

Modified EOX (Epirubicin, Oxaliplatin and Capecitabine) as Palliative First-line Chemotherapy for Gastroesophageal Adenocarcinoma

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Abstract. *Background:* The efficacy of triple-drug combination regimens such as epirubicin, oxaliplatin and capecitabine (EOX) is superior to standard cisplatin/5-fluorouracil, but considerable toxicity needs to be taken into account in patients with upper gastrointestinal adenocarcinoma. Therefore, we aimed to establish a modified version of the EOX regimen with improved tolerability for these patients. *Patients and Methods:* Patients received palliative first-line chemotherapy with a modified EOX regimen repeated every three weeks (epirubicin 50 mg/m² i.v., day 1; oxaliplatin 130 mg/m² i.v., day 1; capecitabine at a twice-daily dose of 1000 mg/m² p.o. for two weeks). *Results:* Out of 51 patients, partial remission was observed in five (10.2%) and stable disease in 31 (60.8%). Progression-free survival was four months, and overall survival twelve months. *Conclusion:* Modified EOX was generally well-tolerated and, therefore, further investigation within prospective clinical trials is warranted.

Considerable progress has been made in the treatment of many malignancies over the past decade. Stomach cancer, however, remains a frequent cause of death as the cancer is usually diagnosed in an advanced stage and therefore curative treatment is not possible. In Western Europe, the

incidence of stomach cancer is low (30/100.000 residents per year) (1). The death rate, however, is relatively high as more than 55,000 Europeans died from this malignancy alone in 2011 (2).

While overall survival (OS) of patients with advanced stomach cancer remains dismal, results of clinical trials indicate that palliative chemotherapy offers the chance to reduce tumor-related symptoms, prolong OS and improve quality of life (QoL) (3).

Results of studies comparing palliative chemotherapy to best supportive care have consistently shown an increase in OS of approximately six months in the chemotherapy arm, and improvements in QoL (4-6). This eventually led to the definition of cisplatin and 5-fluorouracil (CF) as a standard-of-care in the first-line palliative treatment of inoperative or metastatic stomach cancer and as a reference regimen for further clinical trials (7).

A phase III trial by Van Cutsem *et al.* reported superior outcomes in terms of OS when docetaxel was added to CF (DCF) (9.2 versus 8.6 months, $p=0.02$) (7). Similar results were observed in a retrospective analysis using the DCF regimen plus granulocyte-colony stimulating factor prophylaxis (8). In a two-by-two design, Cunningham *et al.* randomly assigned 1002 patients to receive triplet therapy consisting of epirubicin, 5-fluorouracil or capecitabine and cisplatin or oxaliplatin. In this trial, comparable OS was achieved with these triple combinations, while hematological and non-hematological toxicity was reduced. Importantly, patients receiving the EOX regimen had the best survival outcome (11.2 versus 9.9 months on ECF; $p=0.02$) (9). A similar observation was made in two further studies when cisplatin was substituted by oxaliplatin and 5-fluorouracil by capecitabine, resulting in an improved treatment efficacy (10).

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Key Words: Epirubicin, oxaliplatin, capecitabine, gastroesophageal cancer, adenocarcinoma.

Epirubicin, oxaliplatin and capecitabine, however, while reasonably well-tolerated, may be inconvenient due to the necessity for continuous drug delivery (capecitabine from days 1 to 21, cycle repeated on day 22). Furthermore, this regimen was associated with a relatively high rate of severe diarrhea (11.9%) and peripheral neuropathy (4.4%), when compared to epirubicin–5-fluorouracil-cisplatin (2.6% and 0.4%; $p=0.01$) in the REAL-2 trial (10). Therefore, we aimed to establish a better-tolerated modified version of the EOX regimen.

In this retrospective single-institution trial, we analyzed the feasibility and safety of modified EOX consisting of two weeks of capecitabine treatment, followed by one week of rest. This regimen may allow for greater convenience and may provide a safety profile superior to conventional EOX (three weeks capecitabine) in terms of diarrhea, peripheral neuropathy and hand-foot syndrome.

Patients and Methods

The decision for EOX as palliative first-line treatment was taken by an interdisciplinary tumor board for upper gastrointestinal cancer. Patient data were collected at the Comprehensive Cancer Center, Medical University of Vienna. This retrospective analysis was approved by the local Ethics Committee.

Patients. Criteria for treatment inclusion with EOX were as follows: Age 18 years or older; (Eastern Cooperative Oncology Group) performance status (PS) =2; histologically-verified adenocarcinoma of the gastro-esophageal junction (GEJ) in locally advanced inoperable or metastatic stage; adequate bone marrow, renal, and liver function. A left ventricular ejection fraction (LVEF) of $\geq 60\%$ and informed consent, were required to qualify for anthracycline-containing chemotherapy.

During the observation period, 51 consecutive patients with locally advanced inoperable or metastatic stomach cancer and adenocarcinoma of the GEJ received, if there was no human epidermal growth factor receptor-2 positivity (if positivity standard regimen is mandatory according the ToGA trial) (11), chemotherapy with the modified EOX regimen (epirubicin 50 mg/m² *i.v.*, day 1; oxaliplatin 130 mg/m² *i.v.* day 1; capecitabine at a twice-daily dose of 1000 mg/m² *p.o.* for two weeks, followed by one week of rest). EOX regimen was 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 protocols. To prevent hand-foot syndrome due to capecitabine, patients were recommended to use fatty ointments.

Treatment plan and patient evaluation. For baseline staging evaluations, computed tomography (CT) scans of the chest and abdomen were mandatory, when possible with application of contrast agent. Further pre-therapeutic investigations consisted of echocardiography. After every three cycles of chemotherapy, a follow-up CT scan was conducted. CT scans were also performed any time when clinical signs of disease progression occurred. Echocardiography was conducted after the planned six cycles of palliative chemotherapy.

Progression-free survival (PFS) was defined as the primary study end-point and measured from the date of diagnosis of metastatic disease up until documented progression or death. Secondary end-points 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. Treatment side effects were evaluated twice every cycle (day one and fourteen) and measured according to Common Terminology Criteria for Adverse Events (CTCAE) (12). Toxicity is reported as the worst event per patient while on therapy.

Response was assessed using the World Health Organization (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 sum of 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 EOX in order to qualify for response assessment.

Statistical analysis. PFS, RR and OS are reported with 95% confidence intervals (CI). PFS and OS were estimated using the Kaplan-Meier product-limit method. To test for differences between, time to progression (TTP) curves, the log-rank test was used. p -Values=0.05 were considered to indicate statistical significance. The following variables were included in the univariate analysis of TTP: age >65 years; presence of liver metastases; and ECOG PS (2 *versus* <2). The same variables were included in the univariate analysis of OS. All statistics were calculated with the Statistical Package for the Social Sciences (SPSS®) version 19.0 (SPSS Inc., Chicago, IL, USA).

Results

Patients' characteristics. A total of 51 patients (17 females and 34 males) with a median age of 63 (range, 42-86) years, were identified from an upper gastrointestinal cancer database and all received palliative first-line EOX chemotherapy for locally advanced inoperable or metastatic stomach cancer and adenocarcinoma of the GEJ. We identified five (9.8%) patients with stomach cancer and 46 (90.2%) patients with adenocarcinoma of the GEJ, respectively. According to the Siewert-Stein classification (14) five (9.8%) patients presented with adenocarcinoma of the esophago-gastric junction (AEG) type I, 19 (37.3%) with AEG type II, and 22 (43.1%) with AEG type III tumors, respectively.

Fifteen patients had had prior surgery for GEJ cancer with curative intent, while a further four patients underwent prior palliative gastrectomy due to bleeding or tumor rupture. Six patients had received prior neoadjuvant or adjuvant chemotherapy, consisting of a docetaxel-based regimen, and one patient had had prior chemoradiotherapy.

Liver metastases were present in 20 patients, lung metastases in three, peritoneal carcinosis in 25, and nine patients had locally advanced tumors with infiltration of

Table I. Baseline characteristics of the study population.

Characteristics	n (%)	
Entered	51	
Median age years (range)	63	(42-86)
Patients >65 years	29	(56.7%)
Median ECOG Performance Score	2	
ECOG PS >1	24	(47.1%)
Female/male	17/34	
Adenocarcinoma of the stomach/GEJ	5/46	
Grade		
1	1	(2%)
2	13	(25.5%)
3	17	(33.3%)
Stomach cancer	5	(9.8%)
Siewert-Stein classification		
AEG I	5	(9.8%)
AEG II	19	(37.3%)
AEG III	22	(43.1%)
Stage at primary diagnosis		
Localized	6	(11.8%)
Metastatic	45	(88.2%)
Metastatic site		
Bone	6	(11.8%)
Liver	20	(39.2%)
Nodes	19	(37.3%)
Peritoneal carcinosis	27	(52.9%)
Lung	3	(5.9%)
2 Metastatic sites	27	(52.9%)
Prior surgery for stomach or GEJ cancer		
Curative intent	15	(29.4%)
Palliative resection	4	(7.8%)
Adjuvant/neoadjuvant chemotherapy	6	(11.8%)
Adjuvant chemoradiotherapy	1	(2%)

AEG, Adenocarcinoma of the esophago-gastric junction; GEJ, gastro-esophageal junction.

spleen, small intestine, or pancreas. Patients' characteristics are summarized in Table I.

Efficacy. The median duration of observation was nine months (range=3 to 20 months). The median PFS in the overall patient population was five months (95% CI 2.91-5.1 months) (Figure 1). In patients older than 65 years (range= 66-86 years), the median PFS was three months (95% CI=2.02-6.45 months) as compared to five months (95% CI=3.55-6.45 months) in patients of maximum 65 years (range=42-65 years) old ($p=0.051$). No difference in terms of PFS was observed between patients with or without liver metastases, and ECOG PS was not predictive of PFS either. The median OS was 12 months (95% CI=9.08-14.92 months). Neither age, nor presence of liver metastases, nor ECOG PS were significantly associated with OS.

Forty-nine patients were available for evaluation of response. Two patients discontinued EOX chemotherapy after one cycle of treatment for personal reasons.

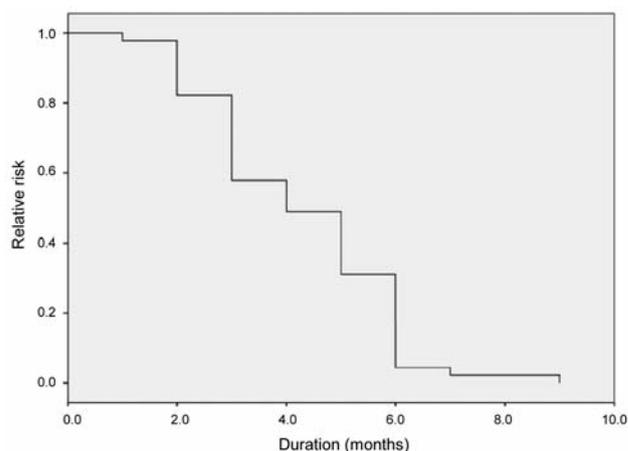


Figure 1. Progression-free survival (months).

A PR was observed in five patients (10.2%; 95% CI=1.90-18.5%), SD for a minimum of six months in 29 patients (56.9%; 95% CI=43.3-70.5%), SD for three months in two patients (3.9%; 95% CI=0-9.2%), and disease in 13 patients (25.5%; 95% CI=13.5-37.5%) progressed despite treatment, translating into a clinical benefit in 34 patients (66.7%; 95% CI= 53.8-79.6).

In patients presenting with liver metastases (n=20), no case of response (*i.e.* CR or PR) was observed, whereas SD for six months was achieved in 13 patients (65%; 95% CI=44.1-85.9%) and SD for three months in one patient (5%; 95% CI=0-14.6%). PD was seen in six patients with liver metastases (30%; 95% CI=9.9-50.1%).

Safety. A total number of 228 (range=1-6) cycles was administered to 51 patients. Overall, EOX combination chemotherapy was well-tolerated and we observed no treatment-related deaths. Side effects are summarized in Table II. Notably, no case of congestive heart failure occurred but a single case of drop in LVEF (15%) was observed. The main toxicities consisted of nausea, hand-foot syndrome, and diarrhea.

We did not evaluate any grade IV toxicity. Grade III diarrhea was observed in one patient (2%), hand-foot syndrome in two patients (3.9%), nausea in three patients (5.9%), constipation (2%) and non-life threatening, therapy-associated or paraneoplastic pulmonary embolism (2%) in one patient. Hematological toxicities of grade III consisted of anemia in two patients (3.9%), neutropenia and thrombocytopenia in one patient each (2%). No case of grade IV hematological toxicity was observed.

Two patients discontinued first-line EOX after one cycle of chemotherapy each at their own wish. One patient had not experienced any side-effects, while the other had grade II

Table II. Main adverse effects of combination therapy.

Toxicity	CTC grade n (%)			
	1	2	3	4
Abdominal pain	1 (2%)	-	-	-
Diarrhea	3 (5.9%)	6 (11.8%)	1 (2%)	-
Constipation	-	1 (2%)	1 (2%)	-
Nausea	6 (11.8%)	8 (15.7%)	3 (5.9%)	-
Emesis	3 (5.9%)	2 (3.9%)	-	-
Stomatitis	-	1 (2%)	-	-
Hand-foot syndrome	1 (2%)	-	2 (3.9%)	-
Fatigue	3 (5.9%)	3 (5.9%)	-	-
Neuropathy	1 (2%)	-	-	-
VTE	2 (3.9%)	1 (2%)	1 (2%)	-
Asymptomatic LVEF drop	1 (2%)	-	-	-
Anemia	3 (5.9%)	4 (7.8%)	2 (3.9%)	-
Neutropenia	2 (3.9%)	2 (3.9%)	1 (2%)	-
Thrombocytopenia	-	2 (3.9%)	1 (2%)	-

CTCAE: LVEF, left ventricular ejection fraction; VTE venous thromboembolic events.

diarrhea, grade II nausea and grade I vomiting. In two patients (3.9%), chemotherapy was continued with capecitabine alone after six cycles of EOX combination chemotherapy. In three patients (5.9%), a delay of cycles was necessary due to side effects; a reduction to 75% of the initially scheduled dose was performed in six patients (11.8%).

Discussion

Palliative chemotherapy is well-established for locally advanced, inoperable or metastatic cancer of the stomach or the GEJ. Standard platinum-based combination regimens have been shown to prolong OS and improve QoL, while the considerable toxicity of currently-used standard triple-drug combinations needs to be taken into account. In this retrospective analysis, we present efficacy and toxicity data of a modified EOX regimen, in which capecitabine was administered at a twice-daily dose of 1000 mg/m² p.o. for two weeks, followed by one week of rest. Our data need to be discussed in the light of efficacy and toxicity data of standard continuous capecitabine EOX and other triple-drug combination regimens.

Modified EOX with non-continuous capecitabine resulted in considerably less severe toxicity, as compared to conventional EOX (9) or DCF (7, 8), which is of potential value in terms of QoL in incurable patients. Indeed, grade III diarrhea was reported in one patient only (2%), and grade III hand-foot syndrome was observed in two patients (3.9%). Other grade III toxicities consisted of constipation, nausea, therapy-associated or paraneoplastic venous

thromboembolic events, as well as hematological side effects; importantly, the frequency of all grade III side effects was below 5%. Furthermore, no case of grade IV toxicity was reported. In the REAL-2 trial incorporating standard continuous capecitabine, frequency of severe diarrhea was considerably higher (11.9% grade III and IV), while the rate of hand-foot syndrome was comparable (3.1% grade III and IV) (9). With DCF, a 19% incidence of severe diarrhea was observed; furthermore, hematological toxicity of DCF (7) was considerably higher as compared to EOX (9). Those data indicate that non-continuous administration of capecitabine apparently reduces the rate of severe diarrhea, while the incidence of hand-foot syndrome is not increased.

The median PFS for the entire study population was four months (95% CI=2.91-5.1 months). In the REAL-2 trial, PFS with standard EOX was seven months, indicating superior activity of continuous capecitabine administration (9). DCF regimen on the other hand, yielded a PFS of 5.6 months (7). Importantly, outcome data in our study were superior in younger patients: In patients with a maximum age of 65 (range=42-65 years) years. The median PFS was five months and therefore well in line with the DCF data, as compared to three months in patients older than 65 years (range=66-86 years) (p=0.051). In older patients, dose reductions due to toxicity were frequently necessary; this may well have compromised efficacy. Notably, the rate of patients older than 65 years was 56.7% in this analysis. It must, therefore, be assumed that our study was not of a highly selected clinical trial population and indeed is more representative of real-life patients with stomach/GEJ cancer. Furthermore, the median OS was comparable between the three regimens: modified EOX; 12 months; standard EOX, 11.2 months; and DCF, 9.2 months (7, 9).

The RR to modified EOX was lower when compared to conventional EOX within the REAL-2 study (9) and to DCF (7) (10.2% versus 47.9% and 35%, respectively). Bearing in mind, however, that the rate of patients with SD for a minimum of six months was high (56.9%), modified EOX apparently offers acceptable clinical activity with reduced toxicity, as compared to standard triple-combination regimens.

Obviously, our study has several limitations. A low overall patient number, as well as a retrospective non-randomized design, limits the validity of our data. Furthermore, no information concerning QoL is available. Therefore, a prospective trial is necessary in order to fully-elucidate the activity and toxicity of modified EOX.

In conclusion, modified EOX apparently provides efficacy similar to conventional EOX and other triple-combination regimens, while notably, the rate of severe toxicity was reduced. Further evaluation of this regimen within a prospective clinical trial is therefore warranted.

Conflicts of Interest

None declared.

Funding

This study had no sponsor or funding source.

Acknowledgements

MH would like to thank Andrea Julia Kreissl, MD, for indirect support.

References

- 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.
- Malvezzi M, Arfe A, Bertuccio P, Levi F, La Vecchia C and Negri E: European cancer mortality predictions for the year 2011. *Ann Oncol* 22: 947-956, 2011.
- 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.
- Murad AM, Santiago FF and Petrioianu A: Modified therapy with 5-fluorouracil, doxorubicin and methotrexate in advanced gastric cancer. *Cancer* 72: 37-41, 1993.
- 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.
- Glimelius B, Ekstrom K, Hoffman K, Graf W, Sjöden 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.
- 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.
- 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.
- Cunningham D, Starling N, Rao S, Iveson T, Nicolson M, Coxon F, Oates J and Norman AR: Capecitabine and oxaliplatin for advanced esophagogastric cancer. *N Engl J Med* 358: 36-44, 2008.
- Al Batran SE, Hartmann JT, Hofheinz R, Homann N, Rathwisch V, Probst S, Stoehlmacher J, Clemens MR, Mahlberg R, Fritz M, Seipelt G, Sievert M, Pauligk C, Atmaca A and Jäger E: Biweekly fluorouracil, leucovorin, oxaliplatin and docetaxel for patients with metastatic adenocarcinoma of the stomach or esophagogastric junction: A phase II trial of the Arbeitsgemeinschaft Internistische Onkologie. *Ann Oncol* 19: 1882-1887, 2008.
- 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.
- 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.
- Miller AB, Hoogstraten B, Staquet M and Winkler A: Reporting results of cancer treatment. *Cancer* 47: 207-214, 1981.
- Siewert JR, Stein HJ and Feith M: Adenocarcinoma of the esophago-gastric junction. *Scand J Surg* 95: 260-269, 2006.

Received December 13, 2013

Revised February 1, 2013

Accepted February 4, 2013