Subsets of Patients with Advanced Gastric Cancer Responding to Second-line Chemotherapy with Docetaxel - Cisplatin

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Abstract. *The role of docetaxel in combination with cisplatin in the management of gastric cancer resistant to first-line chemotherapy has not yet been defined. This multicenter prospective phase II study evaluated the activity and toxicity of the docetaxel-cisplatin combination in gastric cancer patients, whose tumors were primarily resistant to first-line chemotherapy or had tumor recurrence after chemotherapy. Treatment consisted of docetaxel 70 mg/m^2 i.v. followed by cisplatin 70 mg/m^2 both administered on day one, every three weeks. Thirty-two patients were enrolled in the study. The median age was 60 years and the median performance status (ECOG) was 1. Six (19%) patients had tumor progression during adjuvant chemotherapy, 19 (59%) had tumor recurrence after primary chemotherapy and 7 (22%) had tumor progressing while on first-line chemotherapy. Twenty (62%) patients had received non-platinum agents as first-line chemotherapy, while the rest had received the so-called "new generation" regimen that contained cisplatin. Among 32 patients evaluable for response, there were 5 (16%) (CI 95%-8%-35%) partial responses, all in patients that had received non-platinum agents as first-line chemotherapy. Stable disease was recorded in 8 (25%) and progressive disease in 19 (59%) patients. The median response duration was 4 (range 3-6) months, the median time to progression was 5 (range 3-6) months, the median survival after second-line chemotherapy was 6 (range 2-24) months and the median survival after first-line chemotherapy was 12 (range 4-36) months. Myelotoxicity was the main toxicity with grade 3-4 neutropenia occurring in 19 (59%) of the patients and febrile neutropenia in 4 (12%) patients. G-CSF support was given to 25 (78%) patients. Grade 3-4 thrombocytopenia was recorded in 4 (12%) patients. In conclusion, the combination of docetaxel plus cisplatin appears to be a moderately effective regimen with acceptable toxicity when G-CSF support is provided. According to our results, it seems that patients, whose tumors were not exposed to cisplatin during first-line chemotherapy, were more likely to respond to this regimen.*

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Key Words: Docetaxel, cisplatin, gastric cancer.

Patients with gastric cancer typically present with locally advanced or metastatic incurable disease, carrying a median survival of 6-9 months (1). Although systemic chemotherapy, as compared to best supportive treatment, can improve survival and quality of life, only a small number of chemotherapeutic agents provide active palliation. Single-agent trials with anthracyclines, fluoropyrimidines, mitomycin C, etoposide or platinum compounds, considered the most active agents in gastric cancer, have yielded response rates of 20-30% (2). Various combinations of 2 or 3 agents often achieve higher response rates (between 30% and 50%), but without significant improvement in median survival (2). Unfortunately, about half of the patients treated in first-line, even with a so-called "second generation" regimen that contains cisplatin, such as combinations of cisplatinum, epirubicin, 5-fluorouracil, are unresponsive (3). In addition, patients with a good performance status recurring after first-line treatment may require second-line chemotherapy. Therefore, there is an unmet need for the identification of new active agents for this disease.

Among the new agents, paclitaxel in combination with fluorouracil or platinum compounds has shown a

considerable antitumor activity both as first-line chemotherapy, as well as in pre-treated patients (4-8) with locally advanced or metastatic gastric cancer. Docetaxel, another tubulin-inhibiting agent, yielded in patients with advanced gastric cancer response rates similar to that reported with paclitaxel (9-11). Docetaxel was also combined with cisplatin or epirubicin or fluorouracil in a 3-drug combination with interesting response rate, both in chemotherapy-naïve and pre-treated patients (12-17). However, little is known about the effectiveness of these new regimens in patients with tumors primary refractory to chemotherapy, or those recurring after first-line treatment.

In the present study, the docetaxel-cisplatin combination as second-line therapy was evaluated in patients with advanced gastric cancer with tumors either primary resistant to first-line chemotherapy or recurring after chemotherapy, with the primary end-point the response rate.

Patients and Methods

Patient population. Patients were required to have: a) histologically confirmed gastric carcinoma with manifestations of locoregional or metastatic bidimentionaly measurable disease, lesions had to be located outside of a previously irradiated field, unless definite evidence of progression of the in-field lesions could be verified; b) either primary tumors resistant (non-responding or progressing) to first-line chemotherapy or recurring within 3-6 months from first-line chemotherapy. Other eligibility criteria included: a life expectancy of at least 3 months, Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤2, age ≤75 years, hematological parameters and blood chemistry indicating normal organ function [(absolute neutrophil count ≥1.5 x 10q/L, platelet count ≥100 x 10q/L, hemoglobin ≥10 g/dL, normal total bilirubin, AST ≤2.5 times the upper limit of normal value (ULN), alkaline phosphatase ≤6 x ULN and creatinine clearance ≥60 ml/min)]. Exclusion criteria included: prior treatment with docetaxel and hyper-sensitivity to platinum. Patients were excluded from the study if there was a history of prior malignancies, concurrent infection, known central nervous system metastases, intestinal paralysis or obstruction. The study was approved by the Ethics and Scientific Committees of the participating centers and all patients gave their informed consent in order to participate in the study.

Treatment plan. Treatment was given on an out-patient basis and included the administration of docetaxel (Taxotere®; Aventis Pharma, Bridgewater, USA) 70 mg/m^2 was given as a 1-hour *i.v.* infusion followed by cisplatin 70 mg/m^2 both given on day 1. Antiemetic treatment consisted of dexamethasone (8 mg) plus ondansetron (24 mg) given as *i.v.* bolus before chemotherapy. Premedication for docetaxel hypersensitivity reactions and to prevent skin toxicity and fluid retention consisted of oral dexamethasone (8 mg) given 12, 8 and 1 h before docetaxel and 24, 36 and 42 h post infusion. Recombinant human granulocyte-colony stimulating factor (rhG-CSF) (Granocyte®; Aventis Pharma) (5 μg/kg/day) was given as secondary prophylaxis and in subsequent cycles once patients had developed severe neutropenia. The regimen was administered every 3 weeks for a maximum of 6 cycles, unless there was evidence of disease progression, unacceptable toxicity or patient refusal. Treatment cycles were delayed for up to 2 weeks, unless the patient had recovered from hematological and non-hematological toxicity. Before the next course was started, the neutrophil count had to be ≥1.5x10^9/l and platelet ≥100x10^9/l and liver and renal function had to meet the eligibility criteria. The doses of both docetaxel and cisplatin were reduced by 25% in the event of grade 4 hematological toxicity. The cisplatin dose was reduced by 25% in the event of ≥grade 2 peripheral neuropathy and grade 2 nephrotoxicity.

Patient evaluation. Baseline evaluations included: patient history, physical examination, chest X-rays, complete blood count with differential and platelet count, standard blood chemistry and ECG. Computed tomography (CT) scans of the chest, abdomen, pelvis and whole body bone scintigraphy were performed at study entry and CT scan of the brain whenever clinically indicated. Complete blood counts with differential and platelet counts were performed twice weekly or daily in case of grade 3/4 neutropenia, thrombocytopenia or febrile neutropenia until hematological recovery; blood chemistry and physical examination were performed every 3 weeks. Patients were evaluated before each cycle for lesions assessable by physical examination. All patients were evaluated by the appropriate imaging studies indicative of the measurable target lesions every 2 chemotherapy cycles.

Tumor evaluation and criteria for response. Tumor response was assessed after every 2 cycles using the World Health Organization (WHO) response criteria (18). An independent radiologist reviewed all tumor responses. Response duration was calculated from the day on which at least a 50% reduction in tumor volume was documented until the first documentation of progressive disease. Time to tumor progression (TTP) was calculated from the first day of drug administration to the first documentation of tumor progression. Overall survival was measured from the date of first drug administration to death. Patients without progression who died during the study were considered treatment failures.

Monitoring for toxicity. Toxicity evaluations were graded according to the National Cancer Institute (NCI) common toxicity criteria (18). Hematological and clinical chemistry parameters were measured at baseline and then at least weekly throughout treatment. Liver function was monitored at each cycle.

Statistical methods. The primary objective of the study was the overall response rate. All analyses were based on the intent-to-treat population. Confidence intervals (CI) for response rates were calculated according to the method described by Simon (19). Simon's two-stage mini-max design was used to allow for early termination of the trial in the event of a poor response rate. An optimized two-stage plan for accrual was used at a first-stage design with 16 patients. It was calculated that the sample size required for having confidence limits of ±8% would be 32 patients. The survival distributions for response duration, time to progression (TTP) and overall survival were estimated using the Kaplan-Meier method. Dose intensity was expressed in mg/m^2/week.

Results

Patient characteristics. From June 2000 to December 2004, a total of 32 patients were eligible for the study and their characteristics are listed in Table I. Surgery was performed

Table I. *Patient characteristics.*

	Patients	%
Eligible patients	32	100
Age (years)		
Median Range	60 (45-75)	
Gender (male/female)	30/2	
Performance Status (ECOG)		
0	8	25
1	16	50
2	8	25
Previous therapy		
Surgery	25	78
Chemotherapy	32	100
Adjuvant radiotherapy	12	38
Sites of disease		
Liver	27	84
Lymph nodes	18	56
Primary tumor/loco regional disease	7	22
Lung	5	16
Peritoneal cavity	19	59

Table II. *Summary of first-line chemotherapy.*

	Number of patients	%
Regimen		
Mitomycin-Epirubicin-5FU (FEM)	8	25
Etoposide-5FU-Folinic Acid	8	25
Methotrexate-Epirubicin-5FU (FAMXT)	4	12
Epirubicin-Cisplatin-5FU (ECF)	12	38
Number of first-line chemotherapy regimens		
Median	4	
Range	2-6	
Cause of failure		
Tumor recurrence during adjuvant chemotherapy	6	19
Relapse after primary chemotherapy	19	59
Primary metastatic disease progressing on first-line chemotherapy	7	22

5FU: 5-Fluorouracil.

Table III. *Clinical response to chemotherapy.*

	Number	% of all patients (n=32)
Complete response	0	
Partial response	5	16% (95% CI 8-36%)
Stable disease	8	25%
Progressive disease	19	59%

CI: Confidence interval; median duration of response 4 (3-6) months; median time to progression 5 (2-24) months; median survival after second-line chemotherapy 6 (2-24) months; median survival after first-line chemotherapy 12 (4-36) months.

in 25 (78%). All patients had received chemotherapy, while 12 (38%) had been irradiated in the adjuvant setting. Most of the patients had visceral metastases: liver 27 (84%), lung disease 5 (16%), while a great percentage 19 (59%) had disease in the peritoneal cavity. The majority of patients had tumors recurring after primary chemotherapy 19 (59%), 6 (19%) patients had relapsed during adjuvant chemotherapy, while 7 (22%) were progressing on first-line chemotherapy. The agents employed in first-line chemotherapy were those of the so-called "old generation" regimen including mitomycin, epirubicin, methotrexate, etoposide and fluorouracil given in 20 (62%) patients. In addition, 12 (38%) patients received a "second generation" regimen that contained platinum in combination with epirubicin and fluorouracil. Details are presented in Table II.

Response and survival data. All 32 patients were assessable for response and toxicity. Five (16%) patients achieved a partial response for an overall response rate of 16% (95% CI 11-35%), 8 (25%) patients had stable disease and 19 (59%) patients progressive disease. The median time to achieve an objective response was 3 (range 2-4) months and the median response duration was 4 (range 3-6). The median time to progression was 5 (range 3-6) months and the median survival was 6 (range 2-24). The overall median survival of the group from first-line chemotherapy was 12 (range 4-36) months. At the time of analysis, only one responding patient, who had received consolidation radiotherapy in extra-abdominal area (after second-line chemotherapy) was still alive. Responses were observed in all sites of disease, such as liver (n=1 patient) and lymph nodes (n=4 patients). Subgroup analysis indicated that responses were achieved only in patients who had received the "old generation" regimen. Patients whose tumors were exposed to cisplatin during first-line treatment had either stable or progressive disease. The efficacy of the regimen is presented in Table III.

Compliance to treatment. A total of 128 cycles were administered with a median of 3 per patient (range 2-6). A total of 18 treatment cycles (14%) were delayed for 3-14 days (median 7 days), mainly as a result of patients' own choice due to difficulties in traveling from district areas (10 cycles) and 8 cycles due to neutropenia on the day of treatment. The delivered dose intensity was 80% of the planned dose for both agents due to delays and dose reductions.

Toxicity. Myelosuppression was the main toxicity of the combination. Four (12%) patients developed febrile neutropenia well-controlled with G-CSF and oral or *i.v.*

Table IV. *Hematological and non-hematological toxicity per patient and per cycle.*

	Patient	Cycles	Patient	Cycles	Patient	Cycles	Patient	Cycles
Toxicity	Grade 2		Grade 3		Grade 4		Grade 3/4	
Neutropenia	13 (40%)	31%	9 (28%)	14%	10 (31%)	8%	19 (59%)	22%
Febrile neutropenia	-	-	-	-	4 (12%)	6%	4 (12%)	6%
Thrombocytopenia	6 (19%)	6%	2 (6%)	-	2 (6%)	-	4 (12%)	5%
Anemia	6 (19%)	19%	2 (6%)	6%	-	-	-	-
Diarrhea	4 (12%)	9%	2 (6%)	-	-	-	2 (6%)	2%
Nausea/Vomiting	19 (59%)	30%	8 (25%)	19%	-	-	-	-
Alopecia	32(100%)	-	-	-	-	-	-	-
Mucositis	4 (12%)	8%	-	-	-	-	-	-
Skin and nail toxicity	6 (19%)	28%	-	-	-	-	-	-
Nephrotoxicity	6 (19%)	10%	-	-	-	-	-	-
Neurotoxicity	8 (25%)	12%	-	-	-	-	-	-

antibiotics. Grade 3-4 neutropenia was observed in 19 (59%) patients. Neutropenia was short lasting and the neutrophil count usually returned to normal by day 20. Twenty-five (78%) patients received G-CSF for 5 days at least or until the neutrophils reached the normal range. Grade 3-4 thrombocytopenia was rare and occurred in 4 (12%) patients. Grade 2 and 3 anemia were noted in 19% and 6% of patients, respectively. Non-hematological toxicities were relatively rare and included diarrhea, nausea/vomiting and alopecia. Grade 2 diarrhea occurred in 4 (12%) patients and in 9% of cycles. Grade 2 and 3 nausea/vomiting was noted in 19 (59%) and 8 (25%) patients, respectively, while grade 2 alopecia was universal. Neurotoxicity was as follows: grade 2 in 8 (25%) and grade 1 in 12 (38%) patients. Toxicity is presented in Table IV.

Discussion

Taxanes have become interesting agents in the treatment of gastric cancer either in chemotherapy-naïve or in pre-treated patients (5-17). Docetaxel administered as single agent in pre-treated patients yielded response rates between 17% and 24%, with a median survival ranging from 4 to 6 months (10, 11, 20, 21). In pre-treated patients, when docetaxel was combined with cisplatin, response rates between 17% and 32% were documented in the most recent studies, but with median survival similar to that achieved by single agent docetaxel (22-24). The results of the present study demonstrated that several patients treated in a second-line setting can obtain therapeutic benefit with acceptable toxicity. The moderate response rate of 16% achieved in the present study is in the lower range of responses reported by prior studies employing the same regimen (22-24). It is interesting that in our group of patients, all responders had been treated in the past with an "old generation" regimen, in other words their tumors were not exposed to cisplatin. It is also interesting that in a study from Korea, where the highest response rate of 32.4% was documented, all patients received first-line treatment with fluorouracil plus cisplatin or heptaplatin, an agent considered by the authors to be less effective as compared to cisplatin (24). In addition, in a study from Japan, where the docetaxel-cisplatin combination yielded a 26.7% response rate all patients received S-1, a non platinum regimen, as first-line chemotherapy. In fact, the agent S-1 contains a novel oral dihydropyrimidine dehydrogenase (DPD) inhibitory fluoropyrimidine (DIF) based on biochemical modulation of fluorouracil (23). Finally, a low response rate, similar to that documented in our study, was reported in another study from Korea, where most patients received cisplatin, fluorouracil plus leucovorin as first-line treatment (22).

The median survival after second-line chemotherapy documented in our study was 6 months. The calculated overall survival after first-line chemotherapy was 12 months. In all aforementioned studies, where docetaxel-cisplatin was given as second-line chemotherapy, the median survival was 4-6 months. Again, the overall survival after first-line treatment in all these studies, independent of the applied regimen, was 12-13 months (22-24). In the present study, all patients, except one, died due to disease progression. This unique long-term surviving patient is alive 36 months after first-line and 24 months after second-line chemotherapy most probably because he received consolidation radiotherapy in mediastinal and supraclavicular lymph node area.

The major toxicity encountered in our study was myelotoxicity. In the present study, where full dose was administered, grade 3-4 neutropenia was seen in 19 (59%) patients in 22% of cycles while 4 patients had developed febrile neutropenia with no septic death documented. Again, neutropenia was the main reported toxicity in all aforementioned studies, where docetaxel-cisplatin was given as salvage treatment, even though the doses of the two administered agents were smaller (22, 23). It is known that the

toxicity profile of docetaxel can be markedly modified when the agent is administered on a weekly schedule (25). In addition, in several phase I and II studies including our study on gastric carcinoma, weekly docetaxel with cisplatin administration was found to be less toxic than when given every 3 weeks with regard to neutropenia but with similar antitumor activity (26-28). These findings in conjunction with the high activity of the docetaxel-cisplatin-fluorouracil triplet (12), suggest that these agents administered on a weekly schedule should be tested as salvage regimen in gastric cancer.

In conclusion, docetaxel plus cisplatin make a reliable regimen with documented effectiveness as second-line chemotherapy in patients with advanced gastric cancer. According to our findings, it seems that subsets of patients that have not received cisplatin in the past may obtain further therapeutic benefit. Neutropenia remains the main toxicity of the regimen but can be managed well when G-CSF support is provided.

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Received May 10, 2006
Accepted June 26, 2006