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Autore/i: Petrioli R , Francini E , Cherri S , Marrelli D , Rovello F , Fiaschi AI , Miano ST , Savelli V , Calomino N , F

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Feasibility of modified docetaxel, oxaliplatin, capecitabine followed by capecitabine as maintenance chemotherapy as first-line therapy for patients with metastatic gastric or gastroesophageal cancer

Roberto Petrioli^{a,*}, Edoardo Francini^{b,*}, Sara Cherri^a, Daniele Marrelli^c, Franco Rovello^c, Anna Ida Fiaschi^d, Salvatora Tindara Miano^a, Vinno Savelli^c, Natale Calomino^e, Marco Farsi^e, Remo Vernillo^f and Guido Francini^a

The aim of this study was to evaluate the efficacy and safety of modified docetaxel, oxaliplatin, capecitabine (DOC) combination chemotherapy, followed by maintenance capecitabine as first-line therapy for patients with metastatic gastric or gastroesophageal junction (GEJ) cancer. Treatment consisted of docetaxel 35 mg/m² (days 1–8), I-OHP 85 mg/m² (day 1), and capecitabine 750 mg/m² twice daily (days 1–14), every 3 weeks. After six cycles of DOC, patients who did not progress received maintenance treatment with three-weekly capecitabine 1000 mg/m² twice daily (days 1–14), until disease progression or unacceptable toxicity. Six-month disease control rate (DCR) was the primary endpoint and overall survival (OS), progression-free survival (PFS) and safety were the secondary endpoints. The Kaplan–Meier method was applied to estimate OS and PFS. Between July 2014 and September 2017, 37 patients with metastatic gastric or GEJ cancer were enrolled at our institution. Upon completion of the DOC regimen, 35 patients (94.5%) received capecitabine as maintenance chemotherapy for a median of 7 cycles (range, 3–14 cycles). The six-month DCR was 83.7% [95% confidence interval (CI), 71.8–95.6%], median PFS was 8.2 months (95% CI, 6.3–9.8 months), and median OS was 14.4 months (95% CI, 11.7–18.6 months). During DOC chemotherapy, the most

common grade 3–4 adverse events were neutropenia (29.7%), anemia (10.8%), and diarrhea (10.8%). During maintenance treatment, toxicity was sporadic and mainly of grade 1–2. Modified DOC followed by capecitabine as maintenance chemotherapy seems to be an active and well tolerated first-line treatment strategy for patients with metastatic gastric and GEJ cancer. *Anti-Cancer Drugs* 31:292–297 Copyright © 2019 Wolters Kluwer Health, Inc. All rights reserved.

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^aMedical Oncology Unit, Department of Medicine, Surgery and Neurosciences, University of Siena, ^bDepartment of Oncology, La Sapienza University, Rome, ^cGeneral Surgery and Surgical Oncology Department, ^dPharmacology Unit, Department of Medicine, ^eClinical Surgery, Department of Surgery and Bioengineering and ^fClinical Surgery and Surgical Endoscopy, University of Siena, Siena, Italy

Correspondence to Roberto Petrioli, MD, Medical Oncology, University of Siena, Viale Bracci, 53100 Siena, Italy
Tel: +390577586139; fax: +390577586231;
e-mail: r.petrioli@ao-siena.toscana.it

*Dr. Roberto Petrioli and Dr. Edoardo Francini contributed equally to the writing of this article.

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Introduction

Gastric cancer is the fifth most common malignancy and the third leading cause of cancer mortality, worldwide [1]. While surgical resection offers a chance of cure for the localized disease, the majority of patients with gastric or gastroesophageal junction (GEJ) cancer presents at diagnosis with locally advanced or metastatic disease and is candidate to receive systemic chemotherapy [2,3]. Despite the lack of consensus over a standard first-line chemotherapy for metastatic gastric or GEJ cancer, the addition of docetaxel (D) to the combination of cisplatin (CDDP) and 5-fluorouracil (5-FU) (DCF) was shown to significantly prolong overall survival (OS) compared with the doublet chemotherapy alone, in the large clinical trial

V325 [4]. Moreover, a randomized phase II trial showed that DCF is more effective in terms of overall response rate and OS compared with the combination of E, CDDP and 5-FU (ECF) [5]. However, the frequent observation of severe adverse events, particularly myelotoxicity, associated with the DCF regimen limited its clinical adoption [4,5]. For this reason, several studies sought to investigate the activity of possible substitutes for the taxane partners CDDP and 5-FU in the D-based triplet chemotherapy. Namely, I-OHP and Cap showed noninferiority and an improved toxicity profile compared with CDDP and 5-FU, respectively, in randomized clinical trials and thus can be considered suitable replacements for CDDP and 5-FU in the DCF combination regimen [6,7]. In this

respect, our research group is participating in the multicenter randomized trial GastroDOC (Identifier Trial registration number: NCT01876927) conducted by the Romagnolo Scientific Institute-Italian Research Group for Gastric Cancer, which evaluates the combination of D, l-HOP, and Cap (DOC) as neoadjuvant or neoadjuvant/adjuvant chemotherapy for patients with locally advanced gastric cancer. Aiming to improve tolerability, this DOC regimen included a three-weekly lower dose of l-HOP combined with D fractionated on days 1 and 8, and Cap on days 1–14. Preliminary results are promising in terms of clinical and pathological response, progression-free survival (PFS), and toxicity.

Although the efficacy of a maintenance therapy after first-line chemotherapy has been proven for advanced lung and colorectal cancer in multiple studies, it is still debated for metastatic gastric cancer [8,9]. In two prospective reports, the use of Cap as maintenance chemotherapy for patients with metastatic gastric cancer resulted well tolerated and effective [10,11].

Therefore, the current study was performed to evaluate the activity and safety of the modified DOC regimen followed by maintenance capecitabine as first-line strategy for patients with metastatic gastric or GEJ cancer.

Patients and methods

Eligibility criteria

This prospective observational study enrolled patients with histologically and radiologically proven metastatic adenocarcinoma of the stomach or GEJ, who had not received any systemic therapy for advanced disease. Patients who relapsed after adjuvant 5-FU or capecitabine-based chemotherapy were eligible provided they had remained disease free for at least 12 months after completion of adjuvant therapy. The other inclusion criteria were age ≥ 18 years, Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2, bidimensionally measurable disease, a life expectancy of at least 3 months, adequate hematological parameters (an absolute neutrophil count of $\geq 1.5 \times 10^9/L$ and a platelet count of $\geq 100 \times 10^9/L$); creatinine and total bilirubin levels < 1.25 -fold the upper normal limit; aspartate and alanine aminotransferase < 3.0 -fold the upper normal limit, and absence of a second primary tumor other than nonmelanoma skin cancer or in-situ cervical carcinoma. Patients aged ≥ 80 years with > 1 ECOG PS were excluded from the study. Exclusion criteria included also HER-2 positive tumors, operable metastatic disease, severe cardiac dysfunction, chronic diarrhea or uncontrolled sites of infection. All patients gave their written informed consent.

Patient evaluation

The pretreatment evaluation, performed within 2 weeks before study entry, included a detailed history and

physical examination, a complete blood cell count with differential and platelet counts, whole-blood chemistry, and computed tomography (CT) scans or MRI of the chest and abdomen. During DOC treatment, a complete blood cell count with differential and platelet counts was performed on days 1 and 8 of each cycle). In addition, the patients were clinically assessed every 3 weeks. During maintenance with capecitabine, whole-blood chemistry was evaluated every 3 weeks. An echocardiography to monitor the cardiac function was performed within 2 weeks prior to starting and within 2 weeks after six cycles of DOC. Treatment response by means of CT scan or MRI was evaluated every three 3-weekly cycles or sooner if clinically indicated. Tumor response was radiologically estimated using the Response Evaluation Criteria in Solid Tumors (RECIST criteria; version 1.1).

Treatment delivery

Treatment consisted of D 35 mg/m^2 days 1–8, combined with l-OHP 85 mg/m^2 on day 1, and Cap 750 mg/m^2 twice daily on days 1–14, every 3 weeks. To improve tolerability of DOC, the doses of l-HOP and D were reduced by 20% in the first cycle for patients ≥ 75 years. After a maximum of six DOC cycles, patients without evidence of disease progression received maintenance treatment with Cap 1000 mg/m^2 twice a day on days 1–14, every 3 weeks until disease progression or unacceptable toxicity. Four cycles of DOC were planned as induction chemotherapy for patients > 80 years and ECOG PS = 0.

Toxicity

Toxicity was assessed using the common toxicity criteria of the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.02). Treatment was delayed if, on the planned day of treatment, the neutrophil count was less than $1500/\text{mm}^3$, the platelet count was less than $100\,000/\text{mm}^3$, or the patient had persistent diarrhea or stomatitis $> \text{grade } 1$. Patients who required more than 2 weeks for recovery from adverse reactions were excluded from the study. In the case of grade 4 hematological or any other severe ($\geq \text{grade } 3$) nonhematological toxicity, the doses of the chemotherapy agents were reduced by 25% for subsequent courses. The dose of l-OHP was also reduced by 25% in the case of persistent (≥ 14 days) paresthesia or temporary (7–14 days) painful paresthesia or functional impairment. In the case of persistent (≥ 14 days) painful paresthesia or functional impairment, l-HOP was omitted from the subsequent cycles until recovery.

With the aim to prevent nausea and vomiting, hydroxytryptamine-3 antagonists (intravenously) plus dexamethasone 8 mg were administered intravenously before the chemotherapy infusion. Oral loperamide 2 mg every 2 hours and oral rehydration were prescribed in the case of delayed diarrhea. No cytokine prophylactic treatment

was recommended. The other concomitant medications were primarily used to palliate pain.

Statistical considerations

The primary endpoint was 6-month disease-control rate (DCR) defined as the rate of patients who achieved stable disease or partial response (PR) or complete response (CR) within 6 months after the commencement of therapy. Secondary endpoints were PFS, OS, and safety. PFS was calculated as the time from the date of first chemotherapy infusion to the date of disease progression or death from any cause or censored at last follow-up visit, whichever comes first. OS was measured from the date of start of treatment to the date of death or censored at last follow-up visit. The method of Kaplan–Meier was used to estimate PFS and OS. Statistical analyses were conducted by STATA software.

Results

Patient characteristics

Between July 2014 and September 2017, 37 patients were enrolled at our institution. All patients were radiologically evaluated at our hospital. Patients' baseline characteristics are summarized in Table 1. The median age of our study population was 66 years (range, 36–82 years) and 33 (89.2%) patients had ECOG PS of 0 or 1. Overall,

22 (59.5%) patients had poorly differentiated cancer, 23 (62.2%) had liver metastases, and 31 (83.8%) had more than one site of disease. Primary tumor was gastric in 23 (62.2%) patients and GEJ in 14 (37.8%) patients. Six (16.2%) subjects had received prior 5-FU-based adjuvant chemotherapy and 3 (8.1%) patients had received prior l-OHP-based adjuvant treatment. Eleven (29.7%) had undergone resection of their primary tumor with curative intent and were offered DOC after documentation of unresectable progression or metastatic disease.

Treatment efficacy

A total of 209 cycles, with a median of XX cycles, (range, 3–6 cycles) of DOC were administered to the 37 enrolled patients and all of them were evaluable for efficacy and toxicity analyses. After completing the DOC regimen, one patient achieved a CR (2.7%), 20 (54.1%) achieved a PR, 14 (37.8%) had stable disease, and 2 (5.4%) had progressive disease (PD) (Table 2). Thirty-five patients (94.6%) received capecitabine as maintenance chemotherapy for a median of seven cycles (range, 3–14 cycles). The maintenance treatment was discontinued due to PD in 26 patients and two subjects were lost to follow-up for treatment-unrelated reasons after 4 and 5 months from the onset of the maintenance treatment, respectively. The median duration of response was 6.1 months (range, 2.5–8.4 months). The six-month DCR was 83.7% [95% confidence interval (CI), 71.8–95.6%]; 86.9 and 78.5% for patients gastric and GEJ cancer, respectively. After documentation of PD during maintenance treatment, 24 patients received a second-line treatment; 11 patients were administered ramucirumab and paclitaxel, two received ramucirumab alone, eight received epirubicin-based combination regimens, and three resumed l-HOP.

The median PFS was 8.2 months (95% CI, 6.3–9.8 months) and the median OS was 14.4 months (95% CI, 11.7–18.6 months) (Fig. 1). At a median follow-up of 13.2 months (range, 6–27 months), 29 patients had died.

Treatment toxicity

Hematological and nonhematological adverse events during treatment are shown in Table 3. The only grade 4 observed toxicity was neutropenia which occurred in 2 (5.4%) patients who developed febrile neutropenia

Table 1 Patient characteristics

Characteristics	Patients, <i>N</i> =37 (%)
Age, years	
Median	66
Range	(36–82)
Sex	
Male	25 (67.6)
Female	12 (32.4)
ECOG PS	
0	21 (56.8)
1	12 (32.4)
2	4 (10.8)
Tumor location	
Stomach	23 (62.2)
Gastroesophageal junction	14 (37.8)
Differentiation	
Well differentiated	3 (8.1)
Moderate	12 (32.4)
Poorly differentiated	22 (59.5)
Signed ring cell histology	7 (18.9)
Metastatic sites	
Liver	23 (62.2)
Lung	9 (24.3)
Lymph nodes	22 (59.5)
Peritoneum	19 (51.4)
Bone	3 (8.1)
Primary tumor resected	
Yes	11 (29.7)
No	26 (70.3)
No. of sites of disease	
>1	31 (83.8)
Previous adjuvant chemotherapy	
5-fluorouracil based	6 (16.2)
Oxaliplatin based	3 (8.1)
Baseline Hemoglobin, g/dL	
Median	11.4
Range	(9.1–15.2)

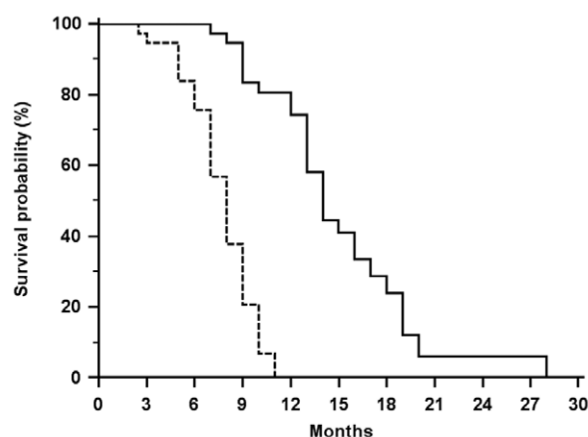
ECOG PS, Eastern Cooperative Oncology Group performance status.

Table 2 Results

Variables	<i>N</i> (%)
Objective response rate	
Complete response	1 (2.7)
Partial response	20 (54.1)
Stable disease	14 (37.8)
Progressive disease	2 (5.4)
6-month disease-control rate, % (95% CI, %)	83.7 (71.8–95.6)
Progression-free survival, months (95% CI, months)	8.2 (6.3–9.8)
Overall survival, months (95% CI, months)	14.4 (11.7–18.6)

CI, confidence interval.

Fig. 1



Kaplan-Meier estimates of PFS (----) and OS (-). PFS, progression-free survival.

Table 3 Adverse events during docetaxel, oxaliplatin, capecitabine combination regimen

Adverse events	Grade ≤ 2 , <i>N</i> (%)	Grade 3, <i>N</i> (%)	Grade 4, <i>N</i> (%)
Hematological toxicity			
Neutropenia	26 (75.6)	9 (24.3)	2 (5.4)
Anemia	9 (24.3)	4 (10.8)	0
Thrombocytopenia	10 (27.0)	3 (8.1)	0
Nonhematological toxicity			
Nausea/vomiting	10 (27.0)	3 (8.1)	0
Diarrhea	6 (16.2)	4 (10.8)	0
Stomatitis	12 (32.4)	3 (8.1)	0
Hand-foot syndrome	3 (8.1)	0	0
Peripheral neuropathy	13 (35.1)	0	0
Fatigue	11 (29.7)	0	0

and rapidly recovered by use of G-CSF and antibiotics. Neutropenia was the most common grade 3–4 toxicity and occurred in 11 (29.7%) patients, while grade 3 anemia and thrombocytopenia were observed in 3 (8.1%) and 4 (10.8%) patients, respectively. None of the patients required platelet or blood red cell transfusions. Other grade 3 adverse events were diarrhea reported in 4 (10.8%) patients, stomatitis in 3 (8.1%), and nausea/vomiting in 3 (8.1%). Grade 3 neurotoxicity was not observed. No serious hepatic, renal, or cardiac dysfunctions were reported during treatment. During induction chemotherapy, a total of 66 (31.5%) cycles were delayed due to toxicity and 9 (24.3%) patients required dose-reductions of DOC. Overall, the relative dose intensity was 93.3% for D (16.3 mg/m²/week), 94.7% for I-HOP (20.1 mg/m²/week), and 87.6% for capecitabine (6898.6 mg/m²/week). For 203 (97%) of all administered cycles, treatment could be administered on an outpatient basis. As expected, toxicity during maintenance treatment was very mild, mostly of grade 1 or 2.

Discussion

Currently, the standard first-line treatment for patients with metastatic gastric or GEJ cancer is still subject of

debate. In the past, the DOC regimen has been investigated in few small studies which demonstrated its activity and few reports documented the efficacy and safety of Cap as maintenance treatment after first-line therapy for metastatic gastric or GEJ cancer [10–13]. However, to the best of our knowledge, the present study is the first to report the efficacy and feasibility of a first-line treatment with modified DOC regimen for a maximum of six cycles followed by Cap as maintenance chemotherapy for metastatic gastric or GEJ cancer patients. Albeit with the limitations of a small prospective observational study, the median PFS of 8.2 months, and the median OS of 14.4 months achieved in our analysis compare well with those reported with most active combination chemotherapies. In this respect, D- or epirubicin-containing triplet regimens typically yield a ≤ 9 -month median PFS and ≤ 12 -month median OS for metastatic gastric cancer [6,14]. Additionally, our results seem better compared with those achieved with the DOC treatment in two recent phase II studies of patients with gastric or GEJ cancer [12,13]. Particularly, in the larger multicenter one, the authors reported a median PFS of 4.1 months (range 1.1–17.4 months) and a median OS 9.8 months (range 1.1–18.7 months) [12], while the smaller analysis achieved a median PFS of 6.9 months (90% CI, 5.5–8.6 months) and a median OS of 13 months (90% CI, 9.5–16.8 months) [13]. It could be postulated that the maintenance treatment with Cap may have contributed to a longer median PFS in our population study, as also suggested by other recent reports in which this oral agent was used as maintenance after induction chemotherapy for advanced gastric cancer [10,11]. In this regard, a phase II multicenter study reported a similar PFS (8.3 months; 95% CI, 7.2–10.9 months) for the combination of DOC plus the antiangiogenic drug bevacizumab (B) followed by Cap plus B as maintenance treatment [10]. Furthermore, the use of the novel mAb ramucirumab, alone or combined with paclitaxel, as second-line treatment for 13 of our patients may have contributed to prolong the median OS, as also suggested by other studies [15,16].

It is known that the incidence of GEJ cancer is progressively increasing worldwide and its prognosis has been typically worse than that of gastric cancer, with median OS not longer than 10 months [17,18]. In this regard, our results suggest that the DOC regimen followed by Cap may achieve a similar efficacy for patients with GEJ cancer (86.9% 6-month DCR, 15.4-month median OS) compared to those with gastric cancer (78.5% 6-month DCR, 13.7-month median OS). Nevertheless, we acknowledge that the small sample size and the monoinstitutional nature of the current study are limitations which do not allow to draw definitive conclusions.

Aiming to improve the clinical outcomes of patients with advanced gastric cancer or GEJ, some innovative agents were recently investigated as first-line treatments

albeit the results not being particularly promising. In this respect, a phase II study led by the Italian Oncology Group for Clinical Research showed that the combination of dose-dense DCF plus the anti-EGFR panitumumab as first-line strategy for metastatic gastric and GEJ cancer achieved an encouraging 62% objective response rate; however, median PFS and OS were only 4.9 and 10 months, respectively [19]. Therefore, despite this stimulating and evolving therapeutic scenario, the DOC regimen followed by Cap as maintenance may still have a useful strategy for striking a balance between prolonged clinical response and good toxicity profile in metastatic gastric and GEJ cancer. In this regard, an interesting point in the present study is that the applied treatment was well tolerated. The proportion of patients suffering from grade 3–4 neutropenia (29.7%), including febrile neutropenia (5.4%), grade 3 nausea and vomiting (8.1%), and diarrhea (10.8%), was lower compared with that usually reported with the conventional epirubicin or docetaxel-based regimens [4,6]. Of note, in an earlier multicenter phase I/II study that evaluated the DOC regimen, the reported toxicity, particularly grade 3 diarrhea, appeared worse than in our study and limited treatment feasibility [12,13]. The higher dose of I-HOP administered per cycle (70 mg/m² on days 1 and 8) in this study, compared with the present report (85 mg/m² on day 1), could possibly explain the more severe toxicity observed [12]. Another DOC regimen analyzing phase II study, despite documenting a generally well tolerated treatment, observed a 41% grade 3–4 neutropenia and a 6% grade 3 peripheral neuropathy [13]. In this case, the worse tolerability could be partly attributed to the increased dose of I-OHP per cycle (100 mg/m²) and to the administration of D (60 mg/m²) on day 1 only, as opposed to being fractionated on days 1 and 2 as in the present study. Additionally, the feasibility of the DOC regimen with the schedule used in the current study seems to be supported also by the relatively low incidence of patients who required dose reductions (24.3%) compared with the typically greater than 50% rate observed with other triplet chemotherapy combinations commonly used for metastatic gastric and GEJ cancer, such as DCF and ECF [4,20]. Moreover, despite L-OHP-related neurotoxicity of grade 2 occurring in 35.1% of patients, no grade 3 was observed. Overall, the rates of the adverse events were in line with those reported in other studies in which CDDP had been replaced with I-OHP [6,21].

In conclusion, the modified DOC regimen for a maximum of six cycles followed by Cap as maintenance treatment as first-line therapy for patients with metastatic gastric or GEJ cancer is feasible and may achieve encouraging results in terms of PFS and OS. Therefore, comparative clinical trials should be performed to correctly evaluate the exact role of this DOC regimen followed by Cap in the treatment of gastric or GEJ cancer.

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All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. Informed consent to be included in the study, or the equivalent, was obtained from all patients.

Conflicts of interest

There are no conflicts of interest.

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