Br J Cancer*. 2005;92:1850-4.
19. Kohne CH, Wils J, Lorenz M, Schoffski P, Voigtmann R, Bokemeyer C, et al. Randomized phase III study of high-dose fluorouracil given as a weekly 24-hour infusion with or without leucovorin versus bolus fluorouracil plus leucovorin in advanced colorectal cancer: European organization of Research and Treatment of Cancer Gastrointestinal Group Study 40952. *J Clin Oncol*. 2003;21:3721-8.
20. Ychou M, Fabbro-Peray P, Perney P, Marcais O, Gouze C, Ribard D, et al. A prospective randomized study comparing high- and low-dose leucovorin combined with same-dose 5-fluorouracil in advanced colorectal cancer. *Am J Clin Oncol*. 1998;21:233-6.
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