Comparison Between DCF (Docetaxel, Cisplatin and 5-Fluorouracil) and Modified EOX (Epirubicin, Oxaliplatin and Capecitabine) as Palliative First-line Chemotherapy for Adenocarcinoma of the Upper Gastrointestinal Tract

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Abstract. *Background: The efficacy of triple-drug combination regimens such as docetaxel, cisplatin and 5-fluorouracil (DCF), and epirubicin, oxaliplatin and capecitabine (EOX), is superior to standard cisplatin/5-fluorouracil in patients with upper gastrointestinal adenocarcinoma. In this analysis, we compare DCF and EOX regarding toxicity and efficacy. Patients and Methods: Patients received either intravenous docetaxel at 75 mg/m^2, cisplatin at 75 mg/m^2, both given on day 1, and 5-fluorouracil at 750 mg/m^2, on days 1 to 5, or epirubicin at 50 mg/m^2 i.v. on day 1, oxaliplatin at 130 mg/m^2 i.v. on day 1 and capecitabine at a twice-daily dose of 1000 mg/m^2 p.o. for two weeks; both regimens were repeated every three weeks. Results: Response rates for DCF and EOX were 28% and 10%, time-to-progression was 26 and 20 weeks, and overall survival were 54 and 52 weeks, respectively. Conclusion: We conclude that further investigations within comparative prospective clinical trials of these regimens are warranted.*

Adenocarcinoma of the upper gastrointestinal (GI) tract remains a frequent cause of death as the cancer is usually diagnosed in an inoperative stage and surgery is still the only curative treatment option. Therefore, palliative chemotherapy has been widely used in the treatment of patients with recurrent, locally advanced or metastatic adenocarcinoma of the upper GI tract (1). This approach can reduce tumor-related symptoms, prolong overall survival (OS) and improve Quality of Life (QoL) (2-5). Platin- and fluoropyrimidine-based chemotherapy is accepted as first-line standard treatment and therefore is the reference regimen for many clinical trials (2, 6, 7). Some patients may also tolerate the addition of docetaxel (2, 7), or epirubicin (2, 8), leading to additional benefit.

Van Cutsem *et al*. reported on improved response rates, progression-free survival times, and OS when docetaxel was added to cisplatin and 5-fluorouracil (DCF), based on the results of a randomized phase III study (7). However, this combination chemotherapy was associated with hematological toxicity, with a 29% incidence of febrile neutropenia or neutropenic infection. To avoid severe myelosuppression as reported in the trial above, we used at the time at the Medical University of Vienna DCF plus granulocyte-colony stimulating factor (G-CSF) prophylaxis (9). DCF plus G-CSF prophylaxis was as effective as previously reported by Van Cutsem *et al*. and was accompanied by less frequent sequelae of neutropenia, which was rated common terminology criteria for adverse event (CTCAE) grade 4 in only one patient out of 18 without febrile episodes.

In a two-by-two design, Cunningham *et al*. randomly assigned 1,002 patients to receive triplet therapy consisting of epirubicin (E), 5-fluorouracil (F) or capecitabine (X) and cisplatin (C) or oxaliplatin (O). In this trial, comparable OS was achieved with these triple combinations, while hematological and non-hematological toxicity were reduced. Importantly, patients receiving the EOX regimen had the best survival outcome (11.2 *versus* 9.9 months on ECF; p=0.02) (8).

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Key Words: Epirubicin, oxaliplatin, capecitabine, docetaxel, cisplatin, 5-fluorouracil, G-CSF, gastroesophageal cancer, adenocarcinoma.

EOX, however, while reasonably well-tolerated, may be inconvenient due to the necessity for continuous drug delivery (capecitabine from days 1 to 21, cycle repeated every three weeks). Furthermore, this regimen was associated with a relatively high rate of severe diarrhea (11.9%) and peripheral neuropathy (4.4%) when compared to ECF (2.6% and 0.4%; p=0.01) in the REAL-2 trial (8). In our own trial, we established a better-tolerated modified version of the EOX regimen using capecitabine from days 1 to 14 followed by one week of rest (10). This modified EOX (mEOX) regimen with non-continuous capecitabine (10) resulted in considerably less severe WHO toxicity in terms of diarrhea (2%) and peripheral neuropathy (0%) as compared to conventional EOX (8).

No data exist of a direct comparison of DCF and mEOX regimen in patients with adenocarcinoma of the upper GI tract. The aim of this study was to compare our own data concerning DCF plus G-CSF and the mEOX regimen collected at the Medical University of Vienna and already separately published in Anticancer Research (9, 10).

Patients and Methods

The decision for DCF or mEOX as palliative first-line treatment was taken by an interdisciplinary tumor board for upper GI tract cancer. Patient data were collected at the Comprehensive Cancer Center, Medical University of Vienna. All patients undergoing either DCF or mEOX chemotherapy had histologically-confirmed adenocarcinoma of the upper GI tract in locally advanced inoperable or metastatic stage with bi-dimensionally measurable disease. All patients receiving palliative chemotherapy had a World Health Organization (WHO) performance status (PS) of ≤2, provided informed consent, and were required to have an expected survival time of more than 12 weeks, adequate bone marrow [hemoglobin ≥10 g/dl, absolute neutrophil count (ANC) ≥3,000/μl, platelet count ≥100,000/μl), adequate renal (serum creatinine concentration ≤1.25 × upper normal limit (UNL)] and adequate hepatic function [total serum bilirubin ≤1.5 × UNL, (GOT) and (GPT) ≤2.5 × UNL, alkaline phosphatase ≤5 × UNL]. A left ventricular ejection fraction (LVEF) of ≥60% was required to qualify for EOX chemotherapy.

Providing if there was no positivity for human epidermal growth factor receptor 2 (if positivity, the standard regimen is mandatory according to the ToGA trial) (11), during the observation period, 69 patients received either chemotherapy with the DCF plus G-CSF (docetaxel and cisplatin both 75 mg/m^2 *i.v.* on day 1, 5-fluorouracil at 750 mg/m^2 as continuous infusion on days 1 to 5, and G-CSF prophylaxis subcutaneously on day 6) or mEOX regimen (epirubicin at 50 mg/m^2 *i.v.* on day 1; oxaliplatin at 130 mg/m^2 *i.v.* on day 1; capecitabine at a twice-daily dose of 1000 mg/m^2 *p.o.* for two weeks, followed by one week of rest). Both regimens were repeated every three weeks for a total of six cycles. Supportive medication consisted of proton pump inhibitors, dexamethasone and 5-hydroxytryptamine receptor antagonists according to local protocol.

Information abstracted from patients' charts included patient's characteristics (age, gender, WHO PS, primary site, number of organs involved, metastatic site, history of primary tumor resection and prior adjuvant chemotherapy) and chemotherapy cycles. Treatment side-effects were measured according to CTCAE (12). Toxicity is reported as the worst event per patient while on therapy.

Progression-free survival (PFS) was defined as the primary study endpoint and measured from the date of diagnosis of metastatic disease up until documented progression or death. Secondary endpoints consisted of the response rate (RR), toxicity and OS. OS was defined as the time interval from diagnosis of locally advanced inoperable or metastatic disease up until death of any cause.

Response was assessed using the WHO response criteria (13). Complete response (CR) was defined as the disappearance of all measurable lesions for a minimum of eight weeks. Partial response (PR) was defined as 50% or more reduction in the sum of the products of the greatest diameters of measurable lesions, no increase of lesion size and no new lesions. Stable disease (SD) was defined as less than 50% decrease and less than 25% increase without the appearance of new lesions. Progressive disease (PD) was defined as greater than 25% increase in tumor size or the appearance of new lesions. Patients were required to have received a minimum of two cycles of mEOX in order to qualify for response assessment.

Results

A total of 20 DCF patients (8 female and 12 male) with a median age of 65 (range, 30-82) years and 51 mEOX patients (17 female and 34 male) with a median age of 63 (range, 42-86) years, were identified from an upper GI cancer database with locally advanced inoperable or metastatic adenocarcinoma of the upper GI tract.

Eight (40%) DCF and 15 (29%) mEOX patients had had prior surgery with curative intent, while a further 4 (8%) mEOX underwent prior palliative gastrectomy due to bleeding or tumor rupture. Three (15%) on DCF and 6 (12%) on mEOX had received prior neoadjuvant or adjuvant chemotherapy, and 1 (2%) on mEOX patient had had prior chemoradiotherapy.

In total, 10 (50%) patients treated with DCF and 24 (42%) mEOX had metastatic disease restricted to a single organ, while the remaining 10 (50%) and 27 (52%) patients, respectively, had multiple metastases involving two or more organs. One patient received DCF chemotherapy in another hospital and was not evaluable for our analysis. A second patient died two weeks after the first DCF administration and was not evaluable either. Consequently, a total of 18 patients were included in this analysis. Forty-nine patients were available for evaluation of response. Two patients discontinued mEOX chemotherapy after one cycle of treatment for personal reasons. Patient's characteristics are summarized in Table I.

A total of 102 and 228 treatment courses according to the DCF and mEOX protocol were administered to 18 and 49 patients, respectively, with the median number of courses being 6 (range, 3-7) and also 6 (range, 1-6). The median PFS

Table I. *Baseline characteristics of the study population.*

Characteristics	DCF, n	mEOX, n
Entered	20	51
Median age, years (range)	65 (30-82)	63 (42-86)
Median WHO performance score	2	2
Female/male	8/12	17/34
Stage at primary diagnosis		
Localized	0	6 (11.8%)
Metastatic	20 (100%)	45 (88.2%)
Metastatic site		
Liver	10 (50.0%)	20 (39.2%)
Lung	3 (15.0%)	3 (5.9%)
Peritoneal carcinosis	7 (35.0%)	27 (52.9%)
Lymph nodes	10 (50.0%)	19 (37.3%)
Bone	0	6 (11.8%)
≥2 Metastatic sites	10 (50.0%)	27 (52.9%)
Prior surgery		
Curative intent	8 (40.0%)	15 (29.4%)
Palliative resection	0	4 (7.8%)
Adjuvant/neoadjuvant chemotherapy	3 (15.0%)	6 (11.8%)
Adjuvant chemoradiotherapy	0	1 (1.9%)

DCF: Docetaxel, cisplatin, 5-fluorouracil; mEOX: epirubicin, oxaliplatin, capecitabine.

was 26 weeks (range, 10-71) in those treated with DCF and 20 weeks (range, 11-21) in those treated with mEOX; the median OS was 54 weeks (range, 13-114) *versus* 52 weeks (range, 36-60). The overall objective response rate was 28% in patients treated with DCF and 10% in those treated with mEOX, including five PRs, respectively. Eleven patients (61%) treated with DCF *versus* 31 (63%) with mEOX showed disease stabilization and 2 (11%) *versus* 13 (27%) patients, respectively, experienced disease progression while on treatment (Table II).

Patients who failed to respond to DCF or mEOX combination chemotherapy or experienced tumor progression within three months after completion of chemotherapy received second-line therapy consisting of various regimens at the discretion of the treating physician.

In patients treated with DCF grade III abdominal pain and anemia occurred in two cases each (11%), alopecia in eight (44%), whereas constipation, emesis, oral mucositis and hypotension were less frequent. Grade IV toxicities were diagnosed as oral mucositis, cardiac ischemia and neutropenia in 1 patient each. Three further patients had grade IV venous thromboembolic events.

In mEOX patients there was no grade IV toxicity. Grade III diarrhea, constipation and non-life threatening, therapy-associated or paraneoplastic pulmonary embolism (2%) was observed in one patient each, and hand-foot syndrome in two patients (4%). Hematological toxicities of grade III consisted of anemia in two patients (4%). All toxicities for both regimens are listed in Table III.

Table II. *Summary of treatment efficacy.*

	DCF No. of patients	mEOX No. of patients
Complete response	0	0
Partial response	5 (27.8%)	5 (10.2%)
Stable disease	11 (61.1%)	31 (63.3%)
Progression	2 (11.1%)	13 (26.5%)
Overall response rate	5 (27.8%)	5 (10.2%)
Median PFS weeks (range)	26 (10-71)	20 (11-21)
Median OS weeks (range)	54 (13-114)	52 (36-60)

DCF: Docetaxel, cisplatin, 5-fluorouracil; mEOX: epirubicin, oxaliplatin, capecitabine.

Discussion

The prognosis of unresectable or metastatic adenocarcinoma of the upper GI tract remains dismal, with a median survival of just 7-10 months. Palliative chemotherapy is well-established, but the survival advantage appears marginal (6). Several regimens have been shown to prolong OS and improve QoL, when compared to best supportive care (3-5). Platin and fluoropyrimidine-containing regimens with and without taxanes (7) or anthracyclines (8) have a significant benefit for the triple-drug combinations, while the considerable toxicity needs to be taken into account. To avoid severe myelosuppression and consequent febrile neutropenia, subcutaneous G-CSF prophylaxis was scheduled on the day after the same DCF combination chemotherapy described by Van Cutsem *et al*. (7) to our patients at the Medical University of Vienna (9). This approach revealed only 6% of cases of CTCAE grade III to IV neutropenia without any neutropenic fever *versus* 29% of cases of febrile neutropenia or neutropenic infection without G-CSF prophylaxis as reported previously (7). In another study, we presented efficacy and toxicity data of a mEOX regimen in which capecitabine was administered at a twice-daily dose of 1000 mg/m^2 *p.o.* for only two weeks, followed by one week of rest (10). This mEOX regimen with non-continuous capecitabine resulted in considerably less severe toxicity as compared to conventional EOX (8), which is of potential value in terms of QoL in incurable patients. The median PFS and OS in both our studies (9, 10) were well in line with the original DCF (7) and EOX data (8). To the best of our knowledge, no direct comparison of DCF and EOX regimen exists, which led us to compare our own published data of DCF plus G-CSF (9) and mEOX (10), which offers effective treatment options for the HER-2-negative subgroup.

The median PFS of 26 weeks *versus* 20 weeks and the median OS of 54 weeks *versus* 52 weeks were comparable between regimens (see Table II). In terms of severe non-

Table III. *Main adverse effects of combination therapy.*

Toxicity	CTCAE Grade n (%)			
	I	II	III	IV
Abdominal pain				
DCF	-	3 (16.7%)	2 (11.2%)	-
mEOX	1 (2%)	-	-	-
Diarrhea				
DCF	1 (5.6%)	6 (33.3%)	-	-
mEOX	3 (6.1%)	6 (12.2%)	1 (2%)	-
Constipation				
DCF	1 (5.6%)	3 (16.7%)	1 (5.6%)	-
mEOX	-	1 (2%)	1 (2%)	-
Emesis				
DCF	1 (5.6%)	13 (72.2%)	1 (5.6%)	-
mEOX	3 (6.1%)	2 (4.1%)	-	-
Oral mucositis				
DCF	-	2 (11.2%)	1 (5.6%)	1 (5.6%)
mEOX	-	1 (2%)	-	-
Hand-foot syndrome				
DCF	-	-	-	-
mEOX	1 (2%)	-	2 (4.1%)	-
Neuropathy				
DCF	-	4 (22.2%)	-	-
mEOX	1 (2%)	-	-	-
Venous thromboembolic events				
DCF	-	-	-	3 (16.7%)
mEOX	2 (4.1%)	1 (2%)	1 (2%)	-
Cardiac ischemia				
DCF	-	-	-	1 (5.6%)
mEOX	1 (2%)	-	-	-
Hypotension				
DCF	-	-	1 (5.6%)	-
mEOX	-	-	-	-
Alopecia				
DCF	-	5 (27.8%)	8 (44.4%)	-
mEOX	-	-	-	-
Anemia				
DCF	7 (38.9%)	9 (50%)	2 (11.2%)	-
mEOX	3 (6.1%)	4 (8.2%)	2 (4.1%)	-
Neutropenia				
DCF	5 (27.8%)	1 (5.6%)	-	1 (5.6%)
mEOX	2 (4.1%)	2 (4.1%)	1 (2%)	-
Thrombocytopenia				
DCF	5 (27.8%)	1 (5.6%)	-	-
mEOX	-	2 (4.1%)	1 (2%)	-

CTCAE: Common terminology criteria for adverse event; DCF: docetaxel, cisplatin, 5-fluorouracil; mEOX: epirubicin, oxaliplatin, capecitabine.

hematological as well as hematological toxicities, there were differences between the regimens. In patients treated with DCF plus G-CSF grade III consisted of abdominal pain alopecia, constipation, emesis, oral mucositis and hypotension. Grade IV toxicities were oral mucositis, cardiac ischemia, neutropenia and venous thromboembolic events. In patients treated with mEOX, the grade III toxicities consisted of diarrhea, constipation, and no grade IV toxicities were seen (see Table III). Based on these findings careful pre-selection of patients scheduled for therapy with DCF plus G-CSF appears more important than for the less toxic mEOX.

Obviously, our study has several limitations. Low and differing overall patient numbers as well as its retrospective non-randomized design, limits the validity of our data. Furthermore, no information concerning QoL is available. Therefore, a prospective, randomized trial is necessary in order to fully elucidate the activity and toxicity of DCF plus G-CSF and mEOX.

Funding

This study had no sponsor or funding source.

Conflicts of Interest

None declared.

References

1 Bertuccio P, Chatenoud L, Levi F, Proud D, Ferlay J, Negri E, Malvezzi M and La Vecchia C: Recent Pattern in gastric cancer: A global overview. Int J Cancer *125*: 666-673, 2009.

2 Wagner AD, Groethe W, Haerting J, Kleber G, Grothey A and Fleig WE: Chemotherapy in advanced gastric cancer: A systematic review and meta-analysis based on aggregate data. J Clin Oncol *24*: 2903-2909, 2006.

3 Murad AM, Santiago FF and Petrioianu A: Modified therapy with 5-fluorouracil, doxorubicin and methotrexate in advanced gastric cancer. Cancer *72*: 37-41, 1993.

4 Pyrhönen S, Kuitunen T, Nyandoto P and Kouri M: Randomized comparison of fluorouracil, epirubicin and methotrexate (FEMTX) plus supportive care with supportive care alone in patients with nonresectable gastric cancer. Br J Cancer *71*: 587-591, 1995.

5 Glimelius B, Ekstrom K, Hoffman K, Graf W, Sjödén PO, Haglund U, Svensson C, Enander LK, Linné T, Sellström H and Heuman R: Randomized comparison between chemotherapy plus best supportive care with best supportive care in advanced gastric cancer. Ann Oncol *8*: 163-168, 1997.

6 Wohrer SS, Raderer M and Hejna M: Palliative chemotherapy for advanced gastric cancer. Ann Oncol *15*: 1585-1595, 2004.

7 Van Cutsem E, Moiseyenko VM, Tjulandin S, Majlis A, Constenla M, Boni C, Rodrigues A, Fodor M, Chao Y, Voznyi E, Risse ML and Ajani J: A Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first line treatment for advanced gastric cancer: A Report of the V325 study group. J Clin Oncol *24*: 4991-4997, 2006.

8 Cunningham D, Starling N, Rao S, Iveson T, Nicolson M, Coxon F, Oates J, Norman AR and Upper Gastrointestinal Clinical Studies Group of the National Cancer Research Institute of the United Kingdom: Capecitabine and oxaliplatin for advanced esophagogastric cancer. N Engl J Med *358*: 36-46, 2008.

9 Bojic M, Pluschnig U, Zacherl J, Thallinger CM, Ba-Ssalamah A, Maresch J, Datler P, Schoppmann SF and Hejna M: Docetaxel, cisplatin and 5-fluorouracil plus granulocyte colony-stimulating factor prophylaxis in patients with metastatic adenocarcinoma of the stomach and gastroesophageal junction: Experience at the Medical University of Vienna. Anticancer Res *31*: 2379-2382, 2011.

10 Pluschnig U, Schoppmann SF, Preusser M, Datler P, Asari R, Ba-Ssalamah A, Schwameis K, Birner P, Zacherl J and Hejna M: Modified EOX (Epirubicin, Oxaliplatin and Capecitabine) as palliative first-line chemotherapy for gastroesophageal adenocarcinoma. Anticancer Res *33(3)*: 1035-1039, 2013.

11 Bang YJ, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, Lordick F, Ohtsu A, Omuro Y, Satoh T, Aprile G, Kulikov E, Hill J, Lehle M, Rüschoff J, Kang YK; ToGA Trial Investigators. Trastuzumab in combination with chemotherapy *versus* chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-esophageal junction cancer (ToGA): a phase 3, open-label, randomized controlled trial. Lancet *376*: 687-697, 2010.

12 US Department of Health and Human Services; National Institutes of Health; National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE). Version 4.03: NIH Publication No. 09-5410, 2010.

13 Miller AB, Hoogstraten B, Staquet M, Winkler A: Reporting results of cancer treatment. Cancer *47*: 207-214, 1981.

Received May 2, 2013
Revised June 6, 2013
Accepted June 7, 2013