Paclitaxel versus docetaxel for advanced gastric cancer: a randomized phase II trial in combination with infusional 5-fluorouracil

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Taxanes have clearly demonstrated activities against gastric cancer. We compared the combination of paclitaxel plus 5-fluorouracil (5-FU) (PF) with docetaxel plus 5-FU (DF) as first-line chemotherapy in patients with measurable metastatic gastric cancer. Seventy-seven patients were randomly assigned to receive paclitaxel 175 mg/m^2 or docetaxel 75 mg/m^2 on day 1, in combination with 5-FU 500 mg/m^2 continuous infusion on days 1–5. Treatment was repeated every 3 weeks. Of 314 chemotherapy cycles delivered (median 5 in both groups), dose reduction was required more frequently in the DF group, being 9 and 19%, respectively ($P<0.01$). PF was associated with, although statistically insignificant, substantially less grade 3 or 4 toxicities than DF (68 versus 85%; $P=0.09$). Global quality of life was similar in both groups, but substantive differences in many symptom scores including pain, dyspnea, constipation and diarrhea favored PF. There were no significant differences in therapeutic efficacy between PF and DF with respect to response rate (42 versus 33%, respectively; $P=0.53$), and failure-free (3.6 versus 4.2 months; $P=0.92$) and overall survival (9.9 versus 9.3 months; $P=0.42$). Both PF and DF appear to have efficacy against metastatic gastric cancer, with different, but acceptable, safety profiles. *Anti-Cancer Drugs* **17:225–229**

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Introduction

Gastric cancer is the most frequently occurring malignancy in Korea and 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 demonstrated that 5-fluorouracil (5-FU)-based chemotherapy is superior to best supportive care in terms of survival and preservation of quality of life [2,3]. Although treatment options for AGC have expanded in recent years to include newer agents such as taxanes (paclitaxel and docetaxel), irinotecan and oxaliplatin, 5-FU remains the backbone of most current chemotherapy protocols [4,5].

Both paclitaxel (Taxol; Bristol-Myers Squibb) and docetaxel (Taxotere; Sanofi-Aventis) are approved in Korea for use in first-line treatment of AGC. Most studies undertaken to date have been phase II trials and in most of these taxanes have been demonstrated to have therapeutic efficacy of around a 20% objective response rate [6,7]. Phase I/II trials have shown that not only paclitaxel, but also docetaxel can be administered in combination with 5-FU, which appeared to be non-cross-resistant. The doses recommended in our phase I study were docetaxel 75 mg/m^2 every 3 weeks, in combination with 5-FU 500 mg/m^2 daily for 5 days [8].

The studies that explored the individual use of paclitaxel and of docetaxel prompted us to design this randomized phase II trial using both agents and 5-FU in order to compare directly their efficacy and safety in patients with AGC who had been previously untreated. Paclitaxel plus 5-FU schedule was chosen to allow an identical 5-FU regimen in both treatment groups.

Patients and methods

Patients

For this single-center, randomized phase II trial, the inclusion criteria were histologically confirmed, measurable metastatic gastric cancer, naive to chemotherapy; age < 75 years; Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2; normal bone marrow functions with neutrophil count $> 1500/mm^3$ and platelet count $> 100\,000/mm^3$; normal hepatic [AST/ALT $\leq 2.5\times$ upper level of normal (ULN), bilirubin ≤ 1.5 mg/dl] and renal functions (creatinine

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clearance ≤ 60 ml/min or creatinine $\leq$ ULN); and the provision of a signed written informed consent. No prior chemotherapy or only adjuvant chemotherapy which had been completed more than 6 months before registration and no radiotherapy within 4 weeks before study registration were allowed. Patients were excluded from the study if they had severe comorbid illness, known history of anaphylaxis of any origin or a history of severe adverse effects to taxanes and/or 5-FU. The study was conducted according to the principles stated in the latest version of the Declaration of Helsinki. This study protocol was reviewed and approved by the Gil Medical Center Institutional Review Board.

Treatment and assessment

Patients were stratified by their performance status (0–1 versus 2) and randomly assigned to receive paclitaxel 175 mg/m^2 (PF) or docetaxel 75 mg/m^2 (DF) on day 1, in combination with continuous infusion 5-FU 500 mg/m^2 daily for 5 days. For both groups, treatment was repeated every 3 weeks. Chemotherapy was administered until disease progression, unacceptable toxicities or a maximum of 6 cycles. Dosage of the subsequent cycles was adjusted according to the toxic effects that developed during the preceding cycle. All patients received standard supportive regimen including oral corticosteroids, antihistamines and anti-emetics. No prophylactic administration of hematopoietic growth factors or diarrhea remedies was allowed. Follow-up history, physical examinations and toxicity assessments were performed before each 3-week cycle of chemotherapy. After this combination chemotherapy had failed, second-line chemotherapy was recommended to all patients if their performance status was preserved [9].

Tumor response was evaluated according to WHO criteria [10] and was assessed by abdominopelvic computed tomography scan or by the same tests used initially to stage the tumor. All tumor measurements were recorded by a gastrointestinal radiologist in millimeters in two dimensions in all measurable lesions. Responses were assessed every 2 cycles of chemotherapy and reviewed by an independent investigator later at the time of analyses. Toxicity grading was based on the National Cancer Institute Common Toxicity Criteria version 2. Quality of life assessment was scheduled to be carried out at baseline, every 2 cycles and at the end of treatment. The Validated Korean version of the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire, which contains 30 questions addressing various aspects of quality of life, was used [11,12].

Statistical consideration

The primary end point was the overall response rate. This randomized phase II trial was treated, statistically, as two simultaneous phase II studies and Fleming's single-stage design was applied separately for each treatment group [13]. The sample size estimation was based on the assumption that the response rate would be 30% or above in each group of the treated population. With a significance level set at 0.05, 35 patients per group were required. The χ^2-test was used for comparison of categorical variables. Quality of life differences between treatment groups were calculated with paired *t*-test. Progression-free, failure-free and overall survivals were estimated according to the Kaplan–Meier method, and the statistical significance of survival curves between the two groups was tested with a log-rank test. All *P* values were two-sided, with $P < 0.05$ indicating statistical significance.

Results

In total, 77 patients were entered in this study between April 2003 and November 2004: 38 in the PF group and 39 in the DF group. One patient assigned to the DF group did not receive protocol therapy because of the rapid deterioration of his general condition. In an intent-to-treat (ITT) analysis, however, the patient was included in the denominator for treatment outcomes. Clinical characteristics were available for all patients and are listed in Table 1. Because of the stratification with their performance status, baseline characteristics are well balanced between the two groups. The most frequent sites of metastatic disease were intra-abdominal lymph nodes, peritoneum and liver.

Toxicity and treatment exposure

There was no significant difference in the number of chemotherapy cycles, with 167 cycles (median 5; range 1–6) given for the PF group and 177 cycles (median 5; range 0–6) given for the DF group ($P = 0.57$). Dose reduction was required more frequently in DF group, being 9 and

Table 1 Patient characteristics

	PF	DF
No. patients (treated)	38 (38)	39 (38)
Age (years) [median (range)]	53 (36–73)	51 (27–74)
Male gender	19	26
Prior anti-tumor treatment		
curative resection	12	16
palliative surgery	15	11
adjuvant chemotherapy	11	13
ECOG performance status		
0–1	30	33
2	8	6
Weight loss >5% within the last 3 months	14	4
Site(s) of metastatic disease[a]		
abdominal lymph node	32	33
peritoneum	23	18
liver	10	11
lung and/or malignant pleural effusion	3	4
ovary	4	5
bone	0	1
supraclavicular lymph node	3	1
brain	1	0

[a]Because patients could have metastases at multiple sites, the total numbers of metastases are greater than the numbers of patients.

Table 2 Maximum grade toxicities per patient [*n* (%)]

	Grade 1/2		Grade 3/4	
	PF	DF	PF	DF
Hemoglobin	9 (24)	5 (13)	1 (3)	6 (16)
Neutrophil	11 (29)	5 (13)	7 (18)	8 (21)
Platelets	8 (21)	6 (16)	2 (5)	2 (5)
Febrile neutropenia			4 (11)	8 (21)
Hepatic	5 (13)	6 (16)	1 (3)	0
Renal	2 (5)	0	0	0
Fatigue	8 (21)	4 (11)	3 (8)	5 (13)
Peripheral neuropathy	3 (8)	5 (13)	15 (40)	4 (11)
Palpitation	2 (5)	4 (11)	0	0
Skin	2 (5)	1 (3)	1 (3)	6 (16)
Nausea and vomiting	9 (24)	10 (26)	6 (16)	13 (34)
Mucositis	4 (11)	1 (3)	5 (13)	16 (42)
Diarrhea	3 (8)	6 (16)	3 (8)	8 (21)

Table 3 Summary of treatment results

	PF ($n=38$)	DF ($n=39$)	*P*
Partial response [*n* (%)]	16 (42)	13 (33)	
Stable disease [*n* (%)]	13 (34)	18 (46)	
Progression [*n* (%)]	8 (21)	5 (13)	
Overall response rate (ITT) [*n* (%; 95% CI)]	16 (42; 26–58)	13 (33; 19–48)	0.53
Duration of response (months) [median (95% CI)]	5.0 (4.1–5.9)	4.9 (4.4–5.4)	0.34
Progression-free survival (months) [median (95% CI)]	4.3 (4.0–4.6)	4.3 (4.1–4.5)	0.28
Failure-free survival (months) [median (95% CI)]	3.6 (2.9–4.2)	4.2 (4.0–4.4)	0.92
Overall survival (months) [median (95% CI)]	9.9 (5.6–14.2)	9.3 (6.0–12.6)	0.42

19%, respectively ($P < 0.01$), for the two groups. In the PF group, 10 patients had a treatment delay of 1 week at some time during therapy and the total number of delayed cycles was 10 (7%). In the DF group, treatment delays were required in five patients over 8 (5%) cycles. The most frequently encountered toxicities were gastrointestinal symptoms and neurotoxicity, which were managed with rest, dose reduction or treatment discontinuation. Although difficult to differentiate from the symptoms of the underlying disease, grade 3 or 4 nausea and vomiting were observed in six and 13 patients in the PF and DF groups, respectively. A summary of toxicity is presented in Table 2. There were four and eight patients with febrile neutropenia in the PF and DF groups, respectively. Two patients in the PF group died between chemotherapy cycles: one patient died of a respiratory distress together with a fever and another patient died after the first cycle due to massive bleeding from the primary tumor. The PF group was associated with, although statistically insignificant, substantially less grade 3 or 4 toxicities than the DF group (68 versus 85%, respectively; $P = 0.09$).

For patients treated with PF, the mean dose intensity of paclitaxel of 51.7 mg/m^2/week corresponded to 89% of the scheduled dose and the median duration of therapy was 2.8 months. For patients in the DF group, the mean dose of docetaxel 22.1 mg/m^2/week corresponded to 88% of the scheduled dose and the median treatment duration was 3.1 months. Relative dose intensities of 5-FU were 89% for patients in the PF group and 84% for those in the DF group ($P = 0.15$).

Efficacy

Disease control (objective response and stable disease) in the ITT population was achieved in 76% of patients in PF and in 79% of patients in DF. Response rate was 42% with PF and 33% with DF ($P = 0.53$; Table 3). At the time of analysis, the median follow-up time was 17 months [95% confidence interval (CI) 13–20 months]. Both groups showed similar failure-free (3.6 months for PF and 4.2 months for DF; $P = 0.92$) and overall survival (9.9 and 9.3 months; $P = 0.42$).

Table 4 Mean scores on EORTC QLQ-C30

	Baseline		Change from baseline	
	PF	DF	PF	DF
Functional scales[a]				
physical	72	76	−5	−3
role	57	64	14	13
emotional	69	60	13	24
cognitive	78	65	3	20
social	80	73	3	−3
Symptoms[b]				
fatigue	35	31	−1	−3
nausea/vomiting	12	27	8	−2
pain	32	28	−13	−3
dyspnea	34	31	−11	−6
insomnia	28	33	−9	−1
appetite loss	15	29	−6	14
constipation	46	64	−31	−22
diarrhea	27	28	−11	−6
economic impact	30	35	−9	−4

[a]Scores range from 0 to 100, with a higher score representing a higher level of function.
[b]Scores range from 0 to 100, with a higher score representing a higher level of symptoms.

Quality of life

Baseline quality of life questionnaires were completed by 59 patients: 29 in the PF group and 30 in the DF group (Table 4). The scores for the global quality of life scale were similar in both groups. The baseline highest score of the symptoms scales and single items was assigned to constipation in both groups, which was significantly improved after chemotherapy. Change in quality of life was defined as the difference between the baseline and mean score reported for each subscale during and after chemotherapy. For both groups, the global quality of life

Table 5 Global quality of life scores[a]

	Baseline		After second cycle		After fourth cycle		After sixth cycle	
	PF	DF	PF	DF	PF	DF	PF	DF
No. of patients	29	30	25	30	23	26	16	21
Mean scores	61.2	59.4	53.3	57.5	69.2	68.9	57.3	63.9
SD	19.2	20.3	17.8	19.1	30.4	32.6	27.0	28.7
Minimum	33	33	33	33	0	0	0	0
Maximum	99	92	83	83	100	100	89	92

[a]Scores range from 0 to 100, with a higher score representing a higher level of function.

scores showed an increase from baseline to the end of the fourth cycle ($P = 0.09$), but this was not sustained and by the end of therapy was no longer significantly different from the baseline score ($P = 0.65$; Table 5). Moreover, significant improvements were observed in the role function scale and the emotional function scale. The cognitive function scale was improved only in the DF group. When we considered a change of 10 or greater in any of the symptoms scores, there were significant improvements in pain, dyspnea, constipation and diarrhea scores in the PF group. Appetite was worsened after chemotherapy in the DF group.

Discussion

The present randomized phase II study was initiated in response to the lack of the reference chemotherapy regimen in AGC, the urgent need for such therapy, and because recent data suggest an efficacy and tolerability with taxanes. In both treatment groups, an identical dose regimen of 5-FU (500 mg/m^2 daily as a 5-day continuous infusion) was used. The results of quality of life assessment suggest a trend toward a better tolerability for the PF group. According to the primary end point, however, both regimens had an acceptable level of anti-tumor activity and a fairly good tolerance in patients with previously untreated AGC.

In the first-line treatment of AGC, a number of randomized trials have been performed to establish a superior chemotherapeutic regimen. Most trials using varied combinations have provided durations of survival ranging from 6 to 10 months in patients with AGC [14]. None of these regimens, however, has been recognized as a standard or superior to 5-FU [4,5,15]. Preliminary data from a trial comparing docetaxel + cisplatin + 5-FU (DCF) and cisplatin + 5-FU (CF) has shown a survival benefit for DCF [16], although there are some concerns with the hematologic toxicity. Although cisplatin is often used in combination with other agents, it is well known that cisplatin is associated with significant toxicity, and usually requires a high level of clinical monitoring and supportive care including intensive i.v. hydration. Thuss-Patience *et al.* reported that DF had similar efficacy to epirubicin + cisplatin + 5-FU (ECF) and even to DCF [17]. It is apparent that the more complex a chemotherapy regimen, the more toxic and difficult for patients to tolerate. Paclitaxel has also been extensively investigated in AGC [14]. In a series of phase II studies, PF or PCF (PF + cisplatin) resulted in objective response rates of 32–66% and a median survival of 6–12 months [18–21], that were consistent with other reports using DF or DCF.

The results of this study should be interpreted cautiously. We do not intend for these data to be interpreted as stating that paclitaxel, particularly in combination with 5-FU, is a better chemotherapeutic agent than docetaxel for patients with AGC. It should be kept in mind that only a small group of patients with AGC was represented in this phase II study, and there was no significant difference in terms of efficacy and safety. A randomized phase II study of paclitaxel versus docetaxel in patients with non-small cell lung cancer showed that higher non-hematologic toxicities were seen with docetaxel [22]. In contrast, paclitaxel and docetaxel showed similar efficacy in a phase II study performed in patients with ovarian cancer, but a docetaxel-containing regimen was associated with substantially less neurotoxicity than paclitaxel [23]. Jones *et al.* recently reported the results of a randomized phase III study comparing paclitaxel and docetaxel in patients with advanced breast cancer [24]. In the study, docetaxel was superior to paclitaxel in terms of survival. This discrepancy has mainly been attributable to patient selection, but the small size of our study, and differences in the way of assessing and reporting outcomes are contributing factors. No factors could be identified that may help explain these differing results.

Both paclitaxel and docetaxel, in combination with 5-FU, can be safely and effectively administered in first-line treatment of AGC. Although our 5-FU schedule was of lower dose intensity compared to published data, as well as the evidence that 5-FU schedules involving weekly or biweekly infusions were better tolerated than the 4- to 5-day infusions every 3–4 weeks [25,26], response and survival in this study compared remarkably well with results previously reported from other investigators. Despite these encouraging observations, we believe that further refinements aimed at improving the efficacy and, at the same time, decreasing the toxicity of the regimens are required. That being said, the survival results reported here are by no means the best yet observed with any chemotherapy regimens for patients with AGC.

Furthermore, the result suggests that taxane-based regimens are not necessarily better than other combinations.

In summary, the present study demonstrated that both paclitaxel and docetaxel, in combination with 5-FU, showed discrete therapeutic efficacy in patients with AGC. The principal difference encountered was a higher incidence of dose reduction with docetaxel, which needs to be confirmed by other studies. Taking into account all the uncertainties described above, there needs to be more studies designed to investigate whether there are real differences between paclitaxel and docetaxel with respect to efficacy and toxicity, and their combination with other agents. Since no combination chemotherapy regimen has yet reached the level of an evidence-based standard treatment, further efforts including combination with other chemotherapeutic agents and/or biologic agents are encouraged as there continues to be an urgent need to improve our therapeutic strategy against AGC.

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