Modified Docetaxel-cisplatin in Combination with Capecitabine as First-line Treatment in Metastatic Gastric Cancer. A Phase II Study

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Abstract. *The combination of docetaxel, cisplatin and fluorouracil is considered to be one of the reference regimens for advanced gastric cancer, but due to its major myelotoxicity, its use in clinical practice has become limited. This prospective phase II study evaluated the activity and toxicity of a modified regimen with lower doses of docetaxel and cisplatin combined with oral capecitabine instead of fluorouracil for patients with advanced gastric cancer. Treatment consisted of docetaxel at 60 mg/m^2 i.v. followed by cisplatin at 60 mg/m^2, both administered on day one, every three weeks. Capecitabine at 2 g/m^2 per day was administered in two divided doses for 14 days (days 2-15). Thirty six patients were enrolled in the study. The median age was 64 years and performance status (ECOG) was 0-1. All patients had advanced disease, 78% with liver metastases, 100% with intra-abdominal lymph node metastases and 67% with peritoneal implants. Out of the 36 patients, 13 had undergone gastric resection, 13 had received adjuvant chemotherapy with irinotecan-leucovorin-fluorouracil, while seven patients had undergone adjuvant radiotherapy. The remaining 23 patients presented with advanced inoperable disease. Among 36 evaluable for response cases, there were 16 (44.4%) (Confidence Internal (CI) 95%=28-60%), partial responses. Stable disease was recorded in 12 (33.3%), resulting in an overall disease control rate of 78% (CI 95%=69-87%), while 8 (22.3%) patients progressed on chemotherapy. The median response duration was 6 (range=3-8) months. The median time-to-progression was 5 (range=3-6) months and the median survival (after the administration of a second-line chemotherapy in 12 patients), was 12 (range=5-24) months. Myelotoxocity was the main toxicity, with grade 3-4 neutropenia occurring in 18 (50%) and febrile neutropenia in six (16%) patients. Granulocyte-Colony Stimulating Factor (G-CSF) support was given to 16 (44.4%) patients, while grade 3 thrombocytopenia was recorded in two (6%). In conclusion, this modified regimen of docetaxel-cisplatin-capecitabine appears to have comparable efficacy with that reported for the reference regimen, with acceptable toxicity when G-CSF support is provided. However, because due to the small size of the study, further investigation is warranted.*

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Advanced gastric cancer is regarded as an incurable disease, with a median survival of 6-9 months (1). Systemic chemotherapy as compared to best supportive care can improve survival and quality of life but only a few chemotherapeutic agents can provide active palliation. Single-agent trials with anthracyclines, fluoropyrimidines, mitomycin, etoposide or platinum compounds that are considered active agents in gastric cancer have yielded response rates of 20-30% (2). Combinations of two or three agents often achieve higher response rates (between 30% and 50%) but without significant improvement in median survival (3). In many countries, the combination of cisplatin plus fluorouracil is considered the

standard reference regimen because of its advantages in response rate and survival as compared to older drug combinations (4, 5). Among the new drugs introduced for gastric cancer, paclitaxel and docetaxel, both tubulin-inhibiting agents, in combination with platinum compounds have shown considerable antitumor activity as first- and second-line treatment (6-9). The combination of docetaxel with cisplatin plus a 5-day continuous infusion of fluorouracil (DCF regimen V325 study) was recently shown to yield high response rates and an improved time-to-tumor progression (TTP) (10). However, substantial toxicities, including a 29% neutropenic fever rate, have limited its use in daily clinical practice and modifications of the regimen have been attempted by several investigators. Among these modifications were: dose modification of the same drugs and the introduction of capecitabine (11-16). Capecitabine, an orally administered fluoropyrimidine, was tested in phase II studies as an alternative to intravenous fluorouracil, demonstrating a 20-30% response rate and a favorable toxicity profile (13-16). Based on these observations, we decided to conduct a prospective phase II study of previously untreated patients with advanced gastric cancer. The purpose of this study was to evaluate the efficacy and toxicity of a modified regimen with lower doses of docetaxel and cisplatin in combination with oral capecitabine.

Patients and Methods

Patient population. Patients were required to have: a) histologically confirmed gastric carcinoma with locoregional or metastatic bi-dimentionally 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) no prior chemotherapy, except for adjuvant treatment. 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 $\geq 1.5\times10^9$/l, platelet count $\geq 100\times10^9$/l, hemoglobin ≥10 g/dl, normal total bilirubin, aspartate aminotransferase (AST)≤2.5 times the upper limit of normal value (ULN), alkaline phosphatase ≤6 × ULN and creatinine clearance ≥60 ml/min)]. Exclusion criteria included: prior treatment with taxanes, and hypersensitivity to platinum, history of prior malignancies, concurrent infection, known central nervous system metastases, intestinal obstruction or ileus. 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 outpatient basis and included the administration of docetaxel (Taxotere®; Aventis) 60 mg/m^2 as a 1-h *i.v.* infusion followed by cisplatin at 60 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 agents to prevent fluid retention consisted of oral dexamethasone (8 mg) given at 12, 8 and 1 h before docetaxel and 24, 36 and 42 h post infusion. Recombinant human granulocyte-colony stimulating factor (rhG-CSF) (5 μg/kg/day) was given as secondary prophylaxis and in subsequent cycles once patients had developed severe neutropenia. Capecitabine was administered orally twice daily with the standard intermittent schedule (14 days of treatment followed by a 7-day rest period every three weeks) to a total dose of 2000 mg/m^2/day starting the next day after *i.v.* chemotherapy. The regimen was administered every three weeks for a maximum of six cycles, unless there was evidence of disease progression, unacceptable toxicity or patient refusal. Treatment cycles could be delayed due to toxicity for up to two weeks, unless the patient had recovered from hematological and non-hematological toxicity. Before the next course was started, the neutrophil count had to be $\geq 1.5\times10^9$/l and the platelet count $\geq 100\times10^9$/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. The daily dose of capecitabine was reduced by 25% at the first occurrence of grade 3 toxicity.

Patient evaluation. Baseline evaluations included: patient history, physical examination, chest X-rays, complete blood count with differential and platelet count, standard blood chemistry and Electrocardiography (ECG). Computed-tomographic (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 cases of grade 3 or 4 neutropenia, thrombocytopenia or febrile neutropenia until hematological recovery, blood chemistry and physical examination were performed every three 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 two chemotherapy cycles.

Tumor evaluation and criteria for response. Tumor response was assessed after every two cycles using the World Health Organization (WHO) response criteria (17). 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. 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 from any cause during the study were considered treatment failures.

Monitoring for toxicity. Toxicity evaluations were graded according to the National Cancer Institute (NCI) common toxicity criteria (17). 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 (18). 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, TTP and overall survival were estimated using the Kaplan Meier method. Dose intensity was expressed in mg/m^2/week.

Results

Patients' characteristics. From June 2007 to December 2010, a total of 36 patients were eligible for the study, and their characteristics are listed in Table I. Surgery was performed in 13 (36%). The remaining 23 (64%) presented with advanced disease; adjuvant chemotherapy with irinotecan-leucovorin-fluorouracil was administered in 13 (36%), while seven (20%) patients were irradiated in the adjuvant treatment setting. Most of the patients had visceral metastases (liver=78%, lung=17%), while a great percentage had peritoneal implants (67%). Details are presented in Table I.

Response and survival data. All 36 patients were assessable for response and toxicity. Sixteen (44.4%) patients achieved a partial response but none a complete response, with an overall response rate of 44.4% (95% CI=18-60%). Twelve (33.3%) patients had stable disease and eight (22.3%) patients progressive disease. The median time to achieve an objective response was 3 months (range=2-4) and the median response duration was 6 months (range=3-8). The median TTP was 5 months (range=3-6) and the median survival was 12 months (range=5-24); 12 patients received second-line chemotherapy with irinotecan plus oxaliplatin. Responses were observed in all sites of disease, such as liver (n=10 patients) lungs and lymph nodes (n=6 patients).

Compliance with treatment. A total of 174 cycles were administered, with a median of four per patient (range=2-6). A total of 16 treatment cycles (10%) were delayed for 3-14 days (median 7 days), mainly as a result of the patients' own choice due to difficulties in traveling from distant areas (six cycles) and due to neutropenia on the day of treatment (four cycles). The delivered dose intensity was 85% of the planned dose for all agents due to treatment delays and dose reductions.

Toxicity. Myelosuppression was the main toxicity of the combination. Six (17%) patients developed febrile neutropenia which was successfully treated with G-CSF and oral or *i.v.* antibiotics. Grade 3-4 neutropenia was observed in 16 (44.4%) patients. Neutropenia was seen during the first courses, it was short-lasting and the neutrophil count usually returned to normal by day 20. Sixteen (44.4%) patients received G-CSF for at least 5 days or until the neutrophils reached the normal range. Grade 3 thromboctytopenia was rare and occurred in 8 (22%) patients. Toxicity is presented in Table II.

Table I. *Patients' characteristics (n=36).*

Characteristic	Patients	%
Median age (years)	64	
Range	38-76	
Gender		
Male	28	78
Female	8	22
Performance status (ECOG)		
0	30	83
1	6	17
Histology		
Enteric type	9	25
Diffuse type	14	39
Linitis plastica	6	16
Other	7	20
Stage IV	36	100
Site of metastases		
Liver	28	78
Lung	6	17
Lymph nodes	12	34
Intra-abdominal lymph nodes	36	100
Peritoneum	24	67
Prior treatment		
Radical resection	5	13.8
Partial resection	8	22.2
Adjuvant radiotherapy	7	19.4
None	23	63.9

Discussion

Several agents or combinations of two or three drugs, including fluorouracil, cisplatin, anthracyclines, irinotecan, oxaliplatin and taxanes, are usually administered in advanced gastric cancer, yielding response rates of 25-45% and a median survival of 7-9 months (19). In the V325 study, the combination of docetaxel-cisplatin plus a 5-day continuous infusion of 5-fluorouracil yielded an overall disease control rate of 67%, with 2% complete and 35% partial responses, and 30% disease stabilization. Additionally, the median survival time reached 9.2 months, with 18% of patients still alive at two years (10). The authors and most of the medical community consider this regimen as one of the reference regimens, but its increased toxicity, with a 29% complicated neutropenia rate, have limited its use in daily clinical practice. The aim of the present study was to apply the most effective agents as those used in the V325 study but also to reduce toxicity. Therefore, the regimen was modified as follows: instead of 75 mg/m^2 of docetaxel and cisplatin, we administered 60 mg/m^2 of both agents and we substituted 5-fluorouracil with capecitabine. With the latter modification, the patients were able to receive treatment on an outpatient basis with no need for a central venous line for continuous infusion of 5-fluorouracil.

Table II. *Hematological and non-hematological toxicity per patient and percentage of cycles.*

	Grade 2		Grade 3		Grade 4		Grade 3/4	
Toxicity	Patients	Cycles	Patients	Cycles	Patients	Cycles	Patients	Cycles
Neutropenia	16 (44.4%)	30.0%	10 (27.7%)	19.0%	6 (16.6%)	4.0%	16 (44.4%)	23.0%
Febrile neutropenia	-	-	-	-	6 (17.0%)	4.0%	-	-
Thrombocytopenia	6 (16.0%)	11.0%	8 (22.0%)	5.0%	-	-	8 (22.0%)	5.0%
Anemia	8 (22.0%)	15.0%	4 (12.0%)	7.5%	-	-	4 (12.0%)	7.5%
Diarrhea	8 (22.0%)	20.0%	-	-	-	-	-	-
Nausea/ vomiting	28 (78.0%)	50.0%	8 (22.0%)	50.0%	-	-	-	-
Nephrotoxicity	8 (22.0%)	15.0%	-	-	-	-	-	-
Neurotoxicity	12 (33.0%)	-	-	-	-	-	-	-
Alopecia	36 (100.0%)	-	-	-	-	-	-	-
Skin and nail toxicity	14 (39.0%)	-	-	-	-	-	-	-
Hand-foot syndrome	6 (14.0%)	26.0%	-	-	-	-	-	-

Regarding the efficacy of the present regimen, we recorded a 44% response rate, a 79% disease control rate, and 12-month median survival, including second-line chemotherapy in 12 patients; we consider these data to be similar to those reported by the V325 study (10). It is interesting that other investigators using the same modified regimen, as applied in our study, have reported a very high response rate (68%) and a much longer overall survival period (14.4 months) but in their study, 25% of the patients were able to undergo surgery after induction chemotherapy (16). In our study, the majority of patients had visceral metastases similar to those reported in the V325 study (10). Another modification of the original V325 study has also been reported from Turkey. In that study, the two agents docetaxel and cisplatin were reduced to 60 mg/m^2 and 5-fluorouracil was reduced to 600 mg/m^2/day for 5 days. The reported disease control was 64.9%, with an overall survival of 10 months (12). Much higher response rates were reported with the combination of docetaxel-cisplatin and S-1 (an oral fluoropyrimidine derivative developed in Japan), for which the overall response rate was 81%, with a median survival of 18.5 months (20). It is interesting that modifications of the three aforementioned agents in another study from Japan have yielded response rates up to 87.1% and a disease control rate up to 100%, with a median survival of 686 days (21). These exceptionally high responses and prolonged survivals should be interpreted with caution because of the Asian origin of the patients. It is known that gastric cancer prognosis is better in patients of Asian race but according to National Cancer Data Base (NCDB), this is valid only for early-stage disease (22). Equally high response rates have been reported by other investigators by applying another triple regimen: the combination of docetaxel-oxaliplatin given every two weeks with one week of capecitabine administration yielded a 59% response rate, a 70% disease control rate and 18-month median survival (23).

The major toxicity encountered in our study was myelotoxicity, with grade 3-4 neutropenia occurring in 16 patients (44.4%) in 23% of the cycles, while six (17%) patients developed febrile neutropenia in 4% of the cycles but with no septic death documented. Febrile neutropenia was successfully treated with G-CSF and oral or *i.v.* antibiotics. Compared to the reported toxicity of the V325 study, where complicated myelotoxity was the major toxicity, our regimen seems to be much better tolerated. In our study, neutropenia usually developed during the first courses of drug administration, similar to that reported in the V325 study. In other studies where the same regimen as in our study was administered, the main toxicity was also neutropenia. In a study from South-Korea, grade 3/4 neutropenia was observed in 62.5% of patients, with 10% developing neutropenic fever (16). It is interesting that the reported toxicity of the docetaxel-cisplatin-S1 combination in two studies from Japan was again mainly hematological, with neutropenia occurring in 77.4% and 72% respectively (20, 21). The aforementioned combination of docetaxel-oxaliplatin-capecitabine was much better tolerated, with grade 3/4 neutropenia in 5% of the cycles (23).

At present, the issue of whether to use a triple-regimen or a cisplatin-fluoropyrimidine combination upfront for a disease where palliation is the main purpose remains controversial. It is well-known that second-line chemotherapies with a docetaxel-containing regimen can offer further survival for such patients (24-26). In a prior study of our group, second-line docetaxel-cisplatin chemotherapy yielded a 16% response rate and a 6-month median survival, resulting in a total

survival of 12 months (24). Similar reports have been presented from Japan, where even smaller doses of the two agents were used (25). In Asia, where compared to Western Countries, the use of multiple lines of chemotherapy is a common practice, salvage chemotherapy with docetaxel yielded a 57% disease control rate and 8.3-month median survival (26). Most recently, a phase II trial demonstrated that salvage chemotherapy for pre-treated gastric cancer significantly improved overall survival as compared to best supportive care (27).

In conclusion, the modified regimen applied in the present study showed efficacy similar to that reported in the V325 study. Although neutropenia remains its main toxicity, this can be successfully managed with G-CSF support. We consider our modification to be a less toxic regimen compared to that of the V325 study, where the authors recommend prophylactic G-CSF administration.

Compared to Asian countries, where multiple salvage treatments are usually administered, in Western countries treatment failure or tumor recurrence is rarely treated with a salvage regimen. In this setting, a regimen that can offer maximum efficacy as the first and only line of chemotherapy is rather preferable. Triplets are effective but rather toxic combinations. Dose reductions might ameliorate side-effects and therefore might represent one solution to the problem of toxicity. Alternatively, new drug combinations and new agents should be evaluated and therefore further studies are warranted.

Conflicts of Interest

None.

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