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ORIGINAL ARTICLE

A phase I/II trial of docetaxel and oxaliplatin in patients with advanced gastric cancer

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Abstract
Purpose We designed this phase I/II study of docetaxel–oxaliplatin combination chemotherapy to determine the dose-limiting toxicity (DLT), maximum tolerated dose and efficacy as a first-line treatment in patients with advanced gastric cancer.
Methods Patients with histologically proven, chemo-naive gastric adenocarcinoma were eligible. For the phase I part, three dose levels of oxaliplatin and docetaxel every 3 weeks were tested in a cohort of three patients for each level (respectively, 100 and 60 mg/m^2, 100 and 75 mg/m^2, 130 and 75 mg/m^2). Patients were treated up to a maximum of nine cycles of oxaliplatin and docetaxel unless there was documented disease progression, an unacceptable adverse event, or withdrawal of consent.
Results No DLT was observed at any of the three levels tested in the phase I portion. Therefore, oxaliplatin 130 mg/m^2 and docetaxel 75 mg/m^2 were recommended for the phase II study. All 47 patients were evaluable for toxicity and treatment response. The overall response rate was 55.3% (95% CI, 40.6–70.1%) and median duration of response was 4.2 months (range 0.9–9.5 months). After a median follow-up duration of 13.3 months, median overall survival was 12.7 months (95% CI: 10.4–14.9). The median time to progression was 5.0 months (95% CI, 3.4–6.5 months). The main toxicities (grade 3 or 4) were febrile neutropenia (14.9%), neutropenia (23.4%), diarrhea (10.6%) and neurotoxicity (8.5%).
Conclusion The combination of docetaxel and oxaliplatin was feasible with favorable toxicity profile and showed a promising anti-tumor activity in unresectable, metastatic gastric cancer patients.

Keywords Docetaxel · Oxaliplatin · Advanced gastric cancer · Chemotherapy

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Introduction

Gastric cancer is the leading cause of cancer death worldwide with an incidence of 18.9/100,000 per year and the mortality rate of 14.7/100,000 per year [3], and is the most common malignancy in Korea [1]. Although the proportion of early gastric cancer is increasing, many patients still present with advanced stage disease. The median survival for patients with metastatic or inoperable advanced gastric cancer ranges from 6 to 9 months and remains a therapeutic challenge for medical oncologists [5, 10, 12, 14]. Despite the numerous efforts of randomized studies on advanced gastric cancer, no globally accepted standard regimen has yet been established. Several randomized trials including older generation regimens such as 5-FU/cisplatin, 5-FU/doxorubicin/mitomycin C, 5-FU/doxorubicin plus high dose methotrexate (FAMTX) demonstrated a median progression-free survival of 3.7–5.0 months and median survival of 6.7–9.6 months [8, 18, 19].

Newer generation cytotoxic agents, including irinotecan, S-1, capecitabine, docetaxel, paclitaxel, and oxaliplatin, have been extensively investigated in gastric cancer. Docetaxel, as a single agent, has modest anti-tumor activity in patients with advanced gastric cancer [16]. Importantly, the

additive effect of docetaxel in combination with 5-FU/cisplatin (CF) for the treatment of advanced gastric cancer was also reported in a randomized phase III study (V325 trial) [17]. In the V325 trial, all efficacy results significantly favored docetaxel plus CF (DCF) over CF alone, with a longer time to progression (TTP; 5.6 vs. 3.7 months), longer overall survival (OS; 9.2 vs. 8.6 months), and higher overall response rate (ORR; 37 vs. 25%) [17]. Although the efficacy of the DCF arm was challenged by the increased incidence of some toxicities especially febrile neutropenia, the trial demonstrated a promising role for docetaxel in the treatment of gastric cancer [17].

Oxaliplatin, a third generation platinum compound is effective in colorectal cancer and has a favorable toxicity profile with considerably lower rates of nephrotoxicity, ototoxicity, and myelosuppression when compared with cisplatin. Using epirubicin-cisplatin-5-fluorouracil (ECF) as a reference regimen, the REAL-2 study showed that oxaliplatin may be substituted for cisplatin [4]. Therefore, based on these encouraging results, we conducted a phase I/II study in order to assess the efficacy and safety of the docetaxel/oxaliplatin as a first-line chemotherapy in patients with metastatic gastric cancer.

Patients and methods

Patient eligibility

Patients with a histopathologically or cytologically confirmed diagnosis of unresectable or metastatic gastric adenocarcinoma, who had never been previously treated, were eligible for the study. Other inclusion criteria were: age $\geq$18 years; ECOG performance status 0–2; unidimensionally measurable disease (i.e., a diameter $\geq$1 cm on spiral CT scan); adequate liver (aspartate aminotransferase (ASAT) and/or [alanine aminotransferase (ALAT) $\leq$3 upper limit of normal (ULN)], renal (serum creatinine $\leq$1.5 ULN), bone marrow function (absolute neutrophil count $\geq 1.5 \times 10^9$/L; platelets $\geq 100 \times 10^9$/L); and written informed consent. Patients were excluded if they had any other malignancy in the past 5 years with the exception of skin basal cell carcinoma or CIS of cervix, serious comorbid diseases, or were pregnant or breast-feeding. The Samsung Medical Center Institutional Review Board approved this study.

Study treatment

All patients received oxaliplatin 100–130 mg/m^2 as a 2-h infusion, followed by docetaxel 60–75 mg/m^2 as a 1-h infusion on day 1, which was repeated every 3 weeks. Patients were treated for at least one cycle and to a maximum of nine cycles unless there was documented disease progression, unacceptable adverse events or withdrawal of consent. Treatment beyond nine cycles, in subjects with documented absence of progression, was considered on a subject-by-subject basis.

In phase I part, no intrapatient dose escalation was allowed. If one patient experienced dose-limiting toxicity (DLT), three additional patients were added to the dose level. If two of six patients experienced dose-limiting toxicity, the maximal tolerated dose (MTD) was defined as that dose level that produced dose-limiting toxicity in $\geq$50% of patients. If none of these three patients experienced a dose-limiting toxicity (DLT), the dose was increased in a subsequent group of three patients. If one of the first three patients experienced DLT, three more patients will be accrued to that dose level. If none of these additional three patients experienced DLT, then the dose will be escalated. If one of the additional three patients experienced DLT, then an additional cohort of patients could be added. If two or more of the second group of three patients experienced DLT, then accrual is stopped. If two of the first three patients experienced DLT, then an additional three patients could be accrued at that dose level, but dose escalation could take place only if none of the additional cohort experienced DLT. Patients who developed DLT will be treated with the next lower dose level. One dose level below MTD will be recommended and used for phase II study. DLT refers only to toxic events occurring during the first cycle of treatment. DLT was defined as follows: grade 4 hematologic toxicities, grade 3 or greater non-hematologic toxicities (except for any grade of alopecia, grade 3 nausea and vomiting or diarrhea in the absence of maximum antidiarrheal therapy), or grade 3 thrombocytopenia with grade 2 hemorrhage. In phase II part, dose reductions were planned in case of severe hematological and/or non-hematological toxicities while on study treatment. Dose adjustments were to be made according to the system showing the greatest degree of toxicity. Toxicities were graded using the CTCAE 3.0. If grade 3 febrile neutropenia occurred, docetaxel and oxaliplatin were dose-reduced by 25%. If grade 4 febrile neutropenia occurred, treatment stopped permanently. If grade 2 neutropenia or thrombocytopenia occurred, treatment was continued at the same dose without reduction or interruption. If grade 3 neutropenia or thrombocytopenia occurred, docetaxel and oxaliplatin were dose-reduced by 25%, a second time by 50%. No dose reductions or interruptions were required for anemia (non-hemolytic) as it could be satisfactorily managed by transfusions. If grade 3 or 4 diarrhea occurred, oxaliplatin was reduced by 25%. On recovery of grade 1 neuropathy between cycles or grade 2 neuropathy for 7 days, the dose of oxaliplatin maintained full dose. In the event of persistent grade 2 neuropathy or grade 3 neuropathy for 7 days, oxaliplatin was

reduced by 25%. If persistent grade 3 neurotoxicity or grade 4 neurotoxicity occurred, oxaliplatin was stopped.

The primary objective of this study was to determine the MTDs in the phase I study and evaluate the overall response rate in phase II study. The secondary objectives were to evaluate the safety and tolerability of the treatment combination and estimate overall survival (OS), the time to progression (TTP), and duration of overall response.

Assessments

Screening evaluations, including a medical history, physical examination, ECG, chest X-ray, laboratory tests, vital signs, and ECOG performance status, and tumor assessments were conducted within 21 days prior to the first administration of drugs. Complete blood counts were performed weekly during the first cycle in phase I and prior to each cycle in phase II. Tumor measurements were performed every three cycles or if disease progression was suspected. The tumor responses were classified according to the response evaluation criteria in solid tumors (RECIST). Toxicities and adverse events were graded and reported using the Common Terminology Criteria for Adverse Events Version 3.0

Statistical analysis

According to a Simon's two-stage phase II optimal design [15], a sample size of 43 was required to accept the hypothesis that the true response rate is greater than 40% with 80% power, and to reject the hypothesis that the response rate is less than 20% at a significance level of 5%. At the first stage, if there were fewer than 3 responses out of the initial 13 patients, an early termination of the study was required. Assuming that 10% of patients were not assessable, a total of 47 patients were planned to be accrued for phase II.

Descriptive statistics were reported as proportions and medians. Kaplan–Meier estimates were used in the analysis of time-to-event variables and the 95% confidence interval (CI) for the median time to event was reported. The dose intensity (DI) was calculated as the ratio of the total dose in milligrams of drug delivered per square meter of body surface area, divided by the total treatment duration expressed in days. The relative DI was calculated as the ratio of the DI actually delivered to the DI planned by the protocol.

Results

Between January 2006 and May 2008, a total of 53 patients were enrolled in the trial (12 in phase I; 47 in phase II). Six of phase I patients participated in phase II. The median age was 55 (range: 35–69) years.

Phase I

Table 1 summarizes the incidence of toxicity in the phase I part of the trial. No DLTS were observed at dose levels I and II. At the dose level of docetaxel 75 mg/m^2 and oxaliplatin 130 mg/m^2 (level 3), one patient developed DLT (febrile neutropenia). However, no DLTs were observed in

Table 1 Toxicity profile (phase I)

	Level 1		Level 2		Level 3	
No. of patients	3		3		6	
Toxicity/grade	All events	Grade 3/4	All events	Grade 3/4	All events	Grade 3/4
Hematological						
Neutropenia	–	–	–	–	–	–
Febrile neutropenia	–	–	–	–	1	1
Thrombocytopenia	–	–	–	–	–	–
Anemia	–	–	–	–	–	–
Nonhematological						
Nausea/vomiting	3	–	3	–	5	–
Peripheral neuropathy	3	–	2	–	3	–
Asthenia	–	–	1	–	2	–
Diarrhea	2	–	2	–	4	–
Constipation	–	–	–	–	2	–
Pain	3	–	3	–	5	–
Cutaneous	1	–	1	–	1	–
Hypersensitivity	1	–	–	–	2	–

the expanded cohort of six at this dose level. Thus, the recommended dose (RD) for phase II was docetaxel 75 mg/m^2, and oxaliplatin 130 mg/m^2 (Table 2).

Phase II

Patients' characteristics

The baseline patient characteristics for the patients enrolled in this study are shown in Table 3. All patients had a histologically proven adenocarcinoma of the stomach and no patient had gastroesophageal junction carcinoma. Approximately half of the patients had poorly differentiated carcinoma. Most patients (88.5%) had metastatic disease with lymph node (83%) and liver (44.7%) being the most commonly involved sites.

Efficacy

In total, 259 cycles were administered with a median of 6 cycles per patient (range 1–9 cycles). Relative dose intensities were 91.6% for docetaxel and 89% for oxaliplatin.

Of the 47 patients, 45 were assessable for treatment response. Two patients were not assessable but were included in the intent-to-treat analysis. They stopped chemotherapy after one cycle because of patients' refusals. All efficacy data are reported using the intent-to-treat patient population. The overall response rate (ORR) was 55.3% (95% CI, 40.6–70.1%) with 26 PRs, and the median duration of response was 4.2 months (range, 0.9–9.5). All CRs and PRs were confirmed at least 4 weeks later. Upon disease progression, 26 patients (55.3%) received the second-line treatment, including irinotecan/5-fluorouracil/folinic acid (mFOLFIRI) ($n = 12$), capecitabine/cisplatin (XP) ($n = 12$), capecitabine ($n = 1$) and sunitinib ($n = 1$); 8 patients (17%) received the third-line chemotherapy. The third-line treatments were 5-fluorouracil/doxorubicin/high dose methotrexate (FAMTX) ($n = 5$), mFOLFIRI ($n = 2$), and TS-1. At the time of writing, three patients are continuing the first-line treatment.

All patients were included in the survival analysis. After a median follow-up duration of 13.3 months (range 7.4–22.3 months), the median survival of all patients was 12.7 months (95% CI: 10.4–14.9 months), and an estimated 1-year survival rate was 52.1% (95% CI, 36.4–67.8%) (Fig. 1). The median TTP was 5.0 months (95% CI, 3.4–6.5 months) (Fig. 2).

Table 3 Patients characteristics

	Phase I No. (%)	Phase II No. (%)
No. of enrolled patients	12	47
Sex		
Male	9 (75)	37 (79)
Female	3 (25)	10 (21)
Median age (range)	53 (35–64)	56 (35–69)
ECOG PS		
0	1 (8)	8 (17)
1	7 (58)	32 (68)
2	4 (33)	7 (15)
Disease status		
Recurrent	2 (17)	5 (11)
Metastatic	10 (83)	42 (89)
Histological grade		
Well differentiated	1 (8)	1 (2)
Moderate differentiated	5 (41)	20 (43)
Poorly differentiated	6 (50)	26 (55)
Metastatic site		
Lymph node	8 (67)	39 (83)
Liver	6 (50)	21 (45)
Lung		5 (11)
Ovary		4 (9)
Rectum		3 (6)
Pancreas		3 (6)
Adrenal gland		3 (6)
Peritoneum		2 (4)
Others(bone, anastomosis site)	6 (50)	5 (11)

Safety

The treatment was generally well tolerated, and the incidence of grade 3–4 toxicities was relatively low. The most common toxicity was neutropenia. Grades 3–4 neutropenia occurred in 11 patients (23.4%) and in 13 of 259 cycles (5.0%); febrile neutropenia was observed in 7 patients (14.9%). Two patients experienced sepsis not febrile neutropenia, one of whom died of septic shock. No

Table 2 DLT and best response (phase I)

Docetaxel (mg/m^2/dose)	Oxaliplatin (mg/m^2/dose)	Total no. of patients	DLT	No. of cycles	Best response
60	100	3	None	17	2PR, 1PD
75	100	3	None	14	1PR,1SD,1PD
75[a]	130[a]	6	1	24	1PR, 2SD,2PD

[a] Recommended dose

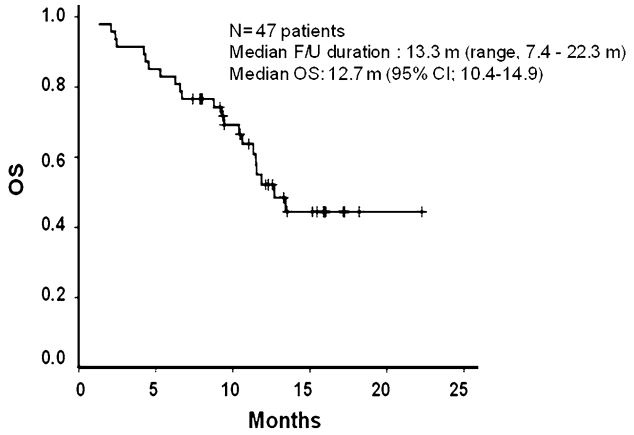

Fig. 1 Overall survival

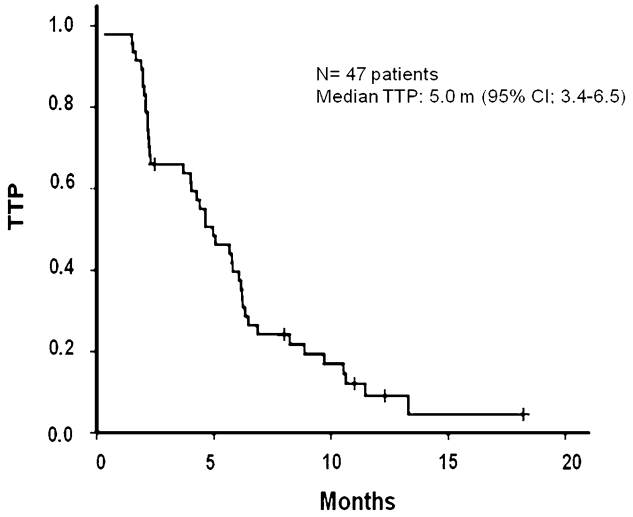

Fig. 2 Time to progression

treatment-related death occurred during this study. Non-hematologic toxicities of grade 3–4 occurred in less than 10% of patients. One patient experienced grade 3 nausea. Although peripheral neuropathy was commonly observed, most patients had mild (grade 1 in 66%, grade 2 in 17% of patients) symptoms, and grade 3 peripheral neuropathy occurred in only four patients (8.5%). Five (10.6%) patients experienced grade 3–4 non-hematologic toxicities leading to dose reductions in subsequent cycles of chemotherapy (Table 4).

Discussion

We conducted a phase I/II clinical trial of docetaxel combined with oxaliplatin to determine the recommended dose for advanced or recurrent gastric cancer in phase I, and to evaluate its efficacy and safety in phase II. In phase I study, 75 mg/m^2 of docetaxel combined with 130 mg/m^2 of oxaliplatin was determined to be the recommended dose for the phase II study. At this recommended dose level, the docetaxel and oxaliplatin combination regimen demonstrated promising efficacy, with a tumor response rate of 55.3% (95% CI, 40.6–70.1%), a median time to progression of 5.0 months (95% CI, 3.4–6.5 months), and a median survival of 12.7 months (95% CI: 10.4–14.9 months). These results are comparable to other studies [4, 6, 17].

We and our colleagues have previously reported that a docetaxel 75 mg/m^2 monotherapy produced a response rate

Table 4 Toxicity Profile (phase II)

Toxicity	Per cycle ($N = 259$)		Per patient ($N = 47$)	
	NCI-CTC grade (%)		NCI-CTC grade (%)	
	Grade 3	Grade 4	Grade 3	Grade 4
Hematologic toxicities				
Neutropenia	4 (1.5)	9 (3.5)	2 (4.3)	9 (19.1)
Febrile neutropenia	6 (2.4)	1 (0.4)	6 (12.8)	1 (2.1)
Thrombocytopenia	–	–	–	–
Anemia	–	–	–	
Non-hematologic toxicities				
Nausea/Vomiting	1 (0.4)	–	1 (2.1)	–
Peripheral neuropathy	N/A		4 (8.5)	–
Asthenia	–	–	–	–
Diarrhea	5 (1.9)	–	5 (10.6)	–
Constipation	–	–	–	–
Pain	1 (0.4)	–	1 (2.1)	–
Cutaneous	–	–	–	–
Infection		2 (0.8)		2 (4.3)

NCI-CTC National Cancer Institute Common Toxicity Criteria

of 15.9%, median time to progression 1.4 months, and median overall survival time of 11.0 months [2]. We previously conducted a phase II trial with docetaxel and cisplatin (DP) which rendered a response rate of 43.5% and median survival duration of 11.5 months [11]. The toxicity profile of the DP regimen seemed to be more favorable than that reported in the DCF regimen of the TAX 325 trial, which showed 84% incidence of grades 3–4 neutropenia and 29% incidence of febrile neutropenia. However, DP regimen was still associated with 17% grade 3 or 4 neutropenia [11, 17].

Kang et al. [6] compared 5FU/cisplatin with capecitabine/cisplatin and that study demonstrated capecitabine can replace 5-FU. Recently SPIRIT trial compared S1 monotherapy with a combination of S-1 and cisplatin [9]. Thus, 5-FU/platinum based chemotherapy is a reasonable standard regimen for advanced gastric cancer in Asian countries. The REAL-2 study recently demonstrated that oxaliplatin was associated with lower incidences of grade 3 or 4 neutropenia, alopecia, renal toxicity and thromboembolism when compared with cisplatin-based regimen [4]. Moreover, oxaliplatin-based regimens (oxaliplatin/5-fluorouracil/epirubicin and oxaliplatin/capecitabine/epirubicin) showed comparable efficacy in terms of survival and response rates, which support the use of oxaliplatin in gastric cancer. Prior phase II trials with docetaxel and oxaliplatin combination chemotherapy employed similar dosages and schedules as ours (docetaxel 60 mg/m^2 and oxaliplatin 130 mg/m^2 [13] docetaxel 65 mg/m^2 and oxaliplatin 120 mg/m^2 [7]), which reported response rates of 36–45% and overall survival of 9 months. Despite the dosage of docetaxel was higher (75 mg/m^2) in our study, the toxicity was not significantly increased. In addition, the response rate was higher (55.3%) with prolonged overall survival (12.7 months as compared with other phase II trials although any conclusive interpretation is not possible due to the nonrandomized nature of the study.

In this study, relative dose intensities were 91.6 and 89% for docetaxel and oxaliplatin, respectively. Although the incidence of grade 3–4 neutropenia was not low (23.4% of patients), neutropenia usually lasted for a short period of time most of which was not associated with neutropenic fever. The other phase II trial with a reduced dose of docetaxel (65 mg/m^2) plus oxaliplatin showed similar frequency of neutropenia grade 3 or 4 (26.1%) with slightly lower incidence of neutropenic fever (9.5%) [7].

For recurrent or metastatic gastric cancer, there have been only a few phase III trials as first-line regimen. Designing a phase III trial, an oxaliplatin-based regimen should be considered based on the favorable toxicity profile of our study as well as the REAL-2 trial.

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