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ORIGINAL ARTICLE

Phase II study of docetaxel and cisplatin combination chemotherapy in metastatic gastric cancer

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Abstract *Purpose*: Docetaxel, as a single agent, has demonstrated activity in patients with advanced gastric cancer and cisplatin has shown lack of overlapping toxicities with docetaxel. Therefore, we conducted a phase II study to assess the efficacy and the toxicity of a combination regimen of docetaxel plus cisplatin in patients with advanced gastric cancer who have never been treated with palliative chemotherapy. *Methods*: Ninety-two patients with metastatic gastric cancer were enrolled from April 2000 to March 2004. Patients with histologically confirmed gastric adenocarcinoma, at least one bi-dimensionally measurable lesion, no prior palliative chemotherapy and at least 6 months from the end of adjuvant chemotherapy were eligible for study entry. Docetaxel 75 mg/m^2 and cisplatin 75 mg/m^2 were given on day 1. The cycle was repeated every 3 weeks. The objective response was evaluated after three cycles of chemotherapy. Toxicity was assessed according to the National Cancer Institute common toxicity criteria scale version 2.0. *Results*: In total, 401 cycles were administered, with a median of 5 cycles per patient (range 1–9 cycles). The median age was 56 years (range 31–76). Eighty-six patients were evaluable for treatment response. The objective response rate was 43.5% (95% CI, 33.4–53.6) with one complete response and 39 partial responses. Twenty patients (21.7%) had stable disease and 26 patients (28.3%) had a progression. The median time to progression was 7.0 months (95% CI, 5.0–9.0) and the median overall survival was 11.5 months (95% CI, 9.5–13.4). The chemotherapy was generally well tolerated and the most common grade 3–4 toxicities were neutropenia (17.4%), nausea/vomiting (13.0%) and diarrhea (7.6%). *Conclusion*: The combination chemotherapy of docetaxel with cisplatin in advanced gastric cancer was tolerable for most patients and showed a promising antitumor activity as a first-line therapy.

Keywords Docetaxel · Cisplatin · Gastric cancer · Chemotherapy

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Introduction

Gastric cancer remains a leading cause of death from malignant neoplasms in Korea [1]. Although the incidence of early gastric cancer (T1N0) is increasing, most patients still present with locally advanced or metastatic disease. The median survival in patients with advanced gastric cancer (AGC) is 6–9 months. A number of randomized clinical trials have confirmed that chemotherapy confers survival benefit when compared to best supportive care alone [2–5]. Median survival

was approximately 7.5–12 months in the chemotherapy group versus 3–5 months for patients receiving best supportive care alone [4, 5]. Single agent chemotherapy with 5-fluorouracil, doxorubicin, mitomycin C and cisplatin produced response rates of approximately 20% [6]. Different combination of anti-tumor drugs has generally produced response rates in the range of 30–50%. However, the median survival did not exceed 1 year in randomized trials [7]. Therefore, the search for newer treatment should be continuously sought in patients with metastatic AGC.

The role of taxanes has been extensively studied in a broad spectrum of human solid tumors including head and neck, lung, breast, ovarian and gastric cancers. Docetaxel, as a single agent, has demonstrated activity in patients with AGC who have been previously treated with chemotherapy. In a European study, 22% of patients with chemo-naïve AGC achieved partial responses for a median duration of 7.5 months after receiving docetaxel 100 mg/m^2 [8]. Recently, a Korean group has reported a response rate of 15.9% with docetaxel 75 mg/m^2 with low incidence of grade 3–4 toxicities [9]. Promising anti-tumor activity of docetaxel has prompted investigators to search for active combination agents. The Swiss Group for Clinical Cancer Research and the European Institute for Oncology in Milan collaboratively studied the combination of docetaxel and cisplatin in a phase II trial of 48 patients with AGC [10]. Docetaxel (85 mg/m^2) was administered with cisplatin (75 mg/m^2) every 3 weeks for up to 8 cycles. This combination regimen has resulted in a response rate of 56% with median time to progression (TTP) of 6.6 months and median overall survival (OS) of 9 months. A three-arm, multi-center phase II trial compared the European standard combination, ECF [epirubucin, cisplatin 5-fluorouracil (5-FU)], with a docetaxel-based regimen, namely DCF (docetaxel, cisplatin 5-FU) or DC (docetaxel, cisplatin). Although preliminary results from the 119 evaluable patients showed that the DCF regimen was superior in response, it was associated with a high rate of complicated neutropenia [11]. Ajani et al. [12] has recently reported their results of randomized phase II trial comparing DC with DCF in chemo-naïve gastric cancer patients, and demonstrated that DCF was superior to DC in terms of response rate, time to progression and overall survival. However, they also observed a high frequency of grade 3 or 4 neutropenia. The V-325 trial, the largest global phase III trial in gastric cancer, randomized 547 patients to receive DCF or CF, and found grade 3–4 neutropenia in 87% of the patients in the DCF arm [13]. The aim of the present study was to confirm the efficacy and tolerability of docetaxel 75 mg/m^2 combined with cisplatin 75 mg/m^2 in a population of Korean patients with metastatic AGC.

Materials and methods

Patient characteristics

This study was a prospective, open-label, phase II study conducted in Korean population in a single institution. The eligibility criteria were as following: histologically proven gastric adenocarcinoma; metastatic disease; at least one bi-dimensionally measurable lesion according to the WHO criteria; age 18 years or older; life expectancy of at least 3 months; no prior palliative chemotherapy; ECOG performance status 0–2, absolute neutrophil count $\geq 1.5 \times 10^9$/l; platelets $\geq 100 \times 10^9$/l; serum creatinine ≤ 140 μmol/l [if borderline (130–140 μmol/l), a creatinine clearance was performed and was > 60 ml/min]; total bilirubin $\leq 1 \times$ upper limit of normal (ULN); aspartate aminotransferase and alanine aminotransferase $\leq 2.5 \times$ ULN; alkaline phosphatase $\leq 5 \times$ ULN; and a signed informed consent in compliance with the institutional guideline before study entry. Prior adjuvant chemotherapy was allowed if at least 6 months from the end of adjuvant chemotherapy has passed at the time of study entry.

Treatment

The treatment consisted of docetaxel 75 mg/m^2 in one hour intravenous infusion followed by cisplatin 75 mg/m^2 in 1 h intravenous infusion given on day 1 every 3 weeks until disease progression. All patients received hyperhydration with at least 3 l normal saline in 24 h and dexamethasone 8 mg p.o. at 12 and 6 h before docetaxel infusion. The recommended antiemetic schedule comprised 5-HT3 inhibitors and dexamethasone 20 mg at the beginning of cisplatin infusion. Toxicity was assessed according to the National Cancer Institute common toxicity criteria (NCI-CTC) scale version 2.0. The severity of any toxicity not defined in the NCI-CTC were graded as 1 = mild, 2 = moderate, 3 = severe, or 4 = very severe. Complete blood counts and blood chemistry were obtained before the beginning of each cycle. A 20% dose reduction of docetaxel was allowed for grade 4 neutropenia. Treatment was stopped upon unacceptable toxicity, clinical deterioration, or patient's refusal.

Tumor response was evaluated according to WHO criteria [14]. Responses were assessed after 2 and after 4 cycles of chemotherapy. A complete response was defined as disappearance of all clinically detectable

disease for at least 4 weeks. Partial response was defined as a $\geq$ 50% decrease in sum of areas of tumor measured by product of perpendicular diameters without the appearance of new disease or increase in any single lesion of more than 25%. Stable disease was defined as no significant change in measurable or assessable malignant disease without the appearance of new lesions. This included a less than 50% decrease in tumor size and a less than 25% increase in any tumor site. Stable disease required no worsening in KPS. Progressive disease was defined as the appearance of new malignant lesions, a $\geq$ 25% increase in measurable disease ($\geq$ 25% increase in estimated size for assessable disease) at any site of more than 2 cm^2, or a $\geq$ 50% increase in size for any site of less than 2 cm^2 in size at the initiation of treatment.

Statistical analysis

According to the Simon's two-stage optimal design, a sample size of 83 was required to accept the hypothesis that the true response rate is greater than 35% with 90% power, and to reject the hypothesis that the response rate is less than 20% with 5% significance. At the first stage, if there were fewer than 8 responses out of the initial 37 patients, the study would terminate. Descriptive statistics were reported as proportions and medians. Kaplan–Meier estimates were used in the analysis of all time-to-event variables, and the 95% confidence interval (CI) for the median time to event was computed. The primary end point was the response rate and the secondary measures were the survival and time to progression. Time to progression of disease was calculated from the first cycle of chemotherapy. Survival was defined as the time elapsed from the starting date of chemotherapy to the date of death or the last follow-up. Survival rates and time to progression were assessed by the Kaplan–Meier method. The dose intensity was calculated as the ratio of the total dose divided by the total treatment duration. The relative dose intensity was calculated as the ratio of the dose intensity actually delivered to the dose intensity planned by the protocol.

Results

From April 2000 to March 2004, 92 patients were enrolled for the study. Patient characteristics are provided in Table 1. The median age was 56 years (range 31–76). ECOG performance status scores were 0 in 23 patients (25%), 1 in 64 patients (70%), and 2 in 5 patients (5%). Thirty-eight percent of patients recurred after curative surgery and 10% of patients had palliative surgery. Regarding tumor status, all patients had metastatic disease at study entry; 37% of patients had peritoneal carcinomatosis, 32% had liver metastases, 25% had lymph node metastases, 3% pulmonary metastases and 1% had ovarian metastasis.

Tumor response and survival

A total of 401 cycles were administered, with a median of 5 cycles per patient (range 1–9 cycles). Of the 92 patients, 86 patients were evaluable for treatment response. Six patients were not evaluable for response owing to early withdrawal after the first cycle. The objective response rate was 43.5% (95% CI, 33.4–53.6 with 1 complete response and 39 partial responses. Twenty patients (21.7%) had stable disease and 26 patients (28.3%) had progressions. The median time to progression was 7.0 months (95% CI, 5.0–9.0) and the median overall survival was 11.5 months (95% CI, 9.5–13.4). Eighty-six and 95% of the planned dose intensity were actually delivered for docetaxel and cisplatin, respectively.

Toxicity

All patients were evaluable for toxicities. The most common grade 3–4 toxicity were neutropenia (17.4%) and nausea/vomiting (13.0%). Five patients with grade 4 neutropenia experienced a transient febrile episode with spontaneous recovery. Non-hematologic toxicities included vomiting, anorexia and fatigue, which were

Table 1 Patient characteristics (n = 92)

	Number of patients (%)
Total	92
Median age (range)	56 (31–76)
Sex	
Male	56
Female	36
Performance status, n (%)	
0	23 (25)
1	64 (70)
2	5 (5)
Previous surgery, n (%)	
None	48 (52)
Curative	35 (38)
Palliative	9 (10)
Metastatic site, n (%)	
Peritoneal carcinomatosis	34 (37)
Liver	29 (32)
Lymph nodes	23 (25)
Lung	3 (3)
Krukenberg tumor	1 (1)
Others	7 (8)

usually mild and manageable. No patients experienced renal failure from cisplatin. Grade 3 or 4 peripheral neuropathy was not frequent (1.1%) in this series of patients. There were no toxic deaths recorded.

Discussion

We evaluated the feasibility and the efficacy of docetaxel in combination with cisplatin in patients with metastatic gastric cancer. The anti-tumor activity of the combination was relatively high. The objective "The objective response rate was 43.5% (95% CI, 33.4–53.6) with 1 complete response and 39 partial responses. The study results are generally consistent with those from previous studies. Kettner et al. [15] and Ridwelski et al. [16] reported response rates of approximately 40% in patients with AGC who received the docetaxel and cisplatin chemotherapy. The median survival times in the two groups were 9 and 10.4 months, respectively. In our study, the median overall survival time was 11.5 months (95% CI, 9.5–13.4). We and our colleagues have previously reported that a docetaxel 75 mg/m^2 monotherapy produced a response rate of 15.9%, median time to progression 1.4 months, and median overall survival time of 11.0 months [9]. Despite of a significant increase in response rate and median time to progression when cisplatin was combined with docetaxel, the survival time seems to be similar between the single agent and combination chemotherapy. Georgoulias et al. [17] used a 3-weekly high-dose regimen of docetaxel 100 mg/m^2 on day 1 and cisplatin 80 mg/m^2 on day 2 with concomitant granulocyte colony-stimulating factor (G-CSF) support. They reported a response rate of 45%, a median time to progression of 8.3 months and median survival of 11 months. Therefore, an escalated dose of docetaxel doesn't seem to confer a clear survival benefit compared with the lower doses used in this study. We have recently reported a phase II study of a combination chemotherapy of epirubicin, docetaxel and cisplatin (EDP) as a first-line therapy in unresectable gastric cancer [18]. In this study, we administered 40 mg/m^2 epirubicin (reduced to 30 mg/m^2 due to high incidence of febrile neutropenia; 75%), followed by 60 mg/m^2 docetaxel, then 75 mg/m^2 cisplatin every 3 weeks. Despite of the objective response rate of 47% (95% CI, 28–66), the median overall survival was 11.0 months (95% CI, 9.5–12.4).

The combination chemotherapy of docetaxel and cisplatin demonstrated acceptable tolerability. Although neutropenia was the most common grade 3–4 toxicity, only five patients experienced neutropenic fever, which eventually recovered without complication. Regardless of prophylactic G-CSF used in a recent randomized phase II trial, grade 3 or 4 neutropenia occurred in 87% of patients and 60% of cycles for docetaxel/cisplatin combination chemotherapy [12]. The incidence of febrile neutropenia or neutropenic infection rate was observed in 27% of patients for the regimen, although there was no toxic death. The low incidence of grade 3 or 4 neutropenia is likely due to the fact that weekly blood counts were not checked in our study. Instead, weekly blood counts were assessed once every 3 weeks. Nausea was the most common grade 3–4 non-hematologic toxicity (13.0% of patients). There were no severe hypersensitivity reactions or fluid retentions. Comparable to other studies, grade 3 or 4 peripheral neuropathy was not a common adverse event [8, 10–17].

The optimal dosing and scheduling of docetaxel-based chemotherapy need to be refined. One of the plausible explanations for better tolerability of our regimen would be lower dosing compared to other trials. Ajani et al. administered higher dose of docetaxel (85 vs. 75 mg/m^2 in this study) and same dose of cisplatin 75 mg/m^2, repeated every 3 weeks [12]. In our previous phase II study of docetaxel and cisplatin combination therapy as a second-line treatment in gastric cancer patients, we used the same dosing and scheduling for this study (docetaxel 75 mg/m^2 on day 1, cisplatin 75 mg/m^2 on day 2, every 3 weeks) and observed grade 3–4 neutropenia in 13.5% of cycles and 28% of patients [19]. The triple combination chemotherapy with docetaxel, cisplatin, and 5-FU (DCF) was compared to a double chemotherapy with cisplatin and 5-FU (CF) in a phase III trial [13]. The results of this phase III trial showed that DCF was superior to CF in terms of time to progression (5.6 vs. 3.7 months, $P = 0.0004$), response rate (37 vs. 25%, $P = 0.0106$), and overall survival (9.2 vs. 8.6 months, $P = 0.0201$). However, a high toxicity profile with grade 3 neutropenia in 82% of patients for DCF remains a concern. Although docetaxel-based chemotherapy is currently recommended as the first-line treatment for untreated gastric cancer patients, more tolerable dosing with alternative schedules such as weekly docetaxel combined with platinum or platinum and 5-FU should be sought in future trials.

In conclusion, this study indicates that the combination chemotherapy of docetaxel 75 mg/m^2 and cisplatin 75 mg/m^2 is active in patients with metastatic, or recurrent AGC as a first-line treatment. The objective response rate of the regimen was comparable to other phase II trials, however, a search for more optimal systemic chemotherapy and clinical trials on new novel anti-tumor agents are still warranted.

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