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ORIGINAL ARTICLE

A phase II study of paclitaxel combined with infusional 5-fluorouracil and low-dose leucovorin for advanced gastric cancer

Chong Kun Im · Hei-Cheul Jeung · Sun Young Rha · Nae Choon Yoo · Sung Hoon Noh · Jae Kyung Roh · Hyun Cheol Chung

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Abstract
Purpose The aim of this study was to investigate the efficacy and safety of the combination chemotherapy of paclitaxel, infusional 5-fluorouracil (5-FU) and leucovorin (FLT regimen) in advanced gastric cancer. The primary end point was the time to progression (TTP).
Methods Patients with evaluable disease with or without measurable lesions received 175 mg/m^2 paclitaxel on day 1 followed by 20 mg/m^2 leucovorin and 24-h infusion of 5-FU 1,000 mg/m^2 (day 1-3) repeated every 3 weeks.
Results Sixty patients were enrolled. The median TTP and overall survival duration were 13 and 60 weeks, respectively. One-year survival rate was 53.3%. Of the 50 patients with measurable lesion, the overall response rate was 31.7%. The most common grade 3–4 adverse event was neutropenia (61.7%).
Conclusion The FLT regimen showed an efficacy comparable to other regimens of cisplatin or anthracycline combinations with the advantage of remarkably low non-hematological toxicity. These data about the efficacy of this regimen need confirmation in a phase III trial.

Keywords Paclitaxel · Advanced gastric cancer · 5-FU · Leucovorin

C. K. Im · H.-C. Jeung · S. Y. Rha · N. C. Yoo · S. H. Noh · J. K. Roh · H. C. Chung (✉)
Cancer Metastasis Research Center,
Yonsei University College of Medicine,
134, Shinchon-Dong, Seodaemun-Ku, CPO Box 8044,
Seoul 120-752, Korea
e-mail: unchung8@yumc.yonsei.ac.kr

C. K. Im · S. Y. Rha · N. C. Yoo · J. K. Roh · H. C. Chung
Department of Internal Medicine,
Yonsei University College of Medicine, Seoul, Korea

S. Y. Rha · S. H. Noh · J. K. Roh · H. C. Chung
Brain Korea 21 Project for Medical Science,
Yonsei University College of Medicine, Seoul, Korea

S. H. Noh
Department of Surgery,
Yonsei University College of Medicine, Seoul, Korea

Introduction

Gastric cancer remains a leading cause of cancer death in Asian countries. The outcome of patients with metastasis as well as with recurrence is dismal with a median survival time, if untreated, being not greater than 5 months [8]. Chemotherapy has been employed in advanced gastric cancer treatments with responses up to 20% with single-agent treatment. Most of combination chemotherapies have employed 5-fluorouracil (5-FU), etoposide, anthracyclines, and cisplatin, which obtained higher tumor response compared to single-agent chemotherapy, but their survival duration was around 9 months [21]. Cisplatin is a widely used chemotherapeutic option, and combination with epirubicin and 5-FU has been investigated mainly in Europe with promising efficacy with marginal survival benefits. However, the benefit seemed to be limited to patients with good performance status and toxicities were not negligible [21]. Therefore, the need is clear for new combination regimens so that the efficacy and safety are improved in patients with advanced gastric cancer.

Paclitaxel is a mitotic spindle poison that induces a mitotic block, and exhibits anti-tumor activity against various cancers including gastric cancer [6, 7, 23]. As a single agent, it has been reported to have response rates between

17 and 29% in gastric cancer [1, 5, 26]. Furthermore, paclitaxel-containing combinations have also been encouraging [4, 21]. Combination regimens, including paclitaxel, 5-FU, cisplatin or etoposide yielded response rates as high as 50% with a median survival of 7–14 months [9, 13–15]. Murad et al. reported a response rate of 66% in a phase II trial treated with 5-FU continuous infusion and paclitaxel every 3 weeks [17]. Bokemeyer et al. treated chemotherapy-naïve gastric cancer with weekly 5-FU plus leucovorin combined with paclitaxel and obtained a response rate of 32% and overall survival of 11 months [3]. Based on these results, we conducted a phase II study in order to assess the efficacy and safety of paclitaxel in combination with infusional 5-FU and leucovorin in advanced gastric cancer.

Patients and methods

Patient eligibility

This study was designed as a single-institutional phase II trial. Patients with histologically proven metastatic and/or relapsed gastric adenocarcinoma were eligible for the study when they met all of the following criteria: aged ≥18 and <75 years; Eastern Cooperative Oncology Group (ECOG) performance scale ≤2; evaluable disease with or without measurable lesion; either chemotherapy-naïve or only one prior chemotherapy regimen for advanced gastric cancer which was completed 3 months before entry; life expectancy ≥3 months; adequate hematological, renal, and hepatic functions. Patients were excluded from the study if they had concurrent cancer, grade ≥2 peripheral neuropathy according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC), brain metastasis or uncontrolled significant comorbid conditions. Informed consent from all the patients was obtained before they entered the study.

Treatment plan

On day 1, 175 mg/m^2 of paclitaxel was intravenously administered in 250 ml of normal saline as a 3-h infusion. Within 2 h after completion of paclitaxel, the patients received 20 mg/m^2 leucovorin as an intravenous bolus injection followed by 1,000 mg/m^2/day 5-FU as a 24-h continuous infusion for 3 days (day 1–3). Granulocyte colony-stimulating factor (G-CSF) was not administered prophylactically, but therapeutically when absolute neutrophil count (ANC) was ≤500/μl. The treatment was repeated every 21 days. If grade ≥3 hematological toxicity occurred, the next cycle was delayed until ANC was ≥1,500/μl and platelet count was ≥100,000/μl. Neither dose reduction nor dose escalation was allowed. Chemotherapy was given until the occurrence of disease progression, unacceptable toxicity or treatment withdrawal. The treatment continued for a maximum of 12 cycles.

Evaluation

Baseline evaluations of each patient included complete medical history with physical examination, complete blood count (CBC), serum chemistry, urine analysis and electrocardiography. A radiological evaluation was completed within 4 weeks prior to the treatment. Fiberoptic gastroduodenoscopy was planned to examine complete response (CR) of all the measurable lesions. During treatment, patients were evaluated by a weekly CBC. Physical examination, performance status and serum chemistry were recorded prior to each subsequent cycle. Radiological studies were repeated every two cycles.

Treatment response was evaluated according to the guideline of the Response Evaluation Criteria in Solid Tumors (RECIST) committee. Patients were considered as assessable for response if they showed evidence of early disease progression clinically or radiologically within two cycles, or if they had received a minimum of two cycles of treatment with at least one tumor measurement. A measurable lesion was defined as 10 mm in the longest dimension, assessed by a spiral CT scan. If a patient was documented as having a CR or a partial response (PR), it was confirmed at least 4 weeks after the first evident response.

Time to progression (TTP) was defined as the time elapsed from the start of treatment until disease progression or death of any cause, and overall survival (OS) was defined from the start of treatment to death. TTP was defined as time interval between initiation of treatment and first documented response (CR or PR). Response duration was measured from the initially documented response until disease progression. All patients were evaluated for toxicity from the time of the first cycle. Toxicity was evaluated as a grade according to the NCI-CTC (version 2.0).

Statistical considerations

The primary end point of this study was TTP and the secondary end points were time to response, response rate, response duration, OS and safety. Time-dependent variables were estimated with a log-rank test using the Kaplan–Meier method. Multivariate analysis was performed using Cox's proportional hazard regression model.

Sample size was calculated using Simon's optimal two-stage design—a lower progression-free rate (PFR) at 6 month of 0.20 (P_0) and a target PFR at 6 month of 0.40 (P_1). A maximum sample size of 54 patients was required to test this hypothesis (type I error, 0.05; type II error, 0.10). At the end of the first stage, at least 5% of progression-free

survivors at 6 months had to be found in 19 patients before continued accrual. Considering 10% of dropout rate, a total of 60 patients were required in this trial.

Results

Patient characteristics

From August 2003 to April 2005, a total of 60 patients were enrolled. All patients were assessable for survival parameters and toxicity, and 56 of them were for tumor response: Four patients were excluded from analysis because they did not complete the minimum two cycles and they withdrew their consent after the first cycle without any definite evidence of disease progression or adverse events. Characteristics of patients are summarized in Table 1. Over half the patients (55.0%) had performance status of ECOG grade 2. Thirty-seven (61.7%) patients received this chemotherapy as the first-line treatment and 13 among them had previously received adjuvant chemotherapy. The main metastatic sites were the abdominal lymph nodes and liver.

Treatment and dose intensity

A total of 280 cycles were administered with the median of four cycles (range, 1–12). Fifty cycles (17.8%) of the chemotherapy were delayed; 42 cycles were due to hematological toxicity, four cycles due to non-hematological toxicity and remaining four cycles were by patients' wishes. Thirty-five patients (58.3%) were transferred to other chemotherapy regimens after disease progression was documented, and six patients (17.1%) showed objective tumor responses.

The median dose intensity of 5-FU was 913 mg/m^2/week (range, 640–1,000 mg/m^2/week) and that of paclitaxel was 53 mg/m^2/week (range, 37–58 mg/m^2/week). The average relative dose intensity of this regimen was 0.91 (range, 0.64–1.0).

Survival

With the median follow-up duration of 53 weeks (range, 4–106 weeks), 53 patients had disease progression, of whom 44 patients (66.7%) expired. The most common relapse site was peritoneum (48.7%) followed by intra-abdominal lymph nodes (27.0%), and liver (19.2%). The median TTP for total patients was 13 weeks (95% CI, 5–22 weeks) by intent-to-treat (ITT) analysis; 19 weeks (95% C.I. 11–27 weeks) for the first-line treatment group and 12 weeks (95% C.I. 8–16 weeks) for the second-line treatment group. ($P = 0.66$) (Figs. 1, 2).

The median OS for the total patients was 60 weeks (95% CI, 44–77 weeks) by ITT analysis; 66 weeks (95% CI, 45–87 weeks) for the first-line treatment group and 55 weeks (95% CI, 29–81 weeks) for the second-line treatment group ($P = 0.64$) (Figs. 1, 3).

Table 1 Patients' characteristics

	Number of patients (%)
Total enrolled patients	60
Evaluable patients	56
Age	
Median (range)	52 (24–69)
Sex	
Male	36 (60.0)
Female	24 (40.0)
ECOG	
0–1	27 (45.0)
2	33 (55.0)
Histology	
Moderately differentiated	11 (18.3)
Poorly differentiated	30 (50.0)
Signet ring cell	13 (21.7)
Mucinous	1 (1.7)
Undetermined	5 (8.3)
Previous gastrectomy	
Yes	32 (51.7)
No	28 (48.3)
Chemotherapy status	
1st line	37 (61.7)
Chemonaive	24 (40.0)
Adjuvant chemotherapy	13 (21.7)
2nd line	23 (38.3)
Disease site	
Abdominal lymph node	33 (28.4)
Peritoneum	33 (28.4)
Liver	12 (10.3)
Stomach mass	11 (9.4)
Cervical lymph node	8 (6.9)
Ovary	5 (4.3)
Others	14 (12.1)
Number of disease sites	
1	20 (33.3)
2	26 (43.3)
3	11 (18.3)
≥4	5 (5.0)

Tumor response

The overall objective response rates are presented in Table 2. Two patients achieved CR and 17 patients achieved PR. The overall response rate was 31.7% by ITT analysis. Of the 19 patients who responded to chemotherapy,

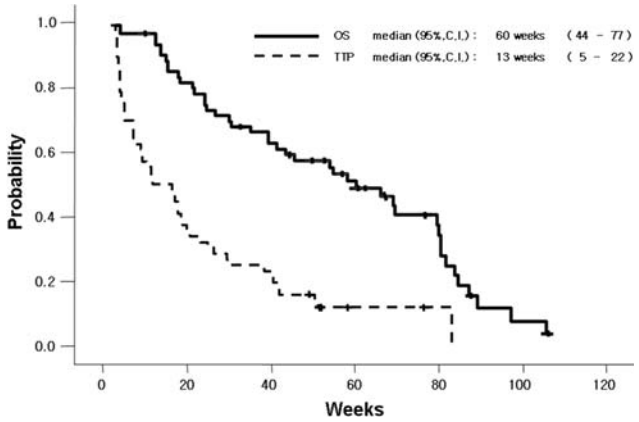

Fig. 1 Overall survival and progression free survival of total patients

nine responses (76.4%) were observed after cycle 2 of chemotherapy and seven responses (24.6%) were observed after cycle 3. The median time to response was 10 weeks (range, 6–20 weeks) and the median response duration was 28 weeks (range, 5–73 weeks). One patient who attained PR underwent radical gastrectomy after 12 cycles.

Tumor response was assessed separately according to the prior exposure to chemotherapy. Among 34 patients of the first-line chemotherapy with measurable lesions, two patients had CR and 11 patients achieved PR, with an overall response rate of 41.2%. Twenty-three patients received chemotherapy as the second-line and 22 patients were evaluable for response. Seven patients achieved PR and the overall response rate was 31.8%.

Two cases of CR were documented; one patient with a metastatic paraaortic lymph node and in another patient with intra-abdominal mass. Their duration of response was 70+ and 40+ weeks, respectively. When the response was evaluated according to the metastatic site, lymph node, intra-abdominal mass and liver, showed relatively favorable response to the chemotherapy compared to the other sites (Table 3).

Prognostic factors

When the survival data were analyzed with univariate analysis by clinical parameters, age and tumor response to the chemotherapy were statistically significant in TTP ($P = 0.016$ and $P < 0.005$, respectively). With multivariate analysis, histology (well-moderately vs. poorly differentiated) and tumor response (responder vs. non-responder) was significant in TTP ($P = 0.037$ and $P < 0.005$, respectively). Histology type and tumor response was also significant in OS ($P = 0.05$, 0.03, respectively).

Adverse events

The most common grade 3–4 hematological toxicity was neutropenia, which was found in 15 (25.0%) and 22 (36.7%) patients, respectively. Febrile neutropenia was observed in two patients. No patient expired from treatment-related toxicity during the whole treatment cycle.

In contrast, non-hematological toxicity was rare. Nausea was the most common (15.0%). Peripheral neuropathy of grade 3 was observed in only three patients (5.0%). The toxicity profiles per patient are summarized in Table 4.

Discussion

In advanced gastric cancer, systemic chemotherapy has been tried as a palliative purpose, leading to improvement of tumor responses, quality of life and survival compared to best supportive care [8, 18]. However, the standard chemotherapy has not yet been established. In Europe, anthracycline-containing regimens, such as epirubicin, cisplatin, 5-FU (ECF), have been used as a reference, while 5-FU plus cisplatin or 5-FU alone has been preferred in Asia and America [12].

Several new agents have recently emerged including taxanes, irinotecan and oxaliplatin. Among them, docetaxel

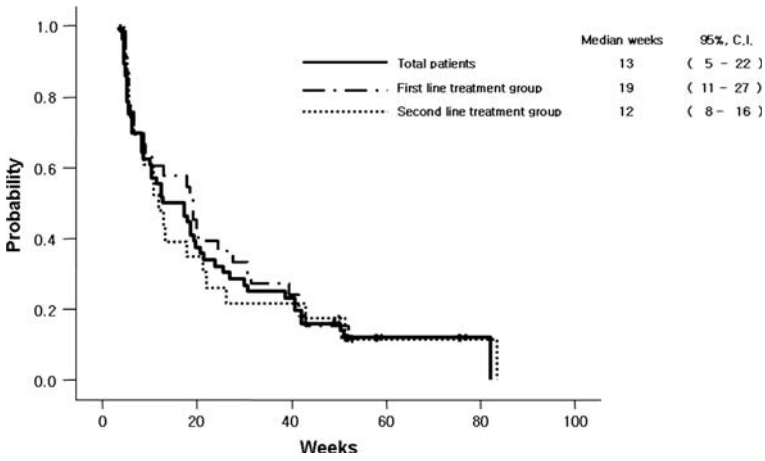

Fig. 2 Progression free survival of total patients, first line and second line treatment group

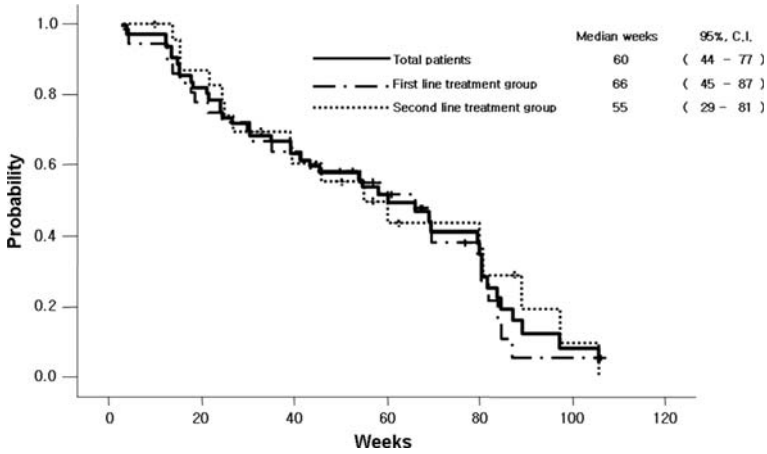

Fig. 3 Overall survival of total patients, first line and second line treatment group

Table 2 Response evaluation

		Enrolled patients			Patients having measurable lesion		
Total patients		60			50		
Evaluable patients		56			46		
	n	ITT (%)	PP (%)		*n*	ITT (%)	PP (%)
Responder	19	31.7	34.0	CR	2	4.0	4.3
				PR	17	34.0	36.9
SD	17	28.3	30.3	SD	11	22.0	23.9
PD	20	33.3	35.7	PD	16	32.0	34.8
Response rate		31.7	35.7			38.0	41.3

n number of patients, *ITT* intent-to-treatment analysis, *PP* per protocol analysis, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *RR* response rate

Table 3 Response evaluation by metastasis sites

Organ	Measurable lesions	CR	PR	SD	PD	RR (%)
Intra-abdominal lymph nodes	33	3	9	10	11	36.3
Abdominal mass	11	1	3	5	2	36.3
Liver	12	1	3	4	4	33.3
Neck node	8	–	2	1	5	25.0
Ovary	5	–	1	3	1	20.0
Others	14	–	3	4	7	21.4
Total	83	5	21	27	30	31.3

CR complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *RR* response rate

was the first one tried in advanced gastric cancer, showing an improved efficacy in several phase II trials [7, 10]. In the V325 study, the combination of docetaxel, cisplatin and 5-FU (DCF) showed better results than cisplatin and 5-FU (CF) in terms of tumor response and survival. However, DCF was accompanied by severe hematologic toxicities of more than 80% [16]. These findings are consistent with other trials of docetaxel. In a phase II trial, they reported 71% of grade 3–4 neutropenia including 12% of febrile neutropenia even with prophylactic administration of G-CSF [10]. The docetaxel combination showed improved efficacy and survival, but also showed substantial hematologic toxicity.

We considered paclitaxel as a mainstay agent and combined 5-FU and leucovorin onto it. The rationale behind this strategy was as follows; (1) the synergistic effect of the combination, (2) no overlapping toxicity, (3) recent results of 5-FU and docetaxel combination and (4) less myelotoxicity of paclitaxel than docetaxel [17, 27]. Continuous infusion of 5-FU combined with leucovorin has been an acceptable regimen in gastrointestinal malignancy [24]. It was evaluated as a salvage therapy for patients having a poor general condition such as acute disseminated intravascular coagulation (DIC) [4]. As for paclitaxel, a phase III trial showed that no additional benefit was found in increasing paclitaxel dose over 175 mg/m^2 with respect to tumor response and survival [19].

In this phase II study, we indicated TTP as the primary endpoint instead of response rate. Advanced gastric cancer includes considerable proportion of non-measurable diseases such as peritoneal seeding or gastric mass. Recent reports on the recurrence pattern of gastric cancer revealed that peritoneal seeding is the most frequented site, especially in Asian population [29]. Furthermore, there is report showing different prognosis between measurable and non-measurable disease [22]. From these findings, we speculated that TTP could reflect the chemotherapy benefit more precisely. The number of studies where TTP is used as the primary endpoint has been increasing recently [11]. However, it needs more studies to evaluate the adequacy of TTP as the primary goal in phase II trial.

In our FLT regimen, we observed overall TTP of 13 weeks. If we limit only to the first-line treatment, TTP was 19 weeks, which is comparable to other previous

Table 4 Frequency of adverse events by per patients

	Number of patients ($N = 60$)			
	Grade 1	Grade 2	Grade 3	Grade 4
Hematologic toxicity				
Neutropenia	8 (13.3)	6 (10.0)	15 (25.0)	22 (36.7)
Leukopenia	15 (25.0)	17 (28.3)	10 (16.7)	2 (3.3)
Anemia	20 (33.3)	37 (61.7)	2 (3.3)	–
Thrombocytopenia	20 (33.3)	–	1 (1.7)	1 (1.7)
Nonhematologic toxicity				
Nausea	18 (30.0)	21 (35.0)	5 (8.3)	4 (6.7)
Vomiting	5 (8.3)	1 (1.7)	–	–
Mucositis	21 (35.0)	4 (6.7)	–	–
Diarrhea	11 (18.3)	5 (8.3)	–	–
Skin	5 (8.3)	–	–	–
Constipation	5 (8.3)	–	–	–
Peripheral neuropathy	1 (1.7)	16 (26.7)	3 (5.0)	–
Hyperbilirubinemia	8 (13.3)	–	–	–
Elevated liver enzyme	13 (21.7)	3 (5.0)	–	–
Elevated creatinine	9 (15.0)	–	–	–

reports. TTP showed a tendency to be longer with the order of chemotherapy-naïve (20 weeks), prior adjuvant chemotherapy (13 weeks) and second-line treatment (11 weeks). Our FLT regimen as the first-line treatment showed a response rate of 41%, which was similar to previous trials. Furthermore, we observed 31% of response rate even in the second-line treatment. These findings confirm again the efficacy of paclitaxel in the advanced gastric cancer.

The OS for the total patients was 60 weeks and chemotherapy-naïve patients showed a tendency of longer survival than the patients exposed previously to chemotherapy including adjuvant chemotherapy (69 vs. 48 weeks). Although difficult to compare directly, our survival duration seemed to be longer than that of other second-generation regimens, even though more than half of the patients were relatively poor performers (ECOG 2). We suggest that this longer survival even in poor performers with our regimen is most likely due to subsequent salvage chemotherapy after disease progression and the maintenance of good performance status due to low toxicity.

Another point to consider is the safety profile. Previous reports showed neutropenia of ≥ grade 3 to be around 40% [17, 28]. Park et al. [20] reported similar efficacy in a randomized phase II trial of paclitaxel versus docetaxel in combination with 5-FU: The incidence of hematologic toxicities was lower in paclitaxel group with similar efficacy. In concordance with the above-mentioned, the major toxicity of our regimen was also neutropenia. However, more patients than we expected experienced neutropenia of ≥ grade 3 (62%). And this could be explained by the frequency of weekly CBC checkup in our patients. In addition, a high proportion of poor performers and old age patients (over 65 years, 20%) could have also contributed to it. However neutropenia was easily manageable with G-CSF and the frequency of febrile neutropenia was low. The median number of G-CSF administration per patient was three. These findings suggest that the FLT combination rarely affected overall compliance of patients. Moreover, our regimen showed low non-hematological toxicity, which is more directly associated with patients' compliance and quality of life. High dose intensity obtained with our regimen is attributable to these traits. This favorable toxicity profile seems to be advantageous for the FLT regimen over previous second-line regimens of anthracycline- or cisplatin-combinations with an attainable effect on survival [2, 25].

In conclusion, the efficacy of FLT regimen seems to be comparable to other cisplatin- or anthracycline combinations with an advantage of low non-hematological toxicity and favorable safety profile in poor performers irrespective of previous exposure to chemotherapy. These data need confirmation in a phase III trial about the efficacy of this regimen.

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Conflicts of interest All authors indicated no potential conflicts of interest.

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