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ORIGINAL ARTICLE

Docetaxel, oxaliplatin, and capecitabine combination chemotherapy for metastatic gastric cancer

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Abstract
Background The incorporation of docetaxel into the cisplatin and fluorouracil backbone has been demonstrated to be an active combination in metastatic gastric cancer. Nevertheless, this regimen is burdened by nonnegligible toxicity. We hypothesized that replacing cisplatin and fluorouracil with oxaliplatin and capecitabine should be an active and safe option for metastatic gastric cancer patients.
Methods In this phase II study, we tested the activity of docetaxel in combination with oxaliplatin and capecitabine (DOC) as a first-line treatment. DOC was administered as follows: docetaxel (60 mg/m^2) and oxaliplatin (100 mg/m^2) on day 1, and capecitabine (500 mg/m^2) was administered orally twice daily given continuously, with cycles repeated every 3 weeks. The primary endpoint was the overall response rate.
Results Forty-eight patients entered the study. All patients had metastatic disease (stage IV). None of the patients had previously received chemotherapy for advanced disease. Performance status was 0, 1, and 2 in 25, 58, and 17 % of patients, respectively; 13 patients (27 %) had adenocarcinoma of the gastroesophageal junction, and 29 patients (60.5 %) had two or more metastatic sites. The overall response rate was 52.1 %. Progression-free survival and overall survival were 6.9 and 12.6 months, respectively. The treatment was well tolerated with no treatment-related deaths. The most common grade 3–4 toxicity was neutropenia (41 %).
Conclusions DOC is an effective and tolerated first-line treatment, and the lower dose of docetaxel and oxaliplatin used in this study compared with other similar regimens does not seem to hamper the antitumor activity.

Keywords Gastric cancer · Docetaxel · Oxaliplatin · Capecitabine · Phase II

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Introduction

Gastric cancer is the fourth most common cancer worldwide and the second leading cause of cancer-related death [1]. The overall outlook for patients with gastric cancer is still dismal, as the majority are diagnosed with locally advanced or metastatic disease with a median survival of 7–10 months [2].

Pioneering randomized clinical trials demonstrated the superiority of palliative chemotherapy over best supportive care alone, with an improvement in survival and in quality of life (QoL) [3–5]. The role of chemotherapy was further confirmed in a meta-analysis, which also suggested that three-drug combinations conferred longer survival compared to monochemotherapy and doublets [6]. Nevertheless, there is no accepted standard regimen for advanced gastric cancer. In Europe, the combinations of epirubicin, cisplatin, and fluorouracil (ECF) and epirubicin, oxaliplatin, and capecitabine (EOX) have been considered as reference regimens [7]. In the United States the combination of docetaxel, cisplatin, and fluorouracil (DCF) is commonly used [8], whereas in Japan cisplatin with S1 has recently entered the therapeutic scenario [9].

During the past few years platinum salts, docetaxel, and trastuzumab have entered the therapeutic arena, demonstrating improved outcomes in randomized trials with a superiority design [10–12]. The incorporation of docetaxel to cisplatin/fluorouracil chemotherapy (DCF) showed superiority over cisplatin/fluorouracil in a randomized phase III trial [8]. Furthermore, in a recent meta-analysis the use of DCF was correlated with a higher response rate than non-taxanes-containing regimens [13]. Nevertheless, the widespread use of DCF was hindered by severe toxicity, such as neutropenic infections and febrile neutropenia.

Evidence of docetaxel activity together with the need of improving the therapeutic index of taxane-containing regimens fueled a series of investigations with alternative schedules, envisioning either weekly or biweekly regimens (modified DCF) or the replacement of partner agents. Capecitabine and oxaliplatin have demonstrated activity in gastric cancer [10, 14]. In randomized studies these compounds were not found inferior to cisplatin and fluorouracil, respectively, with a manageable safety profile [7, 15, 16].

The observations that docetaxel is an active agent together with the noninferiority and better tolerability of capecitabine and oxaliplatin compared to cisplatin and fluorouracil prompted this phase II study aimed at investigating the activity of a three-drug regimen of docetaxel, oxaliplatin, and capecitabine (DOC) in patients with metastatic gastric adenocarcinoma.

We first performed a phase I trial according to the Fibonacci modified schema. Six patients entered this study, and the recommended phase II doses were as follows: docetaxel 60 mg/m^2 and oxaliplatin 100 mg/m^2 on day 1, and capecitabine 500 mg/m^2 orally twice daily given continuously, with cycles repeated every 3 weeks. Given the feasibility of the combination, we started a phase II study to investigate the activity of a three-drug regimen, DOC, in patients with metastatic gastric adenocarcinoma.

Patients and methods

Patient selection

Patients with gastric or gastroesophageal junction (GEJ) adenocarcinoma with measurable distant metastases not previously treated with chemotherapy for their metastatic disease were enrolled in the study. Adjuvant chemotherapy with different agents than those evaluated in the study was allowed if completed at least 6 months before. Patients were required to have measurable disease according to the RECIST 1.1 criteria. Other eligibility criteria included Eastern Cooperative Oncology Group performance status $\leq$2, life expectancy $>$3 months, age between 18 and 75 years, adequate bone marrow (absolute neutrophil count $\geq$1,500/μl, platelet count $\geq$100,000/μl), renal (serum creatinine $\leq$1.5 mg/dl) and liver (serum bilirubin $\leq$1.5 mg/dl) functions, normal cardiac function, absence of second primary tumor other than non-melanoma skin cancer or in situ cervical carcinoma, no central nervous system involvement, no prior radiotherapy in target lesions, and no concurrent uncontrolled medical illness. The protocol was approved by the coordinating centre's Ethics Committee at the "Regina Elena" National Cancer Institute, Rome, and was carried out according to the principles of the Declaration of Helsinki. A written informed consent was obtained from all patients.

Treatment

Treatment consisted of docetaxel 60 mg/m^2 diluted in 500 ml normal saline as a 1-h infusion followed by oxaliplatin 100 mg/m^2 diluted in 500 ml 5 % dextrose as a 2-h infusion on day 1 and continuous capecitabine 500 mg/m^2 orally twice daily. Cycles were repeated every 3 weeks. Prophylactic treatments, such as antiemetic or corticosteroids, were given according to the standard recommendations and physician assessment. Granulocyte colony-stimulating factor (G-CSF) was used only as a secondary prophylaxis if patients experienced febrile neutropenia or documented neutropenic infection. Dose reduction was performed according to toxicity and the physician's decision. Chemotherapy was generally administered on an outpatient basis for a maximum of eight cycles. Treatment was discontinued in case of unacceptable toxicity,

treatment delay longer than 2 weeks, patient refusal, or disease progression.

Pretreatment and follow-up studies

Pretreatment evaluation included clinical history and physical examination, automated blood cell count, biochemical profile, ECG, and computed tomography of the chest and abdomen. Endoscopy was performed only in case of complete remission of all measurable lesions. Blood counts were obtained weekly; a biochemical profile was repeated every 3 weeks. All measurable parameters of disease were reevaluated every 6 weeks and every 2 months during the follow-up period.

Evaluation of response and toxicity

Patients were evaluated for response to chemotherapy every two cycles of treatment. Responses were assessed by at least two observers and were confirmed by an independent radiologist. The RECIST 1.1 criteria were used to evaluate the clinical response. Progression-free survival (PFS) and overall survival (OS) were calculated from the date of first chemotherapy cycle to the date of disease progression, death for any cause, or last follow-up evaluation, respectively. Toxicity was assessed at each treatment cycle using the National Cancer Institute Common Toxicity Criteria (version 4.0).

Statistical analysis

The primary endpoint of this study was to estimate the overall response rate (ORR) of the regimen. Secondary endpoints were PFS, OS, and safety. The optimal Simon two-stage phase II design was used to determine the sample size [17]. An interim analysis was carried out when the first 15 assessable patients had been recruited. If more than 5 responses were observed, 31 additional patients were to be recruited; otherwise, the study was to be terminated. If more than 18 responses were observed in the 46 patients (response rate, $\geq$39.1 %), the regimen was considered sufficiently active, with a significance level of 5 % and power of 80 %, to undergo further evaluation. PFS and OS were analyzed according to the Kaplan–Meier method and were updated until 30 June 2013.

Results

Patient characteristics

From October 2008 to June 2012, 48 patients with metastatic gastric or GEJ cancer were enrolled in five Italian cancer centers. All patients were evaluable for efficacy and toxicity. The pretreatment characteristics of patients are listed in Table 1. None of the patients had previously received chemotherapy for advanced disease; 9 patients had received adjuvant chemotherapy without docetaxel or oxaliplatin with a median disease-free interval of 12 months (range, 8–24).

Table 1 Patient characteristics

Characteristic	No. of patients	Percent (%)
Patients evaluable	48	100
Age (years)		
Median	66	
Range	32–75	
Sex		
Male	28	58
Female	20	42
ECOG PS		
0	12	25
1	28	58
2	8	17
Disease location		
Gastric	35	73
GEJ	13	27
Histological type		
Diffuse	23	48
Intestinal	20	42
Unspecified	5	10
Previous adjuvant chemotherapy	9	19
Status of primary tumor		
Unresected	30	62.5
Resected	18	37.5
Site of metastases		
Liver	28	58
Nodes	26	54
Peritoneum	21	44
Lung	9	19
Bone	5	10
Number of metastatic sites		
1	19	39.5
2	19	39.5
3	10	21

Response

Among 48 assessable patients, we observed 3 (6.25 %) complete responses (CR) and 22 (45.83 %) partial responses (PR), for an ORR of 52.1 % [95 % confidence interval (CI), 38–66.2 %]. Disease remained stable in 15 (31.2 %) patients (Table 2). The disease control rate (DCR) was 83.3 %. Responses were observed in 16 of 28

Table 2 Tumor response in 48 patients according to RECIST 1.1 criteria

Response	No. of patients	Percent (%)
Complete response	3	6.25
Partial response	22	45.83
Stable disease	15	31.2
Progressive disease	8	16.7
Disease control rate: 83.3 %		

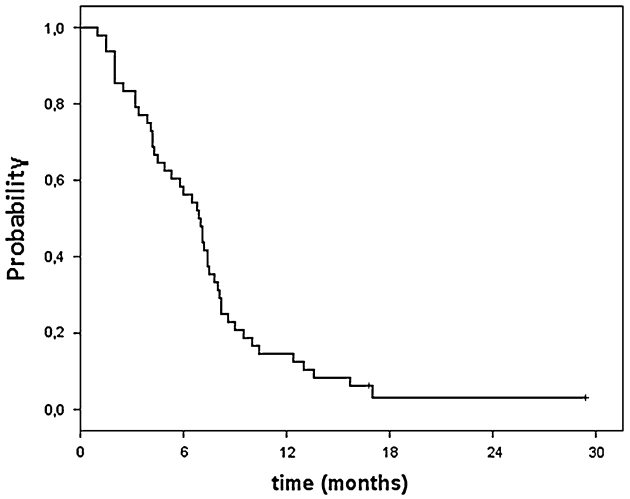

Fig. 1 Progression-free survival (PFS)

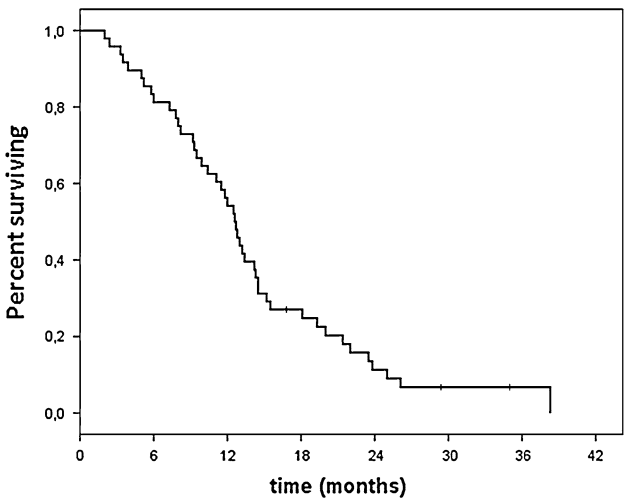

Fig. 2 Overall survival (OS)

patients (57 %) with liver metastases and in 9 of 21 patients (43 %) with peritoneal metastases. Responses were seen in 4 of 9 patients (44.5 %) who received adjuvant chemotherapy and in 21 of 39 chemotherapy-naïve patients (53.8 %). Responses were observed also in 16 of 30 patients (53.3 %) with no resected primary tumor and in 9 of 18 patients (50 %) with primary tumor resected.

Table 3 Grade 3/4 hematological toxicity per cycle and per patient

Toxicity	Percent (%) of 300 cycles		Percent (%) of 48 patients	
	Grade 3	Grade 4	Grade 3	Grade 4
Neutropenia	18	9	31	10
Thrombocytopenia	2	–	4	–
Anemia	2	–	6	–

Three episodes of febrile neutropenia in 2 patients

Response rates did not differ when patients were evaluated according to the primary site of disease (gastric, 51.4 %; GEJ, 53.8 %; respectively). Upon disease progression, 25 patients (52.1 %) received FOLFIRI as second-line therapy, and 7 patients (14.6 %) received third-line chemotherapy (epirubicin or taxol). With a median follow-up of 13 months (range, 2–35), the median PFS was 6.9 months (95 % CI, 5.6–8.1) and median OS was 12.6 months (95 % CI, 11.2–14.0) (Figs. 1, 2). One-year and 2-year survival rates were 54.2 and 11.3 %, respectively. Forty-five patients had died at the time of the present evaluation. Twenty-five of the 36 patients (69.5 %) who had tumor-related symptoms before therapy showed improvement in at least one of their symptoms.

Safety

Hematological toxicities are listed in Table 3. A total of 300 cycles of DOC regimen were analyzed in 48 patients, with a median of 7 cycles administered per patient (range, 1–8). The most common toxicity was neutropenia, which occurred in the majority of cases on day 8 (docetaxel nadir). Grade 3 and 4 neutropenia were observed in 31 and 10 % of the patients, respectively. Three episodes of febrile neutropenia were recorded in 2 patients (4 %). In these patients, despite the use of G-CSF, a 25 % dose reduction of docetaxel was required, whereas treatment was postponed in 2 patients (4 %) and in 8 cycles (2.7 %) because of a delay in bone marrow recovery. Grade 3 anemia was observed in 6 % of patients, and grade 3 thrombocytopenia occurred in 4 % of patients.

Nonhematological toxicity is listed in Table 4. Mild to moderate transient peripheral neuropathy developed in 39 % of the patients, and grade 3 was seen in 3 (6 %) patients. In 6 of these patients (12.5 %), oxaliplatin was reduced by 25 %, and in 1 patient oxaliplatin was permanently discontinued. Capecitabine was reduced by 50 % after five cycles in a patient as a result of G3 diarrhea, and administration of the drug was discontinued after 6 cycles in a different patient for the same reason. Hypersensitivity reactions, which did not preclude chemotherapy continuation, were recorded in 10 % of patients. Grade 3 hand-foot

Table 4 Nonhematological toxicity in 48 patients according to National Cancer Institute Common Terminology Criteria version 4.0

Toxicity	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)
Nausea/vomiting	21	12.5	6
Mucositis	12.5	8	4
Diarrhea	12.5	12.5	4
Fatigue	21	17	6
Alopecia[a]	67	24	
Neurotoxicity	29	10	6
Hand-foot syndrome	12.5	10	6
Hypersensitivity reactions	6	4	–

[a] For alopecia only grade 1–2 are indicated

syndrome was encountered in 6 % of patients, resulting in 25 % dose reduction of capecitabine. Mean docetaxel, oxaliplatin, and capecitabine dose intensities were 19.42, 31.89, and 6.636 mg/m^2 per week, respectively, which are equivalent to 97.1, 95.7, and 94.8 % of the planned dose intensities for these drugs. Severe nausea and vomiting was documented in 3 (6 %) patients and in five cycles (2 %). Alopecia was frequent. Neither cardiotoxicity nor treatment-related deaths were observed.

Discussion

The results of this phase II study show that the combination of docetaxel, oxaliplatin, and capecitabine is active and well tolerated for metastatic gastric cancer or GEJ adenocarcinoma patients in the first-line setting. The ORR and DCR with the DOC regimen were 52.1 and 83.3 %, respectively, whereas PFS and OS were 6.9 and 12.6 months, respectively.

The incorporation of docetaxel into the cisplatin and fluorouracil regimen represents a major step forward in the management of gastric cancer patients. In the phase III V325 study having time to progression as the primary endpoint, patients were randomly assigned to receive standard cisplatin and fluorouracil with or without docetaxel as a first-line therapy [8]. The trial met the primary endpoint; it also demonstrated an advantage in OS and ORR with the triplet. Nevertheless, the three-drug regimen was burdened by toxicities, with a nonnegligible 82 % of severe neutropenia, 29 % of febrile neutropenia, and 49 % of severe gastrointestinal disorders. The V325 prompted a series of investigations aimed at improving the tolerability of DCF with modified schemes, envisioning the use of weekly schedules. Overman et al. [18] retrospectively evaluated data from 95 patients treated with weekly DCF, reporting a dramatic drop in the rate of hematological toxicity and modest activity. Nevertheless, hospitalization was required for 22 patients (23 %) because of nonhematological toxicities. To a similar extent, the ATTAX trial [19], a phase II study with weekly docetaxel, confirmed the low incidence of hematological toxicity, which was however counterbalanced by grade 3–4 gastrointestinal toxicities (anorexia, 18 %; diarrhea, 22 %; stomatitis, 18 %; nausea, 16 %). With the limitations of indirect comparisons, our results suggest that DOC is endowed with a more favorable safety profile than standard and modified DCF regimens. Consistently, grade 3–4 neutropenia was recorded in 41 % of patients, with only 2 patients (4 %) experiencing febrile neutropenia. Furthermore, gastrointestinal toxicities were significantly lower (14 %) than previously reported with modified DCF. Regarding activity, the ORR and DCR reported in our study were 52.1 and 83.3 %, respectively, thus suggesting that the increased tolerability of the DOC schedule is not associated with reduced antitumor activity, but rather our regimen compares favorably with both standard DCF (ORR, 37 %) and modified DCF (ORR, range 34–47 %).

A second wave of investigations aimed to improve the therapeutic index of docetaxel-containing three-drug regimens envisioned the use of oxaliplatin instead of cisplatin. A first phase II study exploring the combination of biweekly docetaxel (50 mg/m^2) with oxaliplatin, leucovorin, and 24-h continuous infusion of fluorouracil (FLOT regimen) in 59 patients with metastatic adenocarcinoma of the stomach or GEJ reported an ORR of 57.7 %, whereas PFS and OS were 5.2 and 11.1 months, respectively [20]. In this study, grade 3–4 hematological and gastrointestinal toxicities were recorded in 57.5 and 24.1 % of patients, respectively. Further attempts of incorporating docetaxel into simplified FOLFOX regimens were reported by Pernot et al. [21]. In this study, 41 patients were treated with a regimen similar to FLOT, mainly differing in the administration of fluorouracil as a 48-h continuous infusion (TEF regimen). The ORR was 66 %, with a PFS of 6.3 months and an OS of 12.1 months. Overall, these results are similar to those obtained by FLOT. However, it is worth considering that the study presented by Pernot et al. included 10 patients (24 %) with more than one metastatic site, whereas in our study there were 29 (60.5 %), thus suggesting that the high ORR reported with TEF may be partially correlated with a consistent fraction of patients with lower tumor burden. Finally, in the multi-arm phase II GATE study, which was presented only in abstract form, 88 patients received a regimen similar to TEF [22]. ORR was 46.6 %, and grade 3 neuropathy and diarrhea were observed in 17 and 11 % of patients, respectively.

At the beginning of the study, we were aware that peripheral neuropathy from docetaxel and oxaliplatin might have hindered patient adherence to chemotherapy

and full-dose treatment. However, in our study the rate of all grades of neuropathy was 45 %, and grade 3 peripheral neuropathy was observed in only 3 patients (6 %). Therefore, the DOC scheme seems to be associated with a lower rate of both all grade and grade 3–4 sensory neuropathy than the FLOT and TEF schedules (all-grade sensory neuropathy for FLOT and TEF, 55.6 and 77.5 %, respectively; grade 3–4 sensory neuropathy for FLOT and TEF, 9.3 and 12.5 %, respectively). The better safety profile of the DOC regimen compared to both FLOT and TEF is mirrored by adherence to therapy. In our study, only 2 patients needed to discontinue capecitabine or oxaliplatin, whereas the rate of toxicity-related treatment discontinuation was 9.3 % with FLOT and 25 % with TEF. Therefore, DOC appeared equally as effective as FLOT and TEF, despite the comparatively lower doses of docetaxel and oxaliplatin that might explain, in turn, the better tolerability profile. Furthermore, although we did not assess quality of life, relief from cancer-related symptoms was recorded in 25 of 36 symptomatic patients (69.5 %). Finally, the use of capecitabine has eliminated the need for positioning a central venous catheter for continuous infusion of fluorouracil.

Next, in the REAL2 trial, ORR for ECF and EOX were 40.7 and 47.9 %, respectively, with median OS of 9.9 and 11.2 months, respectively. However, about 25 % of patients had locally advanced disease and two-thirds of patients had only 0–1 metastatic site [7]. Therefore, the DOC appears as least equally effective with the nonnegligible difference of including patients with higher tumor burden in our study.

Among the plethora of regimens explored in the first-line setting is also capecitabine and oxaliplatin (XELOX). In Asian studies, XELOX was associated with an ORR ranging from 42 % to 63 %, a PFS of about 5.8 months, and an OS spanning from 10.8 to 13.3 months [23–26]. All-grade neurotoxicity was about 60 %, probably because of the higher oxaliplatin dose compared to our study (130 versus 100 mg/m^2). Apparently, DOC compares favorably with the doublet. Nevertheless, we are aware that such indirect comparisons might be further confounded by ethnic factors. Consistently, microRNA expression profiling and next-generation sequencing studies are beginning to unveil the existence of different sets of deregulated genes potentially associated with ethnicity, and differentiation type-related differences exist in dihydropyrimidine dehydrogenase levels [27–29].

To our knowledge, only three phase II studies reported in full text the use of docetaxel with oxaliplatin and capecitabine, and two of them had a small sample size (21 and 27 patients, respectively) [30, 31]. In the largest study, Stein et al. [32] presented results from 55 patients treated with docetaxel 35 mg/m^2 and oxaliplatin 70 mg/m^2 on days 1 and 8 and capecitabine 800 mg/m^2 b.i.d. days 1–14, every 3 weeks. The combination produced an ORR of 43 %, whereas PFS and OS were 6.9 and 13 months, respectively. However, it is worth considering that 20 % of patients had locally advanced disease. More importantly, grade 3–4 diarrhea was reported in 30 % of patients, thus hindering the use of this regimen in clinical practice.

To sum up, the DOC regimen evaluated in the present trial appears an effective and safe treatment option for untreated metastatic gastric cancer patients and may represent an appropriate and promising regimen to be explored in combination with trastuzumab in patients with HER2 overexpression. A potential concern with the modified doses was that efficacy may be compromised. Nevertheless, both our study and a series of other reports exploiting the same doses of capecitabine and oxaliplatin indicated that the therapeutic index was maintained [33–37], as outcomes were comparable with those reported with standard regimens such as DCF, EOX, and ECF. Therefore, comparative trials with the commonly employed regimens mentioned here should be carried out to better define the role of DOC in gastric cancer.

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Conflict of interest The authors have declared no conflicts of interest.

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