The Efficacy of Docetaxel and Cisplatin Combination Chemotherapy for the Treatment of Advanced Gastric Cancer after Failing to 5-Fluorouracil Based Chemotherapy

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Purpose: This study was conducted to confirm the efficacy and toxicity of docetaxel and cisplatin combination chemotherapy (DP) in patients with advanced gastric cancer.

Materials and Methods: Patients with measurable gastric adenocarcinoma received intravenous docetaxel 75 mg/m² and cisplatin 75 mg/m² with premedication on day 1, which was repeated every 3 weeks. All patients received DP as a second-line treatment after failing to 5-FU based chemotherapy.

Results: 34 patients were enrolled in this study between January 1998 and August 2003. A total of 112 cycles (median 3 cycles) were administered. Responses were evaluable in 30 patients. The objective response rate was 16.7% (95% CI: 3.5~30.3), with a stable disease in 56.7% (95% CI: 40.0~74.4) and a progressive disease in 26.7% (95% CI: 10.9~42.5) of patients, with a median follow up duration of 20 months for all the patients. The median

duration of response, time to progression and overall survival were 2.1 months (95% CI: 0.4~3.9), 4.2 months (95% CI: 2.3~6.1) and 6.8 months (95% CI: 1.3~12.3), respectively, with a 1-year survival rate of 32%. The toxicity was evaluated in 30 patients, with neutropenia being most common. Renal impairment was seen in two patients with grade 3 creatinine elevation and liver enzyme elevation in four with grades 3 and 4.

Conclusion: Although DP was an active combination regimen, with a tumor control rate of about 73% and with moderate tolerance, adjustment of the administration schedule, with further evaluation of other combination chemotherapies of docetaxel with new agents, other than cisplatin, seem warranted. (*Cancer Research and Treatment* 2004;36:367-371)

Key Words: Stomach neoplasm, Cisplatin, Docetaxel

INTRODUCTION

According to the 1997 World Health Organization statistics, 765,000 worldwide deaths were due to gastric cancer (1).

According to several studies, 75% of patients with gastric cancer are considered incurable at the time of diagnosis due to an advanced disease. Even among patients with clinically resectable tumors, the relapse rate of such patients is as high as 70 to 80%, with a local residual disease remaining following surgery or developing later (2).

Randomized clinical trials have shown modest improvement in survival with chemotherapy over that of supportive care

alone in patients with advanced gastric cancer (3). 5-Fluorouracil-based chemotherapy is commonly used in the setting of advanced gastric cancer, but is not considered as the standard care due to the limited benefits observed with these regimens (4). Combination chemotherapy generally provides superior response rates over single-agent therapy, but is not associated with a survival advantage (5); therefore, new agents and treatment strategies must be evaluated (6). Docetaxel targets a fundamental step in the cell cycle: enhancing microtubule assembly and inhibiting tubulin depolymerization (7). Docetaxel has been reported to have activity in several human malignancies, including advanced gastric cancer, with proven clinical efficacy in a number of solid tumors (8). Cisplatin has been used in the treatment of gastric cancer in neoadjuvant, adjuvant and palliative settings, with various combination regimens reported to show response rates between 20~71% (9).

Combination chemotherapy of docetaxel and cisplatin has the advantage of obtaining additive or synergistic effects against gastric cancer.

A phase I-II trial to investigate the activity and tolerance of docetaxel in combination with cisplatin was conducted on patients

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with advanced gastric cancer. That study achieved a 53% response rate and median time to progression (TTP) of 7 months, with 85 mg/m² docetaxel and 75 mg/m² cisplatin every three weeks (10). Two studies from Japan also used the combination treatment of docetaxel 60 mg/m² and cisplatin 80 mg/m² in gastric cancer (11,12). In two other studies, the overall response rates were 28 (11) and 25% (12), respectively.

The objective of this study was to confirm the efficacy and toxicity of docetaxel and cisplatin combination chemotherapy in patients with advanced gastric cancer.

MATERIALS AND METHODS

The study enrolled patients with histologically proven gastric adenocarcinomas. As inclusion criteria the patients had to be ≥ 18 years of age, have an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 and a life expectancy > 3 months. The laboratory criteria included an absolute granulocyte count $\geq 1,500$ cells/mm³, platelets $\geq 100,000$ cells/mm³, hemoglobin ≥ 9 g/dl, serum creatinine ≤ 2 mg/dl, bilirubin ≤ 1.5 mg/dl and transaminases ≤ 4 times the normal upper limit. Patients with an unmeasurable disease were excluded. The study enrolled patients with gastric cancer that had recurred or progressed after treatment with 5-FU based chemotherapy regimens. All patients were strictly treated according to the protocol, with no exceptions.

1) Treatment plan

All treatment was administered on an inpatient basis, using standard premedication. Docetaxel was administered at a dose of 75 mg/m², infused over 1 h, and cisplatin at a dose of 75 mg/m², also infused over 1 h, every 3 weeks. Pre- and post-hydration with at least 2,000 ml of normal saline were mandatory. The prophylactic antiemetic medication consisted of the administration of dexamethasone and 5-hydroxytryptamine-3 antagonists. Before docetaxel administration, patients were premedicated with dexamethasone, 20 mg i.v., administered 12 and 6 h prior to treatment, and dephenhydramine, 50 mg i.v., and cimetidine, 300 mg i.v., 30 min prior to therapy to prevent the onset of hypersensitivity reactions and reduce and/or delay skin toxicity and fluid retention.

The patients were evaluated for toxicity after each course, with adjustment for optimal dosage planned to minimize the hematological and nonhematological toxicities. Adverse reactions were evaluated according to WHO standard criteria.

The drug dosage was reduced by 25% in cases of grade 4 febrile neutropenia, grade 1 nephrotoxicity or grade 2 neuropathy, if the lowest platelet count was less than 25,000 cells/mm³, or if any severe ($> \text{WHO grade 2}$) non-hematological toxicity was observed in the previous cycle. Docetaxel was stopped for any cases of grade 4 skin toxicity or a grade 3 anaphylactic reaction. Both chemotherapeutic drugs were discontinued in the event of transitory $\geq \text{grade 2}$ renal toxicity or definitive decrease in creatinine clearance (< 60 ml min⁻¹), $\geq \text{grade 3}$ neuropathy, or if severe toxicity recurred despite dose attenuation. Likewise, any patient who required more than 2 weeks for full recovery from adverse reactions (except alopecia and mild neuropathy) was removed from the study.

2) Response evaluation

The primary efficacy endpoint of this trial was an objective response rate (complete plus partial responses), which was evaluated according to the WHO standard criteria. Tumor assessment for all lesions was performed at the end of every three cycles.

A complete response (CR) was defined as a complete resolution of the disease by physical and radiographic examinations, no new lesions and no disease related symptoms. A partial response (PR) was defined as a $\geq 50\%$ reduction in the sum of the products of perpendicular measurements of all sites of the measurable disease, and a progressive disease (PD) as a $\geq 25\%$ increase in the sum of the products of the perpendicular diameters of all measurable lesions. A stable disease (SD) was defined as any condition other than an objective response or progressive disease.

The time to progression (calculated from the start of therapy to the time of progression or relapse) and overall survival were used as secondary efficacy endpoints.

3) Statistical analysis

According to the optimal two-stage phase II design, the treatment program was designed to reject a response rate less than 15% (P0) and to provide a statistical power of 90% in assessing the activity of the regimen in terms of a response rate of 40% (P1) for an (error less than 0.05. If 2 or fewer responses were noted in the first 16 eligible patients, any accrual would be halted. Because responses were observed, additional patients were enrolled, to a final accrual of 34 patients. 30 of the 34 patients were actually analyzed, with a drop rate of 10%. The efficacy was assessed on the basis of a per protocol analysis. The overall survival and time to progression were calculated using the Kaplan-Meier method.

RESULTS

Thirty-four patients were enrolled in this study between January 1998 and August 2003. Four patients received no treatment due to their poor performance status. Two patients degenerated prior to treatment and two were dropped before their responses could be evaluated. A 77 year old female patient was enrolled, due to an ECOG performance status of 1, and tolerated 3 cycles of chemotherapy without dose reduction. Thirty patients were evaluable for toxicity and response. Table 1. summarizes the patient characteristics.

The median age of the 22 (73%) male and eight (27%) female patients was 59 years (range 28 to 77 years), and the median ECOG performance status was 1 (range, 0-2). 13 (45%) patients underwent surgery, four had previously been treated with a curative resection and remaining nine required palliative surgery due to distant metastasis. A total of 112 cycles (median 3 cycles) were administered. The median follow up duration for all patients was 20 months. 23 (77%) patients had multiple metastasis involving two or more organ systems.

The responses were evaluable in 30 patients. All patients received DP combination chemotherapy as the second-line treatment having failed 5-FU based chemotherapy. On the basis of the previous exposure to 5-FU, 11 (36.7%) patients were defined as chemosensitive, as there had been no relapse of

Table 1. Patient's characteristics

Number of patients	No. of patients	%
Entered	34	100
Evaluable	30	88
Lost to follow-up	4	12
Age (years)		
Median	59	
Range	28~77	
Sex		
Male	22	73
Female	8	27
ECOG performance status		
0	12	40
1	14	47
2	4	13
Previous surgery		
Curative	4	13
Palliative	9	30
None	17	57
Sites of metastases		
Lymph nodes	15	50
Liver	14	33
Peritoneum	8	27
Pleura	1	3
Lung	6	20
Bone	2	7
Number of involved organs		
Single	7	23
Multiple	23	77

greater than 6 months following the completion of 5-FU regimen in an adjuvant setting, or progression for four months following the end of the 5-FU regimens in a metastatic setting; 14 (46.7%) patients were considered chemoresistant, due to a recurrence within 6 months of the 5-FU regimens discontinuation in an adjuvant setting, or progression within four months of the end of the 5-FU regimens in a metastatic setting, while 5 (16.7%) were classified as chemorefractory, due to a recurrence or progression of the disease in metastatic or adjuvant settings.

The overall objective response rate was 16.7% (95% CI: 3.5~30.3), with a stable disease in 56.7% (95% CI: 40.0~74.4) of patients and a progressive disease in 26.7% (95% CI: 10.9~42.5). The responses were also given in relation to previous chemotherapy. All five of the 5-FU refractory patients progressed. For the 5-FU resistant patients: 1 of the 14 patient achieved PR (7.1%). Of the 5-FU sensitive patients: 4 of the 11 patients achieved PR (36.4%). The survivals of all the patients in this study are represented in Fig. 1. The median survival time was 6.8 months (95% CI: 1.3~12.3) for the whole series, with a 1-year survival rate of 32%; 3.3 months (95% CI: 3~3.9) for the 5 refractory patients, 10 months (95% CI: 3.9~16.2) for the 14 resistant patients and 9.4 months (95% CI: 5.5~13.3) for the 11 sensitive patients. The median duration of response and time to progression were 2.1 (95% CI: 0.4~3.9) and 4.2 months (95% CI: 2.3~6.1) (Fig. 1),

Fig. 1. Overall survival and time to progression in the treated population.

respectively.

1) Toxicities

The toxicity was evaluable in 30 patients. The worst toxicities associated with treatment are reported in Table 2. Neutropenia was the most common toxicity, with grades 2 and 3 neutropenia observed in 47% of the 30 patients. Neutropenic fever developed in two patients, who recovered with intravenous antibiotics and G-CSF. Grades 3 and 4 thrombocytopenia was seen in six patients (20%).

The nonhematological toxicities were alopecia, peripheral neuropathy, ARF and nausea or vomiting. Renal impairment was seen in two patients, with grade 3 creatinine elevation and liver enzyme elevation seen in four patients with grades 3 and 4. With regards to liver enzyme elevation, this adverse effect was unusual in the docetaxel and cisplatin combination chemotherapy. Four patients with isolated hyperbilirubinemia had liver metastasis, and the disease progressed despite ongoing chemotherapy. Therefore, there is a possibility that the hyperbilirubinemia was due to disease progression, and not entirely due to the adverse effect of docetaxel.

Treatment was delayed in 36 cycles and the dose reduced in 6. Treatment doses were modified for the following reasons: renal impairment (33.3%), isolated hyperbilirubinemia (33.3%), nausea/vomiting (16.7%) and thrombocytopenia (16.7%). The median dose intensity for the docetaxel and cisplatin was 22.5 mg/m²/week and 22.5 mg/m²/week, respectively (range 18.75~25).

DISCUSSION

The continuing lack of substantial progress after 5-FU, doxorubicin and mitomycin C (FAM) combination chemotherapy, as the standard treatment of advanced gastric cancer, particularly in patients with poor performance status or compromised organ function, who are unlikely to tolerate potentially active, but toxic regimens, have prompted investigators to evaluate new agents and/or drug combinations, including docetaxel, paclitaxel and irinotecan (10,13~17). Docetaxel, however, may be a more active taxane against advanced gastric

Table 2. The worst toxicities associated with treatment

Toxicity	Grade 1 number (%)	Grade 2 number (%)	Grade 3 number (%)	Grade 4 number (%)
Neutropenia	2 (7)	8 (27)	6 (20)	
Anemia	1 (3)	2 (7)	1 (3)	
Thrombocytopenia	1 (3)	2 (7)	5 (17)	1 (3)
Nausea/vomiting	3 (10)	2 (7)	2 (7)	
Diarrhea	1 (3)	1 (3)		
Mucositis	2 (7)			
Neuropathy	2 (7)	2 (7)		
Fluid retention	3 (10)	1 (3)		
Renal impairment	6 (20)		2 (7)	
Hepatic impairment	5 (17)	2 (7)	2 (7)	2 (7)
Hypersensitivity	1 (3)	3 (10)		

cancer than paclitaxel. Docetaxel shares a common mechanism of action with paclitaxel, but preclinical data suggests more activity compared with paclitaxel (7), with available clinical data suggesting incomplete cross-resistance between these taxanes (18).

A previous study with 5-FU, leucovorin and docetaxel reported a response rate of 45% (19), and FEP (5-FU, Etoposide, Cisplatin) combination chemotherapy, as a salvage treatment for advanced gastric cancer, showed a response rate of 32.1% (20).

Docetaxel has an established activity as combination regimen for advanced gastric cancer with different dosage of either 75 mg/m² or 85–100 mg/m², with response rates of 37.2 and 56%, respectively (17,21). Two studies from Japan also used the combination treatment of docetaxel 60 mg/m² and cisplatin 80 mg/m² in gastric cancer (11,12), with overall response rates of 28 (11) and 25% (12), respectively.

In addition, a phase II study with docetaxel for the treatment of 25 patients previously exposed to first-line 5-FU and cisplatin (FP) resulted in a response rate of 20% (9). The objective response rate for the combination of epirubicin 75 mg/m² and docetaxel 75 mg/m² every 3 weeks was 21% (22). In a phase II study of the Southern Italian Oncology Group, the response rate with 100 mg/m² docetaxel as a second-line single-agent was 17% (23).

The present study evaluated the efficacy of combined docetaxel and cisplatin as a second-line chemotherapy for advanced gastric cancer, with an objective response rate, median time to progression and median overall survival of 16.7%, 4.2 months and 6.8 months, respectively, but failed to show superiority to other regimens and phase II studies. Compared with the response rates reported in clinical studies conducted in other countries, the response rate of this study was lower than the European studies, but similar to those in Japan. The reasons for these different response rates are as follows, this study included patients who had previously received chemotherapy as a second-line treatment, with potential differences in the patients' backgrounds. It has recently been reported that the administration of docetaxel in a weekly schedule was effective and well tolerated in women with metastatic breast cancer. The data in that study show that decreasing the amount of drug and shortening the interval between administrations make it possible to maintain the efficacy without the increased risk of neu-

tropenia (24).

CONCLUSIONS

Although the DP regimen has antitumor activity, with a tumor control rate of about 73% and moderate tolerance, adjustment of the administration schedule of the chemotherapeutic drugs, with further evaluation of other combination chemotherapies of docetaxel with new agents, other than cisplatin, seem warranted.

REFERENCES

1. World Health Report 1998: A Vision for All. Geneva, Switzerland: World Health Organization; 1998.
2. Clarke JS, Cruze K, El Farra S, Longmire WP Jr. The natural history and results of surgical therapy for carcinoma of the stomach: an analysis of 250 cases. *Am J Surg.* 1961;102:143-52.
3. 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.
4. Cullinan SA, Moertel CG, Fleming TR, Rubin JR, Krook JE, Everson LK, et al. A comparison of three chemotherapeutic regimens in the treatment of advanced pancreatic and gastric carcinoma. Fluorouracil vs. fluorouracil and doxorubicin vs. fluorouracil, doxorubicin, and mitomycin. *JAMA.* 1985;253:2061-7.
5. Macdonald JS, Schein PS, Woolley PV, Smythe T, Ueno W, Hoth D, et al. 5-Fluorouracil, doxorubicin and mitomycin (FAM) combination chemotherapy for advanced gastric cancer. *Ann Intern Med.* 1980;93:533-6.
6. Kulke MH. The treatment of advanced gastric cancer: in search of the right combination. *J Clin Oncol.* 2000;18:2645-7.
7. Tanaka M, Obata T, Sasaki T. Evaluation of antitumor effects of docetaxel (Taxotere) on human gastric cancers in vitro and in vivo. *Eur J Cancer.* 1996;32A:226-30.
8. Crown J, O'Leary M. The taxanes: an update. *Lancet.* 2000; 355:1176-8.
9. Vanhoefer U, Harstrick A, Wilke H, Achterrath W, Preusser P, Stahö M. Phase II study of docetaxel (D) as salvage chemotherapy in patients with advanced gastric cancer. *Eur J Cancer.* 1999;35(Suppl 4):145.

10. Roth AD, Maibach R, Martinelli N. Taxotere-cisplatin in advanced gastric carcinoma (gastric cancer): an active drug combination. *Proc Annu Meet Am Soc Clin Oncol*. 1998;17:283.
11. Saitoh S, Sakata Y. Docetaxel and cisplatin in patients with advanced gastric cancer: results of Japanese phase I/II study. *Gastric Cancer* 2002;5(Suppl 1):23-6.
12. Mitachi Y, Sakata Y, Ohtsu A, Hyodo I, Katsu K, Sirenji M, et al. Docetaxel and cisplatin in patients with advanced or recurrent gastric cancer: a multicenter phase I/II study. *Gastric Cancer*. 2002;5:160-7.
13. Bokemeyer C, Hartmann JT, Lampe CS, Clemens MR, Quietzsch D, Forkmann L, et al. Paclitaxel and weekly 24-hour infusion of 5-fluorouracil/folinic acid in advanced gastric cancer. *Semin Oncol*. 1997;24:S19-96-S19-100.
14. Boku N, Ohtsu A, Shimada Y, Shirao Y, Seki S, Saito H, et al. Phase II study of a combination of irinotecan and cisplatin against metastatic gastric cancer. *J Clin Oncol*. 1999;17:319-23.
15. Murad AM, Petroianu A, Guimaraes RC, Aragao BC, Cabral LO, Scalabu A, et al. Phase II trial of the combination of paclitaxel and 5-fluorouracil in the treatment of advanced gastric cancer: a novel, safe, and effective regimen. *Am J Clin Oncol*. 1999;22:580-6.
16. Kollmannsberger C, Quietzsch D, Haag C, Lingenfelser T, Schroeder M, Hartmann JT, et al. A phase II study of paclitaxel, weekly, 24-hour continuous infusion 5-fluorouracil, folinic acid and cisplatin in patients with advanced gastric cancer. *Br J Cancer*. 2000;83:458-62.
17. Ridwelski K, Gebauer T, Fahlke J, Kroning H, Kettner E, Meyer F, et al. Combination chemotherapy with docetaxel and cisplatin for locally advanced and metastatic gastric cancer. *Ann Oncol*. 2001;12:47-51.
18. Valero V, Jones SE, Von Hoff DD, Booser DJ, Mennel RG, Ravdin PM, et al. A phase II study of docetaxel in patients with paclitaxel-resistant metastatic breast cancer. *J Clin Oncol*. 1998;16:3362-8.
19. Kim YT, Sohn JH, Kim SH, Rha SY, Kim C, Roh JK, et al. Infusional 5-Fluorouracil, leucovorin and docetaxel in advanced gastric cancer. *Cancer Res Treat*. 2003;35:123-9.
20. Chung JH, Bae YZ, Kim SH, Moon CH, Chung JY, Kwon HC, et al. Salvage treatment of advanced gastric cancer using FEP (5-FU, Etoposide, Cisplatin) combination chemotherapy. *Cancer Res Treat*. 2002;34:382-7.
21. Roth AD, Maibach R, Martinelli N, Fazio N, Aapro MS, Pagani O, et al. Docetaxel (Taxotere)-cisplatin (TC): an effective drug combination in gastric carcinoma. Swiss Group for Clinical Cancer Research (SAKK), and the European Institute of Oncology (EIO). *Ann Oncol*. 2000;11:301-6.
22. Andre T, Louvet C, Ychou M. Docetaxel-epirubicin as second-line treatment for patients with advanced gastric cancer. *Proc Am Soc Clin Oncol*. 1999;18:1062 (Abstr).
23. Giuliani F, Gebbia V, De Vita F, Maiello E, Gebbia N, Paoletti G, et al. Docetaxel (taxotere) as salvage chemotherapy in patients with advanced gastric cancer. A phase II study of the Southern Italian Oncology Group (GOIM). *Ann Oncol*. 2000;11(Suppl 4):67 (Abstr).
24. Burstein HJ, Manola J, Younger J, Parker LM, Bunnell CA, Scheib R, et al. Docetaxel administered on a weekly basis for the metastatic breast cancer. *J Clin Oncol*. 2000;18:1212-9.